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Transatlantic Regulatory Divergence in Pharmaceuticals: Exploring economic and cultural explanations

Presentata da: **Liam Wells**

Coordinatore Dottorato

prof. Andrea Mattozzi

Supervisore

Michael Faure
Elena Reznichenko
Luigi Franzoni

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Transatlantic Regulatory Divergence in Pharmaceuticals

Exploring economic and cultural explanations

Liam Wells

To Charlie, Lucy, Taylor, and Madison

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Liam Wells

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List of Abbreviations

ACT-UP AIDS Coalition to Unleash Power
ADRs Adverse Drug Reactions
AEMPS Spanish Agencia Espanola de Medicamentos y Productos Sanitarios
AFSSaPS Agence française de sécurité sanitaire des produits de santé
AHA American Hospital Association
AIDS Acquired Immudeficiency Syndrome
AIFA Italian Medicines Agency
ALI American Law Institute
AMA American Medical Association
ANDA Abbreviated New Drug Application
ANSM French Agence Nationale de Securite du Medicament et des Produits de Sante
ATLA American Trial Lawyers Association
AUT Austria
BASG Austrian Bundesamt fur Sicherheit im Gesundheitswesen
BBWs Black Box Warning
BE Belgium
BfArM German Bundesinstitut fur Arzneimittel und Medizinprodukte
BSG German Bundesgesundheitsamt
CDER Center for Drug Evaluation and Research
CIA Central Intelligence Agency
CJEU Court of Justice of the EU
CMPH Committee on Medicinal Products for Human Use
CPMP Committee for Proprietary Medicinal Products
CT-GG Cultural Theory of Risk/Grid-Group
CVF Cultural Values Framework
DE Germany
DG Directorate General
DHPC Dear Healthcare Provider Communication
DK Denmark
DMA Danish Medicines Agency
DNC Dimensions of National Culture
DSHEA Dietary Supplement Health and Education Act 1994
DTCA Direct-to-consumer advertising
EASA EU Aviation Safety Agency
EC European Communities
ECHR European Convention on Human Rights
ECtHR European Court of Human Rights
EEA European Economic Area
EFTA European Free Trade Association
EMA European Medicines Agency
EMEA European Medicines Evaluation Agency
EP European Parliament
EPA Environmental Protection Agency
EU European Union
EUMS EU Member State/s
EUPI EU Pharmaceutical Industry
EUR Euros
FAMHP Belgian Federal Agency for Medicines and Health Products
FCC Federal Communications Commission
FDA Food and Drug Administration
FDAAA Food and Drug Administration Amendments Act 2007
FDCA Food Drug and Cosmetics Act 1938
FFDA Federal Food and Drug Act 1906
FMA Finnish Medicines Agency
FR France
FTC Federal Trade Commission
GBP Pounds Sterling
GDP Gross Domestic Product
GLOBE Global Leadership and Organisational Behaviour Effectiveness
GSALE General Sale
Hatch-Waxman The Hatch Waxman Act 1984
HHS Department of Health and Human Services
HMA Heads of Medicines Agencies Board
HPRA Irish Health Products Regulatory Authority
IBM International Business Machines Corporation

ICH International Council for Harmonisation
INN International non-proprietary name
IP Independent pharmacy
LRAC Long Run Average Cost
LRP Large retail pharmacy
MCA UK Medicines Control Agency
MEB Dutch Medicines Evaluation Board
MHRA UK Medicines and Healthcare Products Regulatory Agency
MPA Swedish Medical Products Agency
NAs National agencies
NDA New Drug Application
NDC New Drugs Committee
NEUMS Northern EUMS
NL Netherlands
NOM Greek National Organisation for Medicines
NRPs Nicotine placement products
OECD Organisation for Economic Cooperation and Development
OIRA Office of Information and Regulatory Affairs
OSuE Office for Surveillance and Epidemiology
OTCPRs Over the Counter Pain Relievers
PASS Post Authorisation Safety Studies
PDUFA Prescription Drug User Fee Act 1992
PhRMA Pharmaceutical Research and Manufacturers of America
PLD Product Liability Directive 1985
PO Prescription-only
PRAC Pharmacovigilance Risk Assessment Committee
PSMs Post-market Safety Measures
PSO Pharmacist-supervision-only
RCTs Randomised controlled (clinical) trials
RD Research and development
rHGHG Relatively High-Grid, High-Group
rLGLG Relatively Low-Grid, Low-Group
RMPs Risk Management Plans
SCOTUS Supreme Court of the United States
SEUMS Southern EUMS
SPI System Suggested Public Interest System
SV BOD Swedish Board of Drugs
SWE Sweden
TTAs times to Approval
TUR Traditional Use Registration
U Unlicensed
UK United Kingdom
UK CSM UK Committee on the Safety of Medicines
US United States
USD US Dollars
USPI US Pharmaceutical Industry

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Introduction

I. Overview of the Study

1. Motivation

In many societies the group will not allow the individual to self-regulate on the question of what they put inside their own body. Smokers, the overweight, the underweight, those addicted to opioids, those who overuse prescribed antibiotics, those who accept the Covid-19 vaccine, and those who do not: all face the judgment of others in their group. Looking at history in the United States ('US') and Europe - comprising both the European Union ('EU') and EU Member States ('EUMS') - the earliest and most heavily regulated consumer products are those intended to enter the body: food, pharmaceuticals, and cosmetics, for instance. The prospect of bodily entry seems to prompt calls to exercise some social control over this act via regulation of the product, arguably louder and stronger calls than in the case of consumer products which still pose risks of harm but which are not intended to enter the body.

I have always found this phenomenon very interesting. I have lived or studied in a few different countries, on both sides of the Atlantic, for varying periods of time, and two things about this cross-border mobility stick out in my memory most. The first is food. The sheer diversity of it, and what it means or represents in different places. The second is that there is absolutely no consistency across borders on whether I can buy nicotine gum in a supermarket![1] Foodstuffs and pharmaceuticals, both being consumer products intended to *enter the body*, seem to be regulated in very different ways across different groups. These are an area of product regulation which requires special attention. Unlikely to be explicable *only* by reference to market failures as displayed on graphs, without recourse to some explanation of the *preferences* of consumers, where these come from, how these are shaped.

So that is my motivation for writing a doctoral thesis on regulatory divergence. I chose to focus on the US and the EU because it is transatlantic divergence, which is already discussed at length in the literature,[2] but without yet providing a full account of the pathways through which culture may affect these divergences. I chose to focus upon pharmaceutical products

1 Which is an aspect of Sale Classification: see Chapter Four

2 See, generally, Wiener, Jonathan B, Rogers, Michael D, Hammitt, James K and Sand, Peter H (Ed), "The Reality of Precaution: Comparing risk regulation in the United States and Europe" (2011) RFF Press: Wiener, Jonathan B, "Global Environmental Regulation: Instrument Choice in Legal Context" (1999) Yale Law Journal, Vo. 108, No. 4m pp.677-800: Wiener, Jonathan B, "The Politics of Precaution, and the Reality" (2013) Regulation & Governance: Vogel, David, "The Politics of Precaution: Regulating Health, Safety and Environmental Risks in Europe and the United States" (2012) Princeton University Press: Vogel, David, "The hare and the tortoise revisited: the new politics of consumer and environmental regulation in Europe" (2003) British Journal of Political Science 33 4 557-580.

because there seemed to be a greater number of transatlantic regulatory divergences which are the subject of academic debate in this sector, than in the food sector.[3]

2. Problem Definition

An explanation is needed for why different groups regulate different pharmaceutical products in different ways. One 'extant' theory is that 'public interest' regulators determine the benefit-risk profile of products and, according to this expert analysis will decide questions of market access, sale restrictions and labelling, thus correcting potential market failure. Yet, it seems to me that if 'expertise' represents scientific consensus, then in relation to the same product, these experts, in any country should come to broadly the same conclusion on these matters. Clearly, they do not.

I also know that it is not only experts, acting in the public interest, that make these choices. I am also aware of the other 'extant' theory that interest groups exist, and that they lobby regulators for regulations which further their private interests. And, that bureaucrats in agencies are rational actors who maximise their own maximands.

Moreover, I understand that there are wider institutional constraints, which differ from jurisdiction to jurisdiction, and that these can assist in explaining differences in approach to regulation. Hence, I am also aware of a third 'extant' theory of institutional analysis.[4]

Yet all three of these theories treat human preferences as exogenous and given. I have stated above, the research is motivated by the observation that certain products are very directly linked to our emotions and preferences. I believe that to provide further explanation for regulatory divergence in relation to such products, it is necessary to incorporate an account of how preferences are shaped. Once such an explanation (for preferences) is included in the explanation for regulatory divergence, then a more consistent explanation may be furnished – across several divergences – than that provided by the three 'extant' theories alone.

This is my problem definition: there is no consistent underlying explanation furnished by the extant theories of public interest, private interest, and institutional analysis to explain more than one divergence at once. In the 'methodology' section, below, of this introduction, I set out how I selected six 'cases' of transatlantic regulatory divergence in the pharmaceutical sector. This problem definition is framed again, specifically, in the case of each of the divergences, which I deal with in pairs in Chapter Two, Chapter Three and Chapter Four, respectively. Then I turn, from Chapter Five onwards, to seek a consistent underlying explanation through the application of cultural theory.

3 Although there are many in the food sector too. I also enjoy food too much to spend several years economically analysing it!

4 The existence of socialised healthcare systems in certain jurisdictions, and the cost to the public purse of funding pharmaceuticals, for example, clearly affects the need to contain costs perhaps through regulating to mandate generic substitution in pharmacies.

3. Originality

The regulation of the pharmaceutical sector has been extensively economically analysed,[5] although this line of literature focuses upon the nature and special features of the pharmaceutical sector rather than upon explaining differences between jurisdictions in regulating it. On the other hand, transatlantic regulatory divergence has already been analysed across several sectors[6] including pharmaceuticals – but from a legal rather than an economic perspective - and culture has been identified as a relevant variable. However, none of these accounts have fully explored the pathways through which culture may shape regulatory divergence, nor have they expressly applied the rich body of literature found in cultural theory, which is drawn from anthropology, and sociology. That body of literature is set out in detail in Chapter Five,[7] and in this work I apply the 'Cultural Theory of Risk and Grid-Group typology' ('CT-GG') of culture (as developed by Mary Douglas, Aaron Wildavsky, and others).[8] Thich has been widely applied in many disciplines, for example in political science, to explain a variety of phenomena, but never – so far as I can see – to explain cross-border regulatory divergence.

There is a great body of economic literature which focuses on culture, the relationship between culture and institutions, and the ability of that relationship to explain macroeconomic outcomes,[9] but this body of literature from economics[10] and institutional theory has not 1) consistently applied a specific typology or dimensions of culture; nor, 2) been applied to explain regulatory divergence specifically. On the other hand, Cultural Theory has been harnessed by scholars in the field of risk perception to analyse the extent to which individual perceptions of risk may be conditioned by cultural factors, and this body of work has consistently applied a typology of culture very closely related to that which I select in

5 See e.g. M. Danzon, Patricia and Keuffel, Eric (2014) "Regulation of the Pharmaceutical-Biotechnology Industry" in "Economic Regulation and Reform: What have we learned?" NBER U. Chicago Press June 2014. See also Mossialos, Elias, Monique Mrazek, and Tom Walley. Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality: McGraw-hill education (UK), 2004.: Golec, Joseph H., and Vernon, John A., European Pharmaceutical Price Regulation, Firm Profitability, and R&D Spending NBER Working Paper No. 12676 Issued in November 2006.

6 See, generally, Wiener et al (2011): Wiener, Jonathan B, (2013): Vogel, David (2012): Vogel, David, (2003): British Journal of Political Science 33 4 557-580. Jonathan B, Rogers, et al (2011): See also Michael D, Hsmmitt, James K and Sand, Peter H (Ed), "The Reality of Precaution: Comparing risk regulation in the United States and Europe" (2011) RFF Press: Miller, Francis H, "Medical Errors, New Drug Approval, and Patient Safety".

7 See generally Hofstede, Geert. "Culture and organizations." International Studies of Management & Organization 10, no. 4 (1980): 15-41.

Hofstede, Geert. "The cultural relativity of organizational practices and theories." Journal of international business studies 14, no. 2 (1983): 75-89: Hofstede, Geert. Culture's consequences: International differences in work-related values. Vol. 5. Sage, 1984

8 See Douglas, Mary, and Aaron Wildavsky. Risk and culture: An essay on the selection of technological and environmental dangers. Univ of California Press, 1983.

9 Alesina, Alberto, and Paola Giuliano. "Culture and institutions." Journal of Economic Literature 53, no. 4 (2015): 898-944.

10 See e.g. Thornton, Patricia H. Markets from culture: Institutional logics and organizational decisions in higher education publishing. Stanford University Press, 2004.

Chapter Five.[11] However, this body of literature has not gone so far as to ask whether individual risk perception (culturally conditioned) may affect regulatory outcomes.

A significant methodological input made by this work is in the development of cultural theory such that it is applicable to the analysis of institutions. This is set out in Chapter Five and is an original contribution.

4. Goal of Study and Societal Relevance

The first goal of my study is to investigate the relationship between culture and regulatory divergence. This will involve exploring explanations provided by the 'extant' (including the economic) theories of regulation - public interest theory and private interest theory - as well as institutional analysis and the impact of jurisdiction-wide institutions. Once I have established the extent to which these three extant theories provide a complete explanation for regulatory divergence, then I consider whether the application of cultural theory can provide further explanation. I will consider that the application of cultural theory has provided further explanation if it is able to furnish a consistent explanation for regulatory divergence across the two jurisdictions in the case of several divergences, where the extant theories had failed to do so. By applying both the extant theories and cultural theory, and considering the interaction between them, this goal of my study (the first goal) also seeks to establish *how* underlying culture is affecting regulatory divergence – through which pathways, directly, or indirectly.

A secondary goal of my study – which is the focus of Chapter Five - is to explore the nature of culture itself, and its relationship with other institutions, by tying together the literature from cultural theory, institutional theory, and the economic literature on the relationship between culture, institutions, and macroeconomic outcomes. Doing so may help to shed some light on the questions of: 1) whether, and if so how, culture can change within a jurisdiction; 2) to what extent underlying culture can be affected or changed by a change to other institutions (such as regulations); and 3) what the origins of cultural diversity might be, i.e., where does culture come from?

11 See, for example: Kahan, Dan M., "Cultural Cognition as a Conception of the Cultural Theory of Risk" (2012) S. Roeser, R. Hillerbrand, P. Sandin, M. Peterson (eds), Handbook of Risk Theory, DOI10.1007/978-94-007-1433-5_28 Springer Science + Business Media B.V. 2012: Kahan, Dan M, Jenkins-Smith, Hank, Braman, Donald, "Cultural cognition of scientific consensus" (2011), Journal of Risk Research, 14:", 147-174, DOI: 10.1080/13669877.2010.51124: Kahan, Dan M and Braman, Donald, "Gender, race, and risk perception: The influence of cultural status anxiety" (2005 draft) http://ssrn.com/abstract=723762: Kahan, Dan M., Braman, Donald, "More Statistics, Less Persuasion: A cultural theory of gun-risk perceptions" (2003) University of Pennsylvania Law Review, Vol. 151, No. 4 (April 2003) pp. 1291-1327: Kahan, Dan M, Slovic, Paul, Braman, Donald and Gastil, John, "Book review: Fear of Democracy: A cultural evaluation of Sunstein on risk" (2006) Harvard Law Review 119 1071. See Kahan, Dan M., Donald Braman, Geoffrey L. Cohen, John Gastil, and Paul Slovic. "Who fears the HPV vaccine, who doesn't, and why? An experimental study of the mechanisms of cultural cognition." Law and human behavior 34, no. 6 (2010): 501-516: and KAHAN, Dan M. "A risky science communication environment for vaccines." Science 342, no. 6154 (2013): 53-54.

A third goal of my study is to assert a relative cultural positioning, in accordance with a given typology of culture (in this case the Cultural Theory of Risk and Grid-Group Typology) for the US and the EU, respectively.[12]

The societal relevance of these three goals is strong. First, the regulation of the pharmaceutical sector is of crucial importance to society as a whole because of the very significant benefits posed to society (positive externalities) from the development and availability of medicines to treat diseases. Whilst, at the same time, the risks posed to society from adverse drug reactions ('ADRs') are potentially catastrophic. A better understanding of what variables affect the regulation of the pharmaceutical sector, and in what weighting or mix, will be a valuable contribution to the knowledge base. Particularly for those who have the goal of maximising the sum of the benefits and costs, to society, of the development of pharmaceutical products.

From the perspective of regulatory divergence, this study has societal relevance because it has the potential to assist in answering policy questions regarding the extent to which it is desirable, or even feasible, to harmonise the regulation of the pharmaceutical sector internationally. Regulatory harmonisation is generally seen as desirable in the eyes of industry actors who seek to abolish non-tariff barriers to cross border trade. The goal of this study is to provide a *fuller* explanation for regulatory divergence by fully exploring both economic and cultural explanations. The results of this study will furnish policymakers with a more complete toolkit for approaching the question of regulatory convergence. Whether to attempt it at all, and if so, to what extent and in what way.

In addition, by fully developing an approach to culture and fully exploring the relationship between culture and regulation (in Chapter Five) this study will be of value to society in providing an approach to the relationship between culture and law. A better understanding of this relationship is potentially applicable to a range of legal, ethical, or political differences in (for example) international relations.

Finally, the goal of this study in establishing a relative cultural positioning of the jurisdictions of the US and the EU (and the Clusters of northern and southern EUMS) may pose benefits to society in providing a starting point for the cultural analysis of many issues; for example, the opiod crisis in the US. The cultural positioning developed in this study - alongside the theoretical insights developed regarding the relationship between culture and other institutions within a jurisdiction - may help to shed further light on both issues in future research. The relationship between culture as an institution (here the most basic institution within a group) and risk perception as an informal social institution may be able to account for differences in levels of vaccine hesitancy. It may also assist in explaining the root causes of the opioid crisis in the US, and how best to combat it through, for example, better risk and science communication to consumers from regulators.

12 This relative cultural positioning could then hypothetically be used for further studies covering other areas of divergence between the two jurisdictions.

5. Research Question

My research question is as follows:

"Can cultural theory add further explanation to that already provided by the extant theories of public interest, private interest, and institutional analysis, in the case of transatlantic regulatory divergence in the pharmaceuticals sector?"

This is the primary research question which I focus on throughout the entire work.

While answering this question, albeit not expressly, I necessarily also address two other questions. The first is: *"What is the nature of the relationship between culture and the other institutions binding together a group?"* (This is answered in Chapter Five). The second is: *"Adopting the Typology of Culture Provided by the Cultural Theory of Risk and Grid-Group, how are the jurisdictions of the US and the EU positioned relative to each other in their cultural orientations?"* Answering these second and third questions is instrumental, only, to answering the main research question.

6. A Positive Analysis

What is undertaken in this work is a positive analysis. The primary research question asks whether cultural theory can add further explanation. However, because regulation is an aspect of culture, it is already clear that cultural theory must, by definition, provide *some* explanation for regulatory divergence. Despite this, the regulatory position taken may reflect a cultural orientation which is different from that of the jurisdiction in which it is found.[13] I do not just culturally analyse the regulations, instead I look beyond the regulations, to how and why they were created as they were – applying insights from private interest theories of regulation. Where the cultural orientation of the regulation differs from that of the jurisdiction, therefore, I ask why that was the case and I look deeper into the problem until I find how underlying culture has its effect. Often, the regulatory position taken is due to the lobbying efforts of interest groups, constrained or facilitated by institutions which apply to the whole jurisdiction, and those interest groups and institutions both reflect the underlying culture of the jurisdiction. When I ask, therefore, whether cultural theory can add further explanation to that furnished by public and private interest theories, and institutional analysis, the emphasis is placed on the word 'further' rather than the word 'can'. I will consider the primary research question to be answered in the affirmative if I find that culture has been able to furnish a *consistent* explanation across several (here, six) regulatory divergences. In such a case, whilst private interest and public interest and institutional factors may have been different from divergence to divergence, a consistent underlying cultural orientation *within* each jurisdiction and a consistent underlying difference in cultural orientations *between* jurisdictions, will show that culture has added 'further' explanation to

[13] Indeed, this is the case for some of the regulations considered in this work. See Chapter Seven.

the extant theories. It will do this by showing *how* underlying jurisdictional culture affects the form of the regulation of pharmaceuticals: through the actions of interest groups and the effect of jurisdiction-wide institutions. In other words, I *keep looking* until I find how culture is contributing. That is why this study is a positive analysis only, and why the explanation provided by culture is supplementary only, and not alternative, to the explanation provided by the extant theories.

By the conclusion of this work, I find evidence that underlying jurisdictional culture affects regulatory divergence through the cultural orientation of *groups* which lobby for regulations, and *organisations* which supply regulation, both constrained or facilitated by the effects of jurisdiction-wide *institutions* which share the cultural orientation of the jurisdiction. The public interest, too, is affected by jurisdictional culture in that this affects what is demanded from regulators, by consumers, as an interest group – including determining whether any 'market failure' exists in the first place in the eyes of consumers.

In other words, cultural theory, public interest theory, private interest theory and institutional analysis all provide explanation for regulatory divergence. Arguably, taken together, they provide *full* explanation for regulatory divergence in these six cases. And, because underlying jurisdictional culture remains consistent across all divergences, cultural theory has added *further* explanation to the extant theories. Thus, the primary research question is answered in the affirmative.

7. Structure

This work is divided into seven chapters plus this introduction. In Chapter One I set out some factual and historical information and develop an analysis of the regulatory agencies which is applied throughout the following six Chapters. In Chapters Two, Three, and Four I discuss two divergences apiece. In Chapter Two: Licensing and Direct to Consumer Advertising. In Chapter Three: Pharmacovigilance and Product Liability. And, in Chapter Four: Sale Classification and Generic Substitution. In these three chapters I first set out the transatlantic divergences,[14] then I apply public interest theory, then I apply private interest theory and then I consider the effect of jurisdiction-wide institutions. The reason why I deal with the divergences in three pairs is that ultimately the goal of this study is to see whether the addition of cultural theory can furnish a *consistent* explanation for divergence across *several* divergences. Thus, I need to investigate first whether the extant theories are capable, on their own, of providing a consistent explanation across each pair of divergences (then, eventually, across all six divergences). My conclusion at the end of Chapters Two, Three and Four, respectively, is that public interest theory, private interest theory and institutional analysis together provide *some* explanation in the case of each pair of divergences. However, that explanation is not consistent, in any of these chapters, across both divergences considered in each. For example,

14 There are also some 'system' divergences and 'intra-EU' divergences which are investigated in Chapters Three and Four respectively.

the question always remains – at the conclusion of each of these chapters - why the interest groups and organisations which shaped the regulatory positions have behaved the way that they do, and why the jurisdiction-wide institutions take the form that they do. Thus, by the end of Chapter Four the problem has been fully framed in the case of all six divergences (three pairs) in readiness for the application of cultural theory in Chapters Five to Seven.

8. Methodology

In this work I adopt distinct two distinct methodologies. The first methodology is applied in Chapters One to Four where I consider the divergences, the relevant interest groups, organisations, and institutions - applying the extant theories. The second methodology is applied in Chapters Five to Seven where I apply cultural theory.

The first methodology in Chapters One to Four was adopted for the purposes of:

1) selecting and *precisely* identifying divergences in pharmaceutical regulation between the US and the EU;

2) identifying, explaining and evaluating potential public interest justifications for the regulatory positions drawing upon the theoretical insights of public interest theories of regulation – this includes, in Chapter Three, the development of a model for the optimal regulation of product safety risks through a combination of product liability law and pharmacovigilance regulation, which is called, in this case, the 'suggested public interest system';

3) identifying interest groups, organisations and jurisdiction-wide institutions which are proximate to the shaping of the regulatory positions, according to the standard theoretical approach of private interest theories of regulation;

4) analysing the key characteristics and behaviour of the proximate interest groups and organisations and their differences, relative to each other, in the US and the EU respectively; and

5) applying the theoretical insights taken from private interest theories of regulation, alongside the key characteristics and behaviour of the proximate interest groups, to evidence an account of the development of each regulatory position according to private interest theories of regulation.

Each of 1) to 5) above was done via the means of a systematic literature search using neutral keywords (primarily using google scholar). Initially, the six regulatory divergences were selected based upon the extent to which they are the subject of academic debate. Thus, I began by making general searches using the terms 'Transatlantic' or 'US-EU', 'Regulatory Divergence' and 'Pharmaceuticals' and having read several review papers and books of broad scope, I identified that six regulatory divergences were the ones which appeared to be the

most widely discussed in the academic literature, and thus I selected these for analysis in this work.

Having selected the six divergences, I deepened the literature search in the case of each of 1)–5) above to address the question in each case. The information and analysis set out in Chapters One to Four represents the full literature which I have read on these subjects.

The second methodology was adopted from Chapter Five onwards. I needed to adopt an approach to culture which was compatible with a doctoral thesis in law and economics, and therefore again I systematically searched for literature on the relationship between culture and economics. This literature - focusing less on the contents of culture and more on the relationship between culture as an institution, other institutions, and macroeconomic outcomes - enabled me to develop an institutional approach to culture when I combined it with the institutional literature and the literature from cultural theory. This approach is set out in full in Chapter Five.

As the research project also required me to position the jurisdictions (etc.) relative to each other in cultural terms, I also performed a systematic literature search for theories which provide typologies and dimensions representing the 'contents' of culture. The literature found here came primarily from the management sciences, sociology, anthropology, and political science. I selected a specific typology of culture (the Grid-Group typology linked to the Cultural Theory of Risk) based upon pre-determined criteria for selecting a typology of culture,[15] and those criteria were based on pragmatic concerns related to the workability of the task to be undertaken in Chapters Six and Seven. Another (meta) criterion, was compatibility with the institutional approach to culture which had been developed and adopted in the first half of Chapter Five.

Once the institutional approach, and the chosen typology, had been settled upon, I then devised a way to operationalise the theoretical insights set out in this literature. I did this in a way which would enable me to compare coupled pairs of jurisdictions (or clusters), organisations, groups, and institutions, by positioning them with a cultural orientation relative to each other according to the Grid-Group typology.

I did this as follows. First, I searched all the literature I could find which applied the Grid-Group typology to analyse the cultural orientation of various units of analysis. Then, I systematically collated and documented the views of the various Cultural Theory of Risk scholars on the meaning of the two dimensions, and the four cultural types provided by the Grid-Group typology. From this database of scholarly views, I developed a set of 'predicates' for the relevant cultural types and set these out in Table 71 at the conclusion of Chapter Five. In particular I developed a set of pairs of predicates to distinguish a hierarchical cultural orientation from an individualistic cultural orientation. This set of pairs of predicates was adopted and applied throughout Chapters Six and Seven for the cultural analysis of groups, organisations and institutions which followed. In Chapter Six I drew upon the key characteristics and behaviour of the proximate interest groups and organisation identified

15 This is set out in Chapter Five.

using the first methodology in Chapters One to Four. From these I was able to deduce institutions (rules of intra-group interaction and between-group interaction) governing these groups and organisations. Those institutions were then cross referenced (sometimes expressly, and sometimes impliedly) with the predicates developed at the end of Chapter Five, to identify a relative cultural positioning in the case of each pair: whether relatively more hierarchical or relatively more individualistic. In the case of the jurisdiction-wide institutions, I did this directly by cross referencing those institutions with the predicates. This is how I was able to identify the relative cultural positioning of the jurisdictions, Clusters, groups, organisations, and institutions in Chapters Six and Seven, and thus how I was able to arrive at my overall results and conclusions.

9. Limitations

The major limitation of this work, in relation to the primary research question, is that it is a positive analysis only. Thus, it is assumed that culture *must* affect regulatory divergence because regulation is an example of an institution. And, the definition of culture adopted in this work is that it is also an institution – the most basic institution, or the 'institutional logic' of the group in question. Nevertheless, the institutional approach to culture set out in Chapter Five, tying together the economic literature on culture with the literature on institutional theory does provide valuable and novel insights into the nature of culture itself as an institution and its relationship with other institutions in a group. The theory applied also sheds light on the possibility and nature of cultural change in a jurisdiction, and on the origins of cultural diversity. Moreover, by searching for the effects of culture via the public interest mechanisms, the private interest mechanisms and the jurisdiction-wide institutions, this work provides valuable clarity upon how culture affects regulatory divergence. Previous scholarship has merely assumed that culture must influence regulatory divergence without investigating the pathways. Whilst I do not, here, identify the exact pathways, I do link the effect of culture with those pathways for shaping regulation which are already well established in the private interest and political science literature, and show that underlying culture may be having an effect through these pathways.

Moreover, even though the analysis undertaken here is positive only, the primary research question is capable of being answered in the affirmative. That is because cultural theory adds further explanation to the extant theories by virtue of providing a consistent explanation across several divergences. The consistency is key, and therefore I consider each of the divergences in pairs, applying the extant theories to seek consistent explanations across each pair (and finding this lacking) before turning to apply cultural theory, where a consistent explanation is then found across all divergences.

The second limitation relates to the specific cultural positioning of the jurisdictions, groups etc. This is very much limited by the choice of the typology of culture which was adopted here, and that decision was made for pragmatic reasons. Different typologies or dimensions of culture may have worked just as well. Thus, what has really been found here is a case of

cultural diversity – there are observable and consistent differences, by reference to a fixed set of predicates, between the units analysed. However, the choice to label these 'individualistic' and 'hierarchical' is a pragmatic choice made for the purposes of this project. Others may prefer to describe and analyse the (substantiated) cultural diversity in a different way according to a different typology or dimensions.

A third limitation is the narrow extent to which the idividual EU member states - selected for close scrutiny - represent the EU of 2024 as a whole. The focus is upon Northwestern and Southern EU member states, as well as the UK, which is a former member state. Eastern EU member states are not closely analysed in this way. This choice was made for pragmatic reasons as inclusion of Eastern EU member states may have led to the introduction of another, or possibly several more, cultures and different ways of regulating pharmaceuticals.

The fourth limitation relates to a lack of a quantitative, statistical, empirical approach. In principle, such an approach is possible based upon the theory applied in this work. In Chapter Seven I describe a hypothetical alternative methodology which would have made use of the predicates of hierarchism and individualism and vastly increased the number of regulatory divergences analysed. There, I set out my reasons why I believe such an approach may have glossed over some of the necessary theoretical texture set out in this work. That approach remains possible as a future endeavour, however, I believe that before attempting such a task the rigorous theoretical approach and analysis set out in this work was and is indispensable first. I must accept, however, that due to the limitation to six divergences, and the lack of application of statistical techniques, my results cannot be stated to any order of statistical significance at this stage.

A final limitation is the fact that not all potentially relevant institutions and aspects of pharmaceuticals regulation could be considered in this work. All aspects of the global pharmaceuticals regulatory system are linked together, and space and time precluded me from analysing every single one in detail. I made a judgment call to focus deeply upon six divergences, the most salient which appeared in the literature on regulatory divergence in pharmaceuticals. As such, I do not go into any serious detail on intellectual property regimes, on pharmaceutical reimbursement schemes, on the intricacies of price regulation, or on the regulation of parallel imports for example. Based upon what I have found here in the links between the regulations which I did consider, and underlying culture, I believe a consistent picture would emerge if I continued to apply the same methodology across further divergences. However, there was not the space to do this here. This work is perhaps best seen as a piece of scientific research in its own right, disclosing a robust positive analysis of the relationship between culture and regulatory divergence, but one which is by no means a complete explanation, yet, of the *global* system. It may, however, serve as a prototype theoretical and methodological approach for a future enquiry which might make use of quantitative and statistical tools.

This introduction proceeds in the following way: in Section II I set out some basic market features and the structure of the (global) pharmaceuticals sector; in Section III I introduce public interest theories of regulation as applied to the six divergences considered in this work;

in Section IV I introduce private interest theories of regulation; in Section V. Institutional Theory and the Regulation of Pharmaceuticalsinstitutional theory; in Section VI. Cultural Theory and the Regulation of Pharmaceuticals Cultural Theory and in Section VII. Summary of ChaptersI provide a summary of the chapters.

II. Market Structure and Special Features of the Pharmaceutical Sector

Regulation of the pharmaceutical sector finds its roots in the inherent characteristic of the product in question.[16] That is, that pharmaceutical products pose significant but uncertain risks and benefits to human health.[17] Both economic instruments (price controls) and social instruments (market access regulation) stem from this fact, either directly or indirectly. This central 'risk-information' characteristic gives rise to special features of the sector which are not found elsewhere. Those special features further contribute to the justifications for regulation. The market structure of the pharmaceutical sector[18] is either monopolistic competition or oligopoly with product differentiation. There is no natural monopoly and thus, in particular, the prevalence of price regulation is surprising at first blush.[19] Alongside economic regulation in the form of price controls, social regulation is ubiquitous; market access is controlled through strict prior approval and the imposition of mandatory minimum and uniform standards.[20] Promotion in the form of direct to consumer advertising is also the subject of regulation.[21] It is the special features of the pharmaceuticals sector which account for price regulation.[22] The prevalence of third-party payment, and the fact of physician prescribing, are two of these features. Both features can be traced back to the central risk-information characteristic of pharmaceutical products. Those characteristics account directly for social regulation. Risk and information are therefore central to the problem of regulating pharmaceuticals.

The special features alluded to above include: 1) high research and development ('RD') costs; 2) widespread use of patents; 3) prevalence of third-party payment through public and private insurance; and, 4) the fact of physician prescribing.[23] These features all stem directly or indirectly from the central characteristic of risk and information, and all four are linked. The basic justification for market access regulation on the grounds of safety and efficacy is as follows. Due to uncertainty surrounding the risks and benefits of new pharmaceuticals,

16 See Danzon, Patricia and Keuffel, Eric (2014) in the concluding section.
17 Ibid.
18 In both the US and the EU.
19 Ibid.
20 See Ogus, Anthony, "Regulation: Legal Form and Economic Theory" (2004) Hart Publishing. Oxford and Portland, Oregon. at chapter 10 (4).
21 See Danzon, Patricia and Keuffel, Eric (2014) at page 462 onwards.
22 Ibid concluding section.
23 See Danzon, Patricia and Keuffel, Eric (2014) at page 408 onwards; "Technical background and objectives of regulation".

information deficiencies and/or information asymmetries exist for the potential consumer. Any assessment of the risks and benefits posed by new pharmaceuticals requires this information in order to proceed. That information is a public good, and the collection, assimilation and communication of it is most efficiently undertaken by a public agency with specialist expertise, such as the US Food and Drug Administration ('FDA') or the EU European Medicines Agency ('EMA'). Clearly, the asymmetric information aspect, and the status of pharmaceuticals as experience and/or credence rather than search goods, also justifies the fourth special feature listed above: physician prescribing.

The cost of the information gathered by the agency is passed on to supplier firms (who must provide evidence of safety and efficacy to receive a license). These costs represent the first of the special features, for most of the costs of research and development are in the conducting of clinical trials, and the high failure rate which subsists as a by-product of the high standards set by the EMA and the FDA for safety and efficacy. High RD costs lead inevitably to the second special feature of the sector: the widespread use of patents. In pharmaceuticals, the marginal cost of manufacturing & production is low, but RD costs are very high.[24] This necessitates the use of patents, without which incentives to innovate would be lacking. The third feature: third party payment, is also linked to risk, however the risk in question here is the mirror of the risk-information characteristic posed by pharmaceuticals – being the risk of illness and/or injury posed to all in society. Given the high costs associated with treatment, but relatively low probability of affliction, these risks are pooled and spread through either private or public insurance systems. Coupled with doctor prescribing, this feature leads to supplier moral hazard in the pharmaceutical sector.[25] This is because both third-party payment and doctor prescribing render consumption insensitive to price changes, with the concomitant possibility that suppliers will raise prices and inflation will result. In addition, the prevalence of patents leads to limited monopoly power in the sector - although the extent of this should not be overstated.[26] Taken together, those three features explain the existence of economic regulation in the form of price controls. These need not necessarily be attributed to distributive goals;[27] allocative and productive inefficiency may be the primary concern of the regulator.

24 Ibid page 431 onwards, "Patents".
25 Ibid in introduction and concluding section.
26 Ibid at page 441 onwards, "Regulation of Prices, Reimbursement, Profits and So Forth" 7.6.1 "The Rationale for Price and Profit Regulation".
27 Ibid.

III. Public Interest Theories of Regulation Applied to Pharmaceuticals

Public interest (or 'economic') theories of regulation[28] stipulate that regulators enact regulation to maximise overall social welfare by remedying underlying market failures.[29] It is possible, thus, to seek to 'justify' aspects or whole systems of regulation by reference to underlying market failures, using the insights of public interest theory. However, the 'optimal' (i.e. the position which best serves the 'public interest') regulatory position taken on any one aspect, or indeed the configuration of the whole regulatory system (encompassing several different aspects) may be different from place to place as cultural influences affect the preferences of the regulated group. Moreover, whilst the regulatory approach of the government, and the approach of agencies such as the FDA and the EMA to the relevant risk-benefit trade-off may paradigmatically be based upon science and thus said to 'improve' with advances in the technologies of data gathering and analysis: first, a reliance on science may not be a neutral or rational approach, but rather a culturally laden choice; and second, private interest mechanisms may still be a gateway through which cultural influences affect the approach of those within these agencies. That is to say, the collective preferences of subgroup interest groups within a jurisdiction may affect the objectives of that subgroup and the regulation which they obtain from the regulator. Jurisdiction-wide institutions and other institutions may also affect the choices available both to the primary regulator, and to the subgroups seeking regulation, such that regulatory outcomes differ. Those institutions, too, may reflect the cultural orientation of the jurisdiction.[30]

As stated above, the key market failure justifying *social* regulation of the pharmaceutical sector is the potential overconsumption of products which impose negative externalities

28 See Stigler, George J. (1971), 'The Theory of Economic Regulation', 2 Bell Journal of Economics and Management Science, 3-21. Stigler, George J. (1974), 'Free Riders and Collective Action: an Appendix to Theories of Economic Regulation', 5 Bell Journal of Economics, 359-365. Posner, Richard A. (1974), 'Theories of Economic Regulation', 5 Bell Journal of Economics and Management Science, 335-358. Ogus, Anthony I. (2004), Regulation: Legal Form and Economic Theory, Oxford, Hart Publishing. Ogus, Anthony I. (2004a), W(h)ither the economic theory of regulation? What economic theory of regulation, in: J. Jordana and D. Levi-Faur, The Politics of Regulation, Edward Elgar, Cheltenham, UK, 31-44.

29 See Den Hertog, Johan A. "Review of economic theories of regulation." *Discussion Paper Series/Tjalling C. Koopmans Research Institute* 10, no. 18 (2010). See also Akerlof, George A. (1970), 'The Markets for 'Lemons': Qualitative Uncertainty and the Market Mechanism', 84 Quarterly Journal of Economics, 488-500. Baumol, William J. (1952), Welfare Economics and the Theory of the State, Cambridge Massachusetts, Harvard University Press. Breyer, Stephen G. (1979), 'Analysing Regulatory Failure: Mismatches, Less Restrictive Alternatives, and Reform', 92 Harvard Law Review, 549-609. Coase, Ronald H. (1960), 'The Problem of Social Cost', 3 Journal of Law and Economics, 1- 44.Noll, Roger G. (ed.), Regulatory Policy and the Social Sciences, Berkeley, University of California Press, 200-231. Dewees, Donald N. (ed.) (1983), The Regulation of Quality: Products, Services, Workplaces and the Environment, London, Butterworths. Posner, Richard A. (2001), Natural Monopoly and its Regulation, Washington, Cato Institute

30 Finally, as noted by Danzon and Knueffel, because imperfect information is the central issue (rather than inherent market structure), the optimal regulatory structure may vary over time as technology advances and consumers' willingness to bear risks change with technological change, income changes and other factors: one of which, I say, is collective preferences, which may reflect underlying culture. See Danzon, Patricia and Keuffel, Eric (2014) concluding section.

upon society through ADRs,[31] and potential underconsumption of pharmaceutical products which would bring positive externalities to society by alleviating disease and suffering. This market failure arises from the risk-information characteristic of pharmaceutical products which is set out above. The risk-information characteristic leads to potential information asymmetries between a) pharmaceutical firm and consumer; and b) pharmaceutical firm and regulator/agency. In addition, it also leads to the possibility of latent defects in pharmaceutical products. In this case there is no information asymmetry but information about the product is unknown by everyone. This market failure, caused by this risk-information characteristic, is offered by public interest theories of regulation to justify:

1) Mandatory pre-market licensing of pharmaceutical products.

2) Labelling and advertising (including direct to consumer advertising) regulation of those products.

3) Pharmacovigilance: monitoring of those products after they enter the market.

4) Product liability in tort – this is not regulation *per se* but a private market practice which supplements regulation. This private practice is itself governed by public rules regarding evidence and damages (for example). Product liability is thus a 'regulated' private practice. I refer to product liability in this work as 'regulation' but this may be taken to mean a private practice which is itself regulated, and it is divergences in the regulation of the practice which I scrutinise here.

5) Selling regulation including sale classification in pharmacies, and the need for a doctor prescription.

These aspects of regulation are set out below in Figure 1.

31 Unsafe or improperly labelled or improperly classified for sale products.

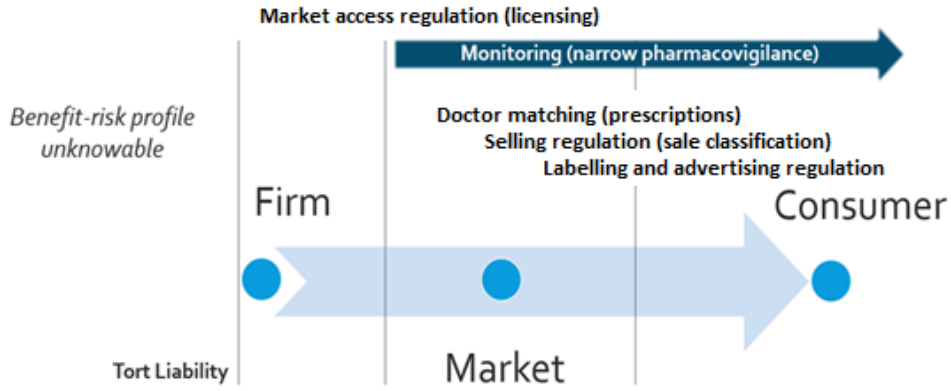

Figure 1 ***Social Regulation of Pharmaceutical Products***

The various instruments and techniques set out in Figure 1 ***Social Regulation of Pharmaceutical Products*** above take effect at different stages in the market process. Moving from left to right: tort liability rules take effect first, through deterrence, before the product ever enters the market. When the pharmaceutical firm develops the product, rules of tort liability incentivise the firm to develop only safe products. Not just products that are safe enough to be granted a market-access license, but which are safe to the extent that the firm will not face liability awards against it if a latent defect is present in the product and cannot be detected at the licensing stage. The licensing stage takes effect next, preventing the firm from placing the product on the market unless the firm can show that the product is safe and effective – i.e., free from patent defects at that stage. The licensing requirement also, of course, disincentivises the firm at the earlier stage from developing products which are unsafe due to patent defects.

Once the product is on the market, labelling and advertising regulation controls the information that a firm may or must provide to consumers and doctors about the product. The requirement for a prescription (in some cases) is in place to ensure that the expertise of a doctor is required before consumption can take place, matching the correct products to the correct consumers. Here, also, sale classification regulation, which applies to pharmacists and pharmacies, governs where and how a consumer may purchase the product including whether a prescription and/or the presence of a licensed pharmacist is required. Pharmacovigilance (in its narrow form – see below and Chapter Three) generally begins after the licensing process ends, and the monitoring of products takes place from the moment the product enters the market until the end of its life cycle. In this thesis I also consider the regulation of generic substitution, which is the situation where a pharmacist must or may substitute a generic (non-branded) version of a pharmaceutical product for an originator (branded) product which is more expensive. The public interest justification for generic substitution and its regulation comes from the special features of the pharmaceutical sector set out in the section above, and it is linked to the use of patents which in turn, themselves, have a public interest justification.

Many of the aspects of regulation considered here are carried out or overseen in the US and EU by regulatory agencies, in particular: licensing, (some) control over information and

advertising, pharmacovigilance, and sale classification regulation. In some countries pharmaceutical price regulation and regulation of pharmacists and generic substitution are also within the competences of an agency. The role of agencies thus requires a separate public interest justification. There is consensus across the EU, the US, and the rest of the world to some extent, that the role of an agency collecting, assimilating, and communicating the relevant risk information as a public good, is necessary. In Chapter One, I turn my attention specifically to agencies, characterising their approach to these tasks. Prior to this, below, Below, I sketch brief details of the public interest justifications in the case of each of the six divergences considered in this thesis.

1. Tort (Product) Liability

Tort (product) liability is an instrument of private law, and its rules seek to avoid overconsumption of unsafe pharmaceutical products by deterring firms from bringing unsafe (inherently unsafe by design, or unsafe due to a lack of adequate labelling) products on to the market. If the market, and this instrument ensured optimal deterrence, then there would, in theory be no need for a licensing regime. However, due to the possibility of latent defects - which cannot be deterred, or which are difficult to deter - tort liability may be insufficient to keep unsafe products off the market: a private law failure, justifying regulation. Tort liability therefore exists in addition to a licensing regime and it supplements (some would say too much)[32] the latter. The deterrent effect of tort liability is ensured by the possibility of compensatory awards to injured claimants. Compensation has an additional distributive justification. Deterrence will be ineffective in the case of pharmaceutical products with unknown and unknowable (truly latent) defects, and the extent to which compensatory awards may be justified on public interest grounds depends upon the availability of social insurance and private insurability against liability awards.[33]

A strict standard of liability may be justified, in the case of product liability, on public interest grounds.[34] In a world of perfect information, Coasean bargaining would result in producer and consumer agreeing a price which reflected the level of product safety (and thus an optimal level of consumption would result). Where information asymmetry exists between producer and consumer regarding that level of safety, and where private bargaining over price in every case is difficult, there is a public interest justification for strict liability. Where liability is strict there is no need for the Claimant to show negligence, and breach, and that breach caused injury – the Claimant need only show that the product was defective, and that the injury was more likely than not caused by the defect. Here, the producer is pushed to add the expected costs of accidents (and the producer's liability) to the price of the product. Moreover, because the producer operated in a presumably competitive marketplace, price competition

32 Viscusi, W. Kip, Wesley A. Magat, and Robert Scharff. "Asymmetric assessments in valuing pharmaceutical risks." Medical care 34, no. 12 (1996): DS34-DS47. Viscusi, W. Kip, and Richard J. Zeckhauser. "Regulating ambiguous risks: the less than rational regulation of pharmaceuticals." The Journal of Legal Studies 44, no. S2 (2015): S387-S422

33 Finally, whilst the administrative costs of product liability are likely to be low relative to market access licensing and pharmacovigilance, transaction costs are likely to be very high.

34 Landes, William M., and Richard A. Posner. "A positive economic analysis of products liability." *The Journal of Legal Studies* 14, no. 3 (1985): 535-567.

incentivises the producer to produce the safest version of the product: as the safest version will be the cheapest version. In these cases, because the price now reveals full information about the product, the overconsumption problem is solved through the price mechanism.

There may be separate but related public interest justifications: for defences to product liability claims, and for the availability of punitive damages in product liability claims, and for procedural aspects of such claims such as the availability of class-action lawsuits. The public interest justifications for product liability are tied up with and to some extent dependent upon the efficient functioning of the insurance system, both social insurance (including socialised healthcare) for the injured, and the availability and smooth functioning of the third-party liability insurance system for firms.[35]

Tort liability may, to some extent, be able to deal with the problem of latent defects - which are not known at the time the product enters the market but which render the product unsafe. Here, the issue is whether the defect in the product *could have* been known by the pharmaceutical firm – with further research - before placing the product on the market. Liability rules can thus incentivise firms to spend more time and resources upon research to discover latent defects. Tort liability will not assist, however, and likely has a distributive rather than economic public interest justification, in cases where the defect was truly latent – both unknown and unknowable. This is where pharmacovigilance becomes relevant.

2. Licensing

Some have argued that if tort liability exists in addition to market-access licensing, overdeterrence will take place which may lead to underconsumption of safe pharmaceutical products, thus exacerbating the central market failure.[36] Hence, some have argued in favour of federal pre-emption of tort liability claims such that if (in this case) the FDA have licensed a pharmaceutical product, the product is then insulated to some extent from private tort liability claims. This suggestion has not been implemented in the US and not completely in the EU.

The public interest justification for licensing comes from the market failure of over or under consumption of unsafe and safe products, respectively. That market failure is linked to the central risk-information characteristic of pharmaceutical products. In the view of Ogus, it is the negative externalities attendant to overconsumption of unsafe products which provide the primary justification for licensing (prior approval) in the case of pharmaceuticals. He points to the very high number of potential consumers, the magnitude of the potential consequences (risk of injury and death) and the length of time which it might take for adverse effects to manifest. These factors, he says,[37] justify ex-ante scrutiny in the form of prior approval of pharmaceuticals. Licensing seeks to remedy the underlying market failure of

35 See Priest, George L. "The current insurance crisis and modern tort law." *Yale Lj* 96 (1986): 1521.
36 Viscusi, W. Kip, Steven R. Rowland, Howard L. Dorfman, and Charles J. Walsh. "Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense." *Seton Hall L. Rev.* 24 (1993): 1437.
37 See Ogus (2004) at chapter 10 (4).

potential overconsumption of unsafe pharmaceutical products by ensuring – through a requirement of prior approval – that the product will not enter the market and be available to consumers for consumption unless it is first proven to be safe, and effective. Those questions are answered taking in to account the labelling of the product and its proposed sale classification.[38] In relation to this, the requirement for efficacy to be proven has a separate but related public interest justification, in that it effectively controls the information which firms may provide to consumers regarding the product. The product will only be licensed for the treatment of certain indications (diseases, ailments) which appear in the license and for which, in turn, the efficacy of the product has been proven to the agency. Firms are then only permitted to market the product for those indications and are not allowed to promote the product 'off-label' (for other indications). This prevents the overconsumption of ineffective products – which would be socially wasteful because the resources spent on developing, marketing, purchasing and consuming these products would better be spent on developing and consuming effective products which bring positive externalities to society.

In many ways, safety and efficacy are two sides of the same coin because, given that all pharmaceutical products will have both positive (treatment) effects and negative (harmful) effects on the body, the only question that needs to be asked is which is greater (even if only for some class of consumers)? If for some class of consumers, some positive effects are greater than negative effects then the product – according to public interest analysis – should be permitted on to the market subject to labelling and a prescription requirement which restricts consumption of that product to that class of consumers. Licensing then has the task of working out what are the health benefits and the health costs of the product. Then, ensuring that the product is only permitted on the market if for some consumers the health benefits outweigh the health costs, and – through the ancillary licensing functions of fixing the product label and sale classification – ensuring the product is only consumed by those consumers.

The requirement of proof of safety and efficacy for some class of consumers is to establish what is known about the product (i.e., to tackle in so far as possible the latent defect problem). Doing so goes some way towards ensuring that products which are net-harmful to all consumers are kept off the market. However, a licensing approach which is too strict presents the possibility that products which are net-beneficial to some consumers are denied to those consumers, and this too harms overall social welfare. The ancillary requirements of fixing the wording of the label and otherwise controlling information claims about the product (including through advertising) as well as the requirement of a prescription, and/or other sale classification regulation, each deal with the information that is known about the product and seek to reduce information asymmetries between consumers and producing firms. This, in turn, seeks to solve the overconsumption problem (albeit by exercising too tight control over information and advertising, an underconsumption problem may be presented).

38 Whether 'prescription-only', in which case doctor matching is available, or 'pharmacist supervision-only', or on 'general sale'.

3. Sale Classification

Sale classification: whether a product will be 1) an unlicensed ('U') product (i.e. it does not require a license and is not considered a pharmaceutical product; 2) licensed but available on general sale ('GSALE') without the need for a prescription or sale by a pharmacist in a pharmacy; 3) licensed and available only under the supervision of a pharmacist, but without the need for a prescription ('PSO'); and 4) available only at a pharmacy and on prescription only ('PO'); is generally decided at the licensing stage by agreement between the sponsoring firm and the agency. However, it takes effect once the product reaches the market by restricting the circumstances in which the product can be purchased for consumption.

For sale classification regulation too, the relevant market failure is overconsumption of unsafe products, and it results from the central risk-information characteristic of pharmaceutical products. Sale classification goes hand in hand with the control of information (labelling and advertising) and the need for doctor-matching (the prescriptions system). At the stage (the licensing stage) that sale classification is decided between the agency and firm, it is considered that enough information is known about the risk-benefit profile of the products to be confident that the product has a positive risk-benefit profile for at least some classes of consumers. Where this is the case, it would be theoretically possible to simply mandate that all this information (about risks and benefits) be placed on the product label and leave it to presumably rational consumers to decide whether or not to purchase and consume the product. In the case of pharmaceuticals however, even with full written information on the product characteristics - which cannot be the case anyway given that these are experience or credence goods, and latent defects may exist - making decisions will still be difficult for the consumer due to bounded rationality.[39] The technical complexity of the information and difficulty correlating this with individual preferences imposes high costs on the consumer.[40] In addition, the mainstream law and economics approach to risk perception notes from empirical research that individuals have a tendency to overestimate low probability risks and underestimate high probability risks.[41] Therefore, in recognition of this, the prescription system and thus the PO category use doctor oversight to ensure that only the 'safe' classes of consumer can consume the product, including use of the ability of the doctor to match the correct product to the correct consumers, and the ability of the doctor to explain the product risks and benefits to the consumer.[42]

What is left are products for which enough information about the risk-benefit profile is known to be confident that for not just some but for *most* classes of consumer the risk-benefit profile of the product is positive. The addition of pharmacist supervision and the PSO category minimises externalities caused by overconsumption in the case of these products. Labels provide information to consumers on safe consumption etc. whilst the oversight of a pharmacist can assist in explaining that information, or acting as a gatekeeper where the information may be too complex for boundedly rational consumers to understand. If a

39 See Ogus (2004) Chapter 9.
40 Ibid.
41 See Ogus (2004) Chapter 9. See also: Viscusi, W.K. (1984), "Regulating Consumer Product Safety" ch 1 in D.Dewees (ed.) "The Regulation of Quality" (1983).
42 Referred to in the Figure below as 'physician matching'

product is placed in the GSALE category, it is considered that labelling alone will be sufficient to ensure that overconsumption does not occur.

4. Pharmacovigilance

Above, I said that after the licensing stage sufficient information is known about the risk-benefit profile of the product to be 'confident' that it poses a positive risk-benefit profile for at least some class of consumers. The level of confidence can never be 100% because of the possibility of latent defects. Pharmacovigilance deals with latent defects. This is where the defect is not known and, it is assumed, cannot be known at the time the product is placed on the market: it is truly latent. Clearly, this follows from the risk-information characteristic, and it presents the possibility of the overconsumption of unsafe products. Latent defects lead to this market failure. Note, also, that fear of latent defects may lead to the underconsumption of safe products, due to over-caution on the part of agencies and doctors, or to the fears of consumers who refuse to use the products even when advised to. The existence of systems of licensing and pharmacovigilance - as well as tort liability to some extent - also potentially remedy this problem and correct this market failure by reassuring (through licensing certification for example) consumers and doctors that products are 'safe' at the time the license was granted. And – in the case of pharmacovigilance – are still 'safe' to the best of everyone's knowledge as signalled by their continued presence on the market. Advertising may also solve the underconsumption problem by providing information directly to consumers.

Pharmacovigilance thus aims to solve both overconsumption and underconsumption problems by keeping 'safe' - for some classes of consumer when properly labelled, classified, and used as directed - and *only* 'safe' products on the market. The key to this is information gathering (updating) through monitoring, as consumption of the product in the wider world adds data points to those already provided by clinical trials pre-licensing. The benefit-risk profile of a pharmaceutical product is never known in full due to the possibility of latent defects. Some risks of the product may only become known – thus changing the benefit risk profile of the product – once the product has been used for a long time by many people. This information problem makes it impossible to ensure that all products on the market are perfectly 'safe'.[43] The problem is partially mitigated through licensing,[44] however, no amount of (pre-licensing) clinical trials data can guarantee a positive benefit risk profile for every possible case of consumption of the product.[45] An agency must therefore make a choice based on the imperfect information which it has at the licensing stage.

Step in pharmacovigilance, which is the monitoring of products to 1) gather information about them and 2) manage risk accordingly. In this thesis (particularly Chapter Three) I distinguish

43 And it also makes perfect labelling impossible.

44 Because a license for market access would only be granted based on clinical trials data, collected pre-licensing, which showed the product to be safe and effective.

45 Or rather, the costs to the sponsoring firm of proving that data would be so high as to deter any pharmaceutical innovation. On top of this lies the problem that data collected in the setting of pre-market-access clinical trials is not a perfect (or even a very good) indicator of the effects of the product when used in clinical practice.

between 'narrow' and 'broad' pharmacovigilance. Narrow pharmacovigilance is a technical exercise focused on 1) above. Broad pharmacovigilance encompasses both parts of the definition. The information gathering element of broad pharmacovigilance is justified by the information problem described above. The aim of broad pharmacovigilance is to maximise the sum of the costs and benefits from pharmaceutical products. This includes minimising externalities whilst ensuring that safe products are made available on the market. This can only be ensured by the possibility of risk-management steps being taken in response to new information gathered through pharmacovigilance. These steps may include: withdrawing the product licence (and removal from the market); and/or communication of new risk information to doctors and consumers. In Chapter Two I refer to these as 'Post-market Safety Measures' ('PSMs'). As pharmacovigilance and licensing are closely related, discussion of these risk management steps takes place in both Chapter Two and Chapter Three.

In Chapter Three a discussion takes place regarding the optimal regulation of product safety risks through a combination of the techniques of product liability law and pharmacovigilance regulation. A model is developed based upon insights taken from public interest theory, and it is called the 'suggested public interest system.' This system would limit the availability of product liability claims only to cases where the defendant firm had intentionally concealed information from the regulatory agency. In this case punitive damages would be made available against the firm. Otherwise, the system would rely entirely upon broad pharmacovigilance to solve the underlying market failure. With pharmaceutical firms incentivised to provide all relevant data truthfully and promptly to the regulatory agency, then that agency – fully furnished with the data – is in a better position to manage the risks posed by pharmaceutical products than are the courts through liability rules.

5. Direct to Consumer Advertising of Prescription-Only Products

Once a pharmaceutical product reaches the market (has been granted a license) it will be assigned both a sale classification and mandatory labelling. In addition to information which appears on the label, agencies and regulators may exercise further control over claims that a firm may make (and information it may provide), and towards whom, in relation to that product. I said already that one dimension of this seeks to prevent wasteful social expenditure on ineffective products. Thus, no jurisdiction which has a licensing system and specific approved indications for a product is likely to allow the product to be marketed for (and claims of efficacy made) in relation to indications which were not approved in the license. As to efficacy claims and advertising in the case of approved indications, to permit these in the case of GSALE and PSO products is less controversial than in the case of PO products. For PO products advertising directly to doctors (detailing) is subject to fewer restrictions worldwide than 'direct-to-consumer-advertising of prescription-only products' ('DTCA'). Broadcast DTCA is only permitted, worldwide, in the US and in New Zealand. In the US it is widespread, and the US pharmaceutical industry ('USPI') spends many billions of dollars upon it every year.

The public interest justifications for regulating information (efficacy claims) has already been set out above, at least in the case where an indication is not approved. Public interest arguments militate both for and against permitting DTCA. These justifications relate both to the potential market failures of over and under consumption, and to the special characteristics of the pharmaceutical sector, the most relevant of which in this case are: 1) prevalence of third-party payment through public and private insurance; and 2) the fact of doctor prescribing.

Dealing first with over and under consumption, again this potential market failure arises from the risk-information characteristic described above. On overconsumption, there is the risk that a product with a latent defect is widely consumed because of DTCA, and this will increase the magnitude of the harm (negative externalities) caused by the latent defect. Secondly, there is a risk that the safety provided by doctor-matching is undermined because of DTCA. If a product has been placed in the PO category then the agency has determined that it is only safe to use under doctor supervision. Where DTCA is permitted, doctor supervision may be less effective due to the need for doctors (at least in some jurisdictions such as the US) to retain their patients by keeping them happy, thus acceding to demands to prescribe a particular product which has been the subject of DTCA.

Finally, this second problem can be exacerbated, from a public interest perspective, when the information provided in DTCA lacks balance – I.e., much information is provided about benefits, but little information is provided about the risks of the product. This can exacerbate pre-existing asymmetries of information as between the consumer and the producing firm, which doctor-matching (the PO category) was put in place to remedy. That problem is also made worse by the inability of consumers to understand some risk information and to correctly compute relative risks, due to human bounded rationality. Some would argue that the requirement of a prescription remedies the second two problems, because the doctor can exercise oversight. Again, however, this assumes that the doctor is not susceptible to various pressures including time pressures, consumer demands and the imperative to retain patients.

On the other hand, the underconsumption market failure can exist in relation to some pharmaceuticals products for diseases which are underdiagnosed. By allowing DTCA, so the public interest arguments go, more consumers are likely to visit doctors to seek a diagnosis in cases where before they may not have been aware that a treatment was available. This, so it is argued, can potentially solve the underconsumption problem.

A separate public interest justification may be offered for *banning* DTCA based upon 'price failure.' Price failure becomes relevant to the public interest justifications both for banning DTCA and for permitting (or mandating) generic substitution. Price failure results from some of the special features of the pharmaceutical sector: 1) prevalence of third-party payment through public and private insurance; and 2) the fact of physician prescribing. This makes demand inelastic to price - that is the price failure. What are seen by some as excessively high pharmaceutical product prices can result from this, and this can be exacerbated by permitting DTCA. A firm can heavily advertise a product direct to consumers knowing that consumers will not be put off by high prices.

Moreover, the firm can justify its high prices by reference to its development costs which may include the cost of marketing including the (very high) costs of running DTCA. In public interest terms, even in a system of private insurance, there will be socially wasteful expenditure by

firms on developing products with little therapeutic advantage - known as 'me-too' products - and receiving patents for them. These resources arguably would have been better invested in developing products with significant therapeutic advantages over existing products, but instead the resources are spent on DTCA. In a private insurance system, spiralling pharmaceutical prices can lead to unaffordable insurance premiums. In a public or social insurance system, it will lead to budget pressures and high taxes.

6. Generic Substitution

The price failure also justifies, in public interest terms, permitting or mandating generic substitution through regulation. Here, all the special features of the pharmaceutical sector described above become relevant. Again, these are: 1) high RD costs; 2) widespread use of patents; 3) prevalence of third-party payment through public and private insurance; and 4) the fact of physician prescribing. Together, 3) and 4) lead to the price failure described above. In addition, 1) justifies 2), above and the existence of patents leads to the problem of brand loyalty, which can make the effects of price failure more damaging – i.e., it can increase the level of social resources which are spent wastefully on pharmaceutical products. In this case the additional resources are spent on the 'branding' element of originator products which have no therapeutic benefit to consumers and which, due to 'brand loyalty,' are over-consumed relative to generic products which are under-consumed.

Arguably, therefore, the public interest justification for the regulation of generic substitution is also founded upon the risk-information characteristic of pharmaceutical products described above. The risk-information characteristic leads to the necessity for licensing and pre-market access clinical trials which is very costly for firms. The justification for patents is found in that cost, i.e., that without intellectual property protections guaranteeing market exclusivity for some period, there would be little or no incentive for pharmaceutical firms to innovate and develop new products which could pose very large benefits for society. However, with patents and market exclusivity comes brand loyalty.

On the other hand, the risk-information characteristic of pharmaceutical products separately justifies the use of doctor matching (prescribing). When doctor prescribing is combined with third-party payment the price failure takes effect, and pharmaceutical product price inflation occurs. That price inflation is exacerbated by the problem of brand loyalty because brand loyalty means that consumers (and doctors) reject cheaper generic products in favour of more expensive branded originator products even once these have come off-patent. In addition, brand loyalty can act as a *de facto* barrier to generic entry into the pharmaceutical market further lending originator firms (monopoly) power over the prices they charge for originator products. In turn, price inflation in pharmaceutical products leads to a need for third-party payment through private or social insurance, as the cost of treating illness becomes so high that society needs to spread the risk through broad social insurance pools or narrower private insurance pools.

Systems of Regulation

The above represent only six aspects of regulation of the pharmaceutical sector. There are more, and this thesis cannot cover all of them, although many more are touched upon in passing when discussing the six above. Together, all aspects of pharmaceutical regulation within one legal jurisdiction will form a 'system' of regulation of pharmaceutical products. Within that system, any given jurisdiction may (for example) make greater use of product liability to tackle the overconsumption market failure, and relatively less use of licensing to do so. Another jurisdiction may make relatively more use of pharmacovigilance, and relatively less use of licensing and product liability. Yet another system may impose direct price regulation, instead of generic substitution, to tackle the price failure, and a fourth may do the opposite.

Public interest theory says that the choice of system should be driven in part by a consideration of public administration costs. I.e., all aspects of pharmaceutical regulation should be combined in quantities which results in the best outcome (for overall social welfare) at the lowest possible administration costs. If this were the whole story, then every jurisdiction on earth would have the same system with an identical mix of these instruments, in identical weights. Moreover, this would be the lowest cost potential system to administer. That is not the case. I show in Chapter Three that when choosing between product liability, licensing, and pharmacovigilance, that both the US and the EU systems adopt an approach which is costly (for a likely worse social welfare outcome) than public interest theory would clearly justify. The observed variety of approaches over the six aspects of regulation, considered in this work, implemented variously in the US, the EU and between the EUMS, indicates that the regulation of pharmaceuticals does not accord with public interest theory.

There must be additional factors engaged which affect regulatory outcomes and cause these to depart from what the public interest would suggest. Therefore I then apply private interest theory to examine the question further. It is also the case that the choice of regulatory system in any jurisdiction is affected by the preferences of the group which is the jurisdiction. Jurisdiction-wide institutions, which reflect those preferences, may constrain, or widen the choices available to regulators when deciding upon how the whole system of regulation is configured. It is by turning, eventually (in Chapters Five and Six) to the question of collective preferences, and how these are shaped by culture, that I seek to add further explanation for transatlantic divergences in the regulation of pharmaceuticals. Before I turn to institutions, I first explain what I mean by private interest approaches to regulation.

IV. Private Interest Theories of Regulation Applied to Pharmaceuticals

Private interest (sometimes referred to as 'political economy') approaches to regulation do not completely deny the veracity of public interest theories. They are better characterised as a refinement of public interest theory which recognises that the maximisation of social welfare is only likely to be achieved where political systems are structured so that regulators are perfectly incentivised to regulate in the public interest.[46] As such, private interest approaches treat those who make, or who impact upon the creation of, regulation, as rational actors maximising their return on some good valuable to them. This rational actor approach can be applied to interest groups, perhaps acting through a lobbying organisation. It can also be applied to organisations[47] staffed by bureaucrats who maximise some good for the organisation, or to individual bureaucrats within the organisation.

The core insights of private interest approaches are that interest groups will lobby regulators seeking regulation[48] which benefits the group (rent seeking) according to its preferences;[49] and, that politicians and bureaucrats provide that regulation – in the market – where to do so maximises their own return according to their own preferences.[50] One such interest group is consumers (i.e., the general public),[51] which may thus result in a market which supplies regulation in the public interest.[52] However, due in part to cognitive biases and the bounded

46 See Levine, Michael E. and Forrence, Jennifer L. (1990), 'Regulatory Capture, Public Interest, and the Public Agenda: Toward a Synthesis', 6(S) Journal of Law, Economics, and Organization, 167-198. Joskow, Paul L. and Noll, Roger C. (1981), 'Regulation in Theory and Practice: An Overview', in Fromm, Gary (ed.), Studies in Public Regulation, Cambridge, MA, The MIT Press, 1-66. Joskow, Paul L. and Richard Schmalensee (1986), Incentive Regulation for Electric Utilities, Yale Journal on Regulation, vol. 4: 1.

47 See Simon, Herbert A. (1948), Administrative Behavior: a Study of Decision-Making Processes in Administrative Organization, New York, Macmillan. See also Olson, Mancur (1965), The Logic of Collective Action. Public Goods and the Theory of Groups, Cambridge, MA, Harvard University Press

48 See Becker, Gary S. (1983), 'A Theory of Competition among Pressure Groups for Political Influence', XCVIII Quarterly Journal of Economics, 371-400. Becker, Gary S. (1985a), 'Public Policies, Pressure Groups, and Dead Weight Costs', 28 Journal of Public Economics, 329-347. Becker, Gary S. (1985b), 'Pressure Groups and Political Behavior', in Coe, Richard D. Owen, Bruce M. and Braeutigam, Ronald R. (1978), The Regulation Game: Strategic Use of the Administrative Process, Cambridge, MA, Ballinger, 271

49 See Tullock, Gordon (1967), 'The Welfare Costs of Tariffs, Monopolies and Theft', 5 Western Economic Journal, 224-232. Buchanan, James M. and Tullock, Gordon (1975), 'Polluters' Profits and Political Response: Direct Controls Versus Taxes', 65 American Economic Review, 139-147. Buchanan, James M., Tollison, Robert D. and Tullock, Gordon (1980), Toward a Theory of the Rent-Seeking Society, College Station, Texas A&M; University Press. Tullock, Gordon (1993), Rent Seeking, Aldershot, Edward Elgar.

50 See Weingast, Barry (1981), 'Regulation, Reregulation, and Deregulation: The Political Foundations of Agency Clientele Relationships', 44 Law and Contemporary Problems, 147- 177. Krueger, Anne O. (1974), 'The Political Economy of the Rent-seeking Society', 64 American Economic Review, 291-303. Noll, Roger G. (1983), 'The Political Foundations of Regulatory Policy', 139 Journal of Institutional and Theoretical Economics, 377-404. Noll, Roger G. (1989a), 'Economic Perspectives on the Politics of Regulation', in Schmalensee, Richard and Willig, Robert D. (eds.), Handbook of Industrial Organization II, Amsterdam, North Holland, 1253-1287.

51 See Waterson, Michael (2003), The Role of Consumers in Competition and Competition Policy, International Journal of Industrial Organization, 129-150.

52 Note that this is a modified version of public interest theory,which treats consumers as an interest group, recognising their bounded rationality may mean that they do not seek regulatory outcomes which public interest

rationality of consumers, the regulation which they demand - even before the supply side is considered - may not necessarily maximise social welfare. In addition, consumers must compete with other interest groups – such as industries, or professions – which may be better organised or better resourced, and which seek to maximise their own benefits.

Turning to private interest analyses of the use of prior approval and mandatory standards; *public interest* principles dictate that rational policy makers would approach the task of formulating mandatory standards in a certain way. They would consider the various options and weigh the costs and benefits of each[53]. However in reality, and not just in the case of pharmaceuticals, standards are set which are significantly more, or less,[54] stringent that public interest goals allow.[55]

Various private interest explanations are presented for this phenomenon, as well as other reasons. Disasters and tragedies such as thalidomide, which are widely reported by the media, may prompt electoral influences on politicians and so-called 'pendulum effects' whereby public policymakers overreact to a situation by imposing more stringent regulation than necessary.[56] This may be in the form of a requirement for prior approval which is not justified on public interest grounds and/or by the imposition of standards which are stricter than necessary. In these cases, the electorate may exert pressure on politicians to act quickly and, because politicians stand to gain in the short term from being seen to act strongly, but bear few of the costs in the long run - as these are widely spread amongst consumers and firms - an overreaction is likely to result[57]. This may be an exception to the quotidian situation in the regulation of industries such as pharmaceuticals, whereby opposition to regulation (coming from firms) is generally well organised due to the costs of regulation being concentrated on those opposing firms, whilst weaker from the side proposing regulation given that the benefits are diffuse.[58] Pressure groups do however, also exist on the proposition side, including consumer lobbies. Such pressure groups may be capable of influencing voter behaviour and thus capable of pressuring politicians into placating them.

As politics will usually involve navigating a compromise between different interest groups, the political outcomes of this ongoing drama may vary from time to time in their overall direction; thus, the exogenous shock of a media crisis will provide a good explanation for particular upswings in precautionary approaches to the regulation of pharmaceuticals.[59] On

theory would consider to be in the 'public interest'. Once cultural theory has been introduced, and collective (shared) preferences become key, the treatment of consumers themselves as an interest group becomes the logical approach.

53 Ogus (2004) Chapter 8 Standards.

54 Private interest lobbying can result in both lenient or strict standards, depending upon the compliance costs of incumbent industry actors. Where incumbent actors have the requisite technology to comply with stringent standards and thus a cost advantage over potential market entrants, they are likely to lobby for those standards in order to bring about a barrier to market entry. On the other hand, where the standards are entirely new and require costly compliance measures by the incumbent firms, those firms are likely to lobby for lenient standards.

55 Ibid.

56 Ibid.

57 Ibid.

58 Ibid.

59 See, generally, Vogel (2012) Chapter 2.

the opposite side, firms too may exert pressure on politicians in line with the private interest lobbying and rent seeking analysis. Large firms stand to gain a competitive advantage over smaller firms from the imposition of stricter minimum standards. That is because of high RD costs - the risk of refusal of grant, has a proportionately greater effect upon smaller firms who are less well placed to spread that risk across multiple research and development projects.[60] Moreover, capture theory suggests that firms may seek to capture agencies such as the FDA and EMA, a problem which is particularly prescient in the case of pharmaceuticals due to the volume of information coming from the applicant firm, upon which the agency will rely.[61] Within the agency, private interest theory warns of the propensity of bureaucrats to make decisions which will increase the budget of the agency or the prestige of the individual bureaucrat.[62] These phenomena provide an additional explanation for the activities of those agencies, which must also be considered when seeking to explain divergences in regulatory approach between the US and the EU. I consider this question in detail in Chapters One and Two.

In this thesis I consider several interest groups in detail. These include the professions of doctors, lawyers, and pharmacists. It also includes the interest group of consumers and of the pharmaceutical industry. In each case I am looking at two groups, one in the US and the other, corresponding group, in the EU. Each time, I am comparing them, their behaviour, their objectives, their impact upon the creation of regulation in each of the jurisdictions. Ultimately I also compare them in their cultural orientations. In addition to these groups, I consider key organisations: the regulatory agencies of the FDA, the EMA and the national regulatory agencies in the EUMS ('NAs'). These organisations are relevant to all the six divergences considered in this work, so I devote much of Chapter One to analysing them. In Chapter Six I analyse the cultural orientation of all these groups using cultural theory.

V. Institutional Theory and the Regulation of Pharmaceuticals

North[63] defines institutions as, *"the humanly devised constraints that structure human interactions"* and he says they include both, *"formal constraints (rules, laws, constitutions), (and) informal constraints (norms of behaviour, convention, and self-imposed codes of conduct)"* and their enforcement characteristics.[64] In Chapter Five I develop this definition further, adopting the broadest possible definition of 'institutions' for the purposes of this work: which includes not only formal legal rules but also informal social customs and practices. In Table 1 below I provide some examples.

60 See Ogus (2004) Chapter 10 (4).
61 Ibid.
62 Ibid.
63 See North, Douglass C. "A transaction cost theory of politics." Journal of theoretical politics 2, no. 4 (1990): 355-367. And Milgrom, Paul R., Douglass C. North, and Barry R. Weingast. "The role of institutions in the revival of trade: The law merchant, private judges, and the champagne fairs." Economics & Politics 2, no. 1 (1990): 1-23.
64 North's definition is set out in Alesina and Giuliano (2015).

Table 1 Examples of Formal and Informal Institutions

Type of Institution	Example
Formal Legal Institutions	Constitutional free speech protections Strict liability for defective products Specific regulations (e.g. banning DTCA)
Informal Social Custom/Practice	Hierarchical doctor-consumer relationship Practice of giving public apologies Shared heuristic of perception e.g. 'natural-is-better'

Institutions come into this work from two distinct angles. In Chapters Two through Four I consider the effects of jurisdiction-wide institutions which constrain or widen the choices available to regulators and interest groups demanding and supplying regulation in the pharmaceutical sector. Here, I refer to several specific pairs of jurisdiction-wide institutions which I later analyse culturally in Chapter Six. Those pairs of institutions are shown in Table 2 below.

Table 2 Jurisdiction-Wide Institutions Considered in Chapters Two-Four and Analysed in Chapter Six

JURISDICTION-WIDE INSTITUTIONS	
US Free Speech Protections	EU Free Speech Protections
Private Healthcare	Socialised Healthcare
US Common Law	EU Legal System
No Price Regulation	Price Regulation
Norm of Litigiousness	Norm against Litigiousness
US Product Perceptions	EU Product Perceptions

In Chapter Five, where I introduce cultural theory, institutions and institutional theory take on a much broader significance in the research project. There, I adopt an 'institutional approach' to culture. I argue that culture resides within groups, and that groups are defined by the institutions through which group members interact with each other. Thus, when I turn to analyse the cultural orientation of the relevant groups in Chapter Six, I do so by deducing, from the behaviour of those groups, the institutions which govern those groups. I then deduce the cultural orientation of the group itself by cross referencing those institutions with the set of predicates for cultural orientations which I develop in Chapter Five.

VI. Cultural Theory and the Regulation of Pharmaceuticals

I do not introduce cultural theory until Chapter Five. My research question asks whether cultural theory can add some further explanation for regulatory divergence to that already provided by the extant theories: public interest, private interest, and institutional analysis. The introduction of cultural theory represents a supplement to methodological individualism, which is the approach of public interest and private interest (political economy) both rooted in the rational choice model. I define culture here as the values and norms shared within groups. As such, I say group culture shapes the preferences of individuals. This necessitates a modification to public interest theory from that point forward, as I must then consider the preferences of the public (consumers) for the benefit of whom regulation is enacted, according to private interest theory. A narrow focus on market failures therefore becomes less significant, and the specific demands of consumers for particular forms of regulation, become more important.

I have touched, above, upon the 'institutional approach' to culture which I adopt in Chapter Five. In addition to the institutional approach, I select, in Chapter Five, a typology of cultural 'types' which is parsimonious enough to enable me to draw comparisons between the cultural orientation of the jurisdictions, groups, organisations and jurisdiction-wide institutions which I analyse in Chapter Six. That typology is taken from the Cultural Theory of Risk and the Grid-Group typology of culture, which asserts that there exist four cultural orientations which can be applied to analyse almost anything in the social world. Those are: hierarchism, individualism, egalitarianism, and fatalism (plus a fifth type: autonomy, which is not useful for this work). In Chapter Five I operationalise this typology by developing a set of pairs of predicates for the cultural orientations of hierarchism and individualism. This assists me, in Chapter Six, to analyse the cultural orientation of the jurisdictions, groups, organisations and institutions which were found, in Chapters Two through Four, to be proximate to the shaping of the six regulatory divergences considered in this work.

VII. Summary of Chapters

In Chapter One I set out the historical background and an overview of the pharmaceutical regulatory systems in the US and in Europe. Then, I use this factual and historical information - combined with analysis found in the literature on the regulatory agencies - to analyse the FDA, the EMA, and the national agencies at the EU Member State Level. This analysis allows me to present some key characteristics of these agencies, which are then employed in Chapters Two to Four when undertaking the private interest analysis of the regulatory divergences.

In Chapter Two I consider licensing and DTCA. Here, application of public interest theory indicates that the US and the EU both have 'systems' (encompassing both areas of regulation) which may be justified in public interest terms, but that these systems are configured differently. The US exercises caution in licensing whilst the EU exercises it in DTCA. I apply private interest theories of regulation to seek explanation for the different configurations, considering the role of organisations and groups including the FDA, the EMA, the NAs and doctors and consumers in the US and the EU. My conclusion is that private interest theories aptly explain their respective approaches to licensing, however the model produces a

contradictory result when DTCA is considered. This puzzle is solved when jurisdiction-wide institutions are considered in addition to groups and organisations. The transatlantic divergence is therefore shown to be a product of differences between the characteristics of groups and organisations, and the form of key institutions.

In Chapter Three I turn to pharmacovigilance and product liability. Transatlantic divergences exist in the case of both, and these cannot be fully justified by the public interest theory of regulation. Private interest and institutional analysis suggest that differences in the behaviour of the regulatory agencies, the objectives of the pharmaceutical industries, and the influence of lawyers on lawmaking, help to explain the divergences further. Various key institutions are also observed to have an effect.

In Chapter Four I consider sale classification and generic substitution. Here, divergences exist both between the US and the EU, and between the north and south of the EU. These differences in regulation both impact upon, and are reflective of, the role of pharmacists in each jurisdiction. Where public interest theory fails to do so, private interest analysis of pharmacists and other relevant interest groups, organisations and institutions, assists further in explaining the regulatory divergences, albeit not fully.

In Chapter Five I draw upon various cultural theories to develop a framework which I will use to analyse the groups, organisations, and institutions in Chapter Six. I begin by adopting an institutional approach to culture, and then I seek dimensions or typologies of culture which can provide some content to that approach. I discuss Hofstede's Dimensions of National Culture ('DNC') and CT-GG for this purpose. Having decided that the latter fits best with the institutional approach to culture, I then operationalise this theoretical framework, developing predicates for the cultural orientations which can then be employed in Chapter Six.

In Chapter Six I take the theory of culture adopted in Chapter Five and apply this to analyse the jurisdictions, and the proximate groups, organisations, and institutions in the case of each pair of divergences. I seek to identify whether there is a consistent underlying within-jurisdiction cultural orientation between the jurisdictions, groups, organisations, and institutions; and, consistent between-jurisdiction cultural difference between these. I find this is the case across all divergences and therefore that the addition of culture has been able to provide further explanation to the extant theories in the case of these six divergences. In addition to consistently explaining the transatlantic divergences in each case, the addition of cultural theory was able to consistently explain the 'system divergence' in the case of pharmacovigilance and product liability, and the 'intra-EU' divergence in the case of sale classification and generic substitution.

Chapter Seven builds upon the cultural analysis undertaken in Chapter Six. Now, the regulatory positions themselves are analysed culturally. It is shown that the regulatory positions do not consistently reflect the cultural orientation of the jurisdictions. Therefore, it is only first through application of public interest theory, private interest theory and institutional analysis, that culture is shown to shape regulatory divergence. Thus, it was only through cultural analysis of the groups (including consumers), organisations and institutions in Chapter Six, that the application of cultural theory was able to provide further - but not alternative - and consistent explanation in these six cases. In this way, the methodology adopted in this work, and the approach to culture used here, is vindicated, as an approach to positively analyse the relationship between culture and regulatory divergence. The results of

this positive analysis are summarised, and some implications are set out in relation to the question of international regulatory harmonisation. Neither (hierarchical) efforts towards harmonisation nor (individualistic) calls for regulatory diversity are advocated. Like the interdependent cultural orientations of individualism and hierarchism, regulatory convergence and regulatory divergence rely upon each other for their viability as policy agendas

Chapter One: Overview, History, and Analysis of Agencies

"They had always been accustomed to eat a great deal of smoked sausage, and how could they know that what they bought in America was not the same—that its color was made by chemicals, and its smoky flavor by more chemicals, and that it was full of "potato flour" besides? Potato flour is the waste of potato after the starch and alcohol have been extracted; it has no more food value than so much wood, and as its use as a food adulterant is a penal offense in Europe, thousands of tons of it are shipped to America every year"[1]

Upton Sinclair *The Jungle* (1906)

1.1 Introduction

As far back as 1906, it seems, European regulation of food safety was considered superior to that in America – at least to Upton Sinclair and his 'progressive' readers.

Developments from 1906 onwards, - partly the result of Sinclair's novel - turned the tables, in food and - even more remarkably - in pharmaceuticals regulation. The US Food and Drug Administration (FDA) assumed a central role in this. By the 1960s it was Europeans who looked to the other side of the Atlantic for guidance on this front, after the tragedy of Thalidomide. Only then did European nations adopt mandatory licensing procedures and (even later) establish regulatory agencies for pharmaceutical products. In Chapters Two through Four I discuss six transatlantic regulatory divergences. It is necessary at the outset to provide historical context and some overview of the US and EU regulatory systems. Moreover, the relevant agencies: the FDA, the European National Agencies (NAs) and the EU European Medicines Agency (EMA), are all relevant to most of the divergences considered in Chapters Two through Four. So, in this Chapter I make use of the factual and historical information, to develop an analysis and 'characterisation' of these agencies which is then adopted for the whole of the remainder of this thesis.

1 Sinclair, Upton. *The Jungle:(1906)*. CreateSpace Independent Publishing Platform, 2014. Chapter 11, Page 6

1.2 Overview, History and Analysis of Pharmaceutical Regulation in the US

Whilst the FDA itself receives detailed analysis in Section 1.4 Key Characteristics of the Food and Drug Administrationbelow, the history of the US pharmaceuticals regulatory system is inseparable from the history of this agency. The FDA is responsible for all pharmaceutical product licensing[1] – *"ensuring the safety, efficacy and security of human and veterinary drugs, biological products, and medical devices; and.. ensuring the safety of (the US) food supply, cosmetics and products that emit radiation."*[2] It is a Federal agency but not a fully independent one, being under the US Government department of Health and Human Services. It does not specifically regulate the advertising of pharmaceutical products, which is the task of another agency, the Federal Trade Commission.[3] However, the FDA does so indirectly through limiting (in the grant of a license) the acceptable uses (indications) for which a product may be legally marketed, and by mandating the information on the product label. Moreover, throughout the 20th Century the FDA exercised some oversight of the advertising of pharmaceutical products for example through regulations[4] in 1969, a voluntary moratorium on broadcast Direct to Consumer Advertising of prescription-only pharmaceutical products (DTCA) between 1983 and 1985, guidance in 1997, and further regulations in 1999 and in 2004.[5] However, decisions of the US Court of Appeals in 1999[6] and then the Supreme Court of the United States ('SCOTUS') in 2002[7] held that the FDA did not have strong authority to regulate the advertisement of pharmaceutical products.

The FDA is older than any pharmaceuticals regulatory agency found in the EU or the EU Member States (EUMS). Most give the date of the 'creation' of the FDA as 1906 at the time of the Federal Food and Drugs Act ('FFDA 1906'). However, according to Hutt et al[8] the FDA

1 Its remit is wider than many EUMS agencies which regulate licensing, and wider than that of the EMA, not only because the FDA is the only agency at State or Federal level doing this but also because it covers a wider range of products, also regulating cosmetics and food for example.

2 https://www.fda.gov/about-fda/what-we-do... *"The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation. FDA also has responsibility for regulating the manufacturing, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors. FDA is responsible for advancing the public health by helping to speed innovations that make medical products more effective, safer, and more affordable and by helping the public get the accurate, science-based information they need to use medical products and foods to maintain and improve their health. FDA also plays a significant role in the Nation's counterterrorism capability. FDA fulfills this responsibility by ensuring the security of the food supply and by fostering development of medical products to respond to deliberate and naturally emerging public health threats."*

3 https://www.fda.gov/about-fda/fda-basics/what-does-fda-regulate *"The Federal Trade Commission is a federal agency that regulates many types of advertising. The FTC protects consumers by stopping unfair, deceptive or fraudulent practices in the marketplace."*

4 Code of Federal Regulations, Title 21, Volume 4, Subchapter C, Part 202.

5 See Greene JA, Herzberg D. Hidden in plain sight: Marketing prescription drugs to consumers in the twentieth century. *Am J Public Health.* 2010;100(5):793–803 and Ventola C. L. (2011). Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic?. *P & T : a peer-reviewed journal for formulary management*, *36*(10), 669–684.

6 Pearson v Shalala [164 F.3d 650 (D.C. Cir.1999)]

7 Thompson v Western States Medical Center [535 US 357 (2002)]

8 Hutt, Peter Barton, Arthur Daemmrich, and Joanna Radin. "Turning points in FDA history." *Perspectives on Risk and Regulation: The FDA at* 100 (2007): 14-28 at pg. 15

can trace its origins back to Article One of the US Constitution (1787) which states that *"…Congress shall have power… To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries."* In 1850 an Agriculture Division (by 1862 a full government department, the Department of Agriculture') - endowed with a chemical laboratory and employed chemists - was established within the patent office, as Congress sought to invest in science in support of the US agricultural industry. In 1862 The chemical laboratory was renamed the Chemical Division. In 1902 it became the Bureau of Chemistry. In 1927 the Food, Drug, and Insecticide Administration and in 1930 the Food and Drug Administration.[9] Barton, Daemmrich and Radin[10] highlight ten turning points in the history of the FDA. I use some of these as markers in the history of the US pharmaceuticals regulatory system, and I characterise that progression in five stages. First, the FDA and its predecessors supported industry (pre 1900s). Then, it regulated on a consumer protection basis but with measures *for the benefit o*f industry (up to 1938). Next it openly tackled industry (1938-1962). After that it assumed its role as a champion of consumer protection (1962-1985). Most recently, it underwent neoliberal reform which rebalanced its responsiveness to consumers and industry respectively (1985 onwards).

1.2.1 Up to 1938: FDA Assisting Industry then also Protecting Consumers

The Progressive Era, the Jungle, and the FFDA 1906

In the first stage, up until 1901 (what would later become) the FDA was supporting the agricultural industry by facilitating scientific innovation. Between 1901 and 1943 Congress intervened in the food, cosmetics, and pharmaceutical market on a consumer protection basis but with certain measures – short of licensing requirements – which benefitted incumbent industry actors. They did this by setting standards which represented a barrier to entry from low-cost competitors. The most important of these came as the result of grassroots consumer activism[11] in response to a scandal revealed by investigative journalism.[12] Upton Sinclair's 1906 novel *'The Jungle'* sought to highlight the working conditions in Chicago's meatpacking yards. *The Jungle* shocked readers in two distinct ways. First it exposed the plight of unpaid and overworked workers. Second, it revealed the adulterations and impurities which might be present in consumer food products. It was the latter which prompted the strongest response from US consumers and thus a legislative response from Congress. In Sinclair's words, *"I aimed at the public's hearts and by accident I hit it in the stomach."*[13]

9 Hutt, Barton, Daemmrich, and Radin (2007) at pg. 15
10 Ibid.
11 *"A grassroots movement is one that uses the people in a given district, region, or community as the basis for a political or economic movement." Webster's Third New International Dictionary of the English Language, Unabridged*. Cambridge, Massachusetts: Riverside Press
12 Kantor, Arlene F. "Upton Sinclair and the Pure Food and Drugs Act of 1906." I aimed at the public's heart and by accident I hit it in the stomach"." *American Journal of Public Health* 66, no. 12 (1976): 1202-1205.
13 Kantor (1976) at pg. 1202

At the time of publication of *the Jungle*, the US was in the middle of the 'progressive' era. This was before the modern consumer movement, and was one of its forerunners, it embraced both a social conscience and a concern about the safety and quality of consumer goods. According to Buenker, Boosham, and Crunden[14] the progressive era *"was a period of widespread social activism and political reform across the United States of America that spanned the 1890s to the 1920s. Progressive reformers were typically middle-class society women or Christian ministers."* These were closely related to the movements seeking prohibition in the US up to the 1920s. Even before the publication of *the Jungle*, Kantor[15] notes that *"…conditions were right for a campaign in support of food and drug standards after 1902. Progressive fervor was being generated"* due to earlier investigations into food adulteration. However, manufacturers pressed Congress to oppose the measures. The tide turned in 1905 as Congress was replaced by members *"elected in (Theodore) Roosevelt's landslide in November 1904"* and Roosevelt announced plans to introduce standards legislation for the food and drug industries in his State of the Union address in December 1905. Sinclair's novel came the following year. It was one of the bestsellers of 1906 and was translated (according to Sinclair) into more than 20 languages. Senator Beveridge read *the Jungle* and drafted a legislative proposal which would later become the FFDA 1906. It was passed by the Senate in May 1906, *"as a direct result of disclosures made in Sinclair's novel"*.[16]

The FFDA's[17] main purpose was to ban interstate transportation of 'adulterated' or 'mislabelled' food and pharmaceutical products. It set specific standards in respect of identifying the latter: active ingredients now had to be stated on product labels, and minimum standards of purity were required as stated in the 'US Pharmacopeia'. The FFDA contained provisions directing the FDA (then the 'Bureau of Chemistry') to police the standards in the Act through product inspections and by referring suspected offenders to prosecutors. Whilst the FFDA was a response to consumer outrage, arguably these standards benefitted incumbent industry actors as much as they protected consumers. The purity and labelling requirements of the FFDA kept out of the food and pharmaceuticals market those producers who would cut corners and undercut incumbents on price – quality being subject to asymmetric information as between producers and consumers. According to Swann, *"the law was principally a "truth in labeling" law designed to raise standards in the food and drug industries and protect the reputations and pocketbooks of honest businessmen."*[18]

At this stage, there was no premarket licensing requirement for food or pharmaceutical products (except biologics since 1901) requiring proof of safety or efficacy. In addition, the FDA was still unknown to most of the US public. Despite this, the FFDA 1906 and the scandal it was founded upon represented a turn away from the FDA and its predecessors just supporting industry, to one in which it both supported industry and protected consumers. The latter function was to become a more significant part of its mission and its reputation

14 John D. Buenker, John C. Boosham, and Robert M. Crunden, *Progressivism* (1986) pp 3–21

15 Kantor (1976) at pg. 1202

16 Ibid.

17 Public Law 59-384 *"an Act for preventing the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors, and for regulating traffic therein, and for other purposes"*

18 Swann, Ph.D., John P. "The 1906 Food and Drugs Act and Its Enforcement". FDA History - Part I. U.S. Food and Drug Administration. Retrieved 10 April 2013.

following successive disasters and public scandals up to the time of the Kefauver-Harris amendments in 1962, which created the licensing system which continues today.

Developments in the years between 1906 and the next major scandal in 1937 followed from the types of standards (and their rationale) already set by the FFDA. In 1911 in the case of *US v Johnson*[19] SCOTUS began to push back on the FDA's regulation of speech, ruling that the FFDA, *"does not prohibit false therapeutic claims but only false and misleading statements about the ingredients or identity of a drug."*[20] This supports the view that the FFDA was still as much pro-industry as it was pro-consumer. Although in 1924, in *U.S. v. 95 Barrels Alleged Apple Cider Vinegar,*[21] SCOTUS ruled that the FFDA *"condemns every statement, design, or device on a product's label that may mislead or deceive, even if technically true."* In response to *US v Johnson* in 1912, Congress introduced the Sherley amendment which prohibited the *"labelling of pharmaceutical products with false therapeutic claims intended to defraud the purchaser"* a standard which was *"difficult to prove"*.[22] Mandatory product labelling began with the Gould Amendment in 1913 (for foodstuffs, stating net quantity).[23] However, this did not yet apply to pharmaceutical products. Mandatory labelling regarding instructions for use – i.e., the main way in which the FDA could exercise safety oversight regarding the use and later the efficacy of products through the product label, did not begin to appear until the provisions of the Food Drug and Cosmetics Act 1938 ('FDCA 1938'). However, in 1914, the Harrison Narcotics Act introduced the first mandatory prescriptions requirement and record keeping requirements for doctors for 'narcotics.'

Elixir Sulfanilimide, the FDCA 1938, Mandatory Labelling and Mandatory Prescriptions

Everything changed in the 1930s after a high-profile disaster concerning a pharmaceutical product. As early as 1933, it was recognised that the FFDA 1906 was out of date and the FDA recommended its, *"complete revision"* thus *"launching a five-year legislative battle."*[24] However, it was not until the Elixir Sulfanilamide tragedy killed 107 people, mostly children, in 15 states from Virginia to California between September and October 1937[25] that this occurred.[26] This product was obviously unsafe – this was not a case of a 'latent' defect. In fact, *"a few simple tests"* or simply *"a review of the current existing scientific literature"* would have indicated that the contents of the Elixir were toxic and would cause kidney failure. The FFDA 1906, however, did not require any pre-market safety testing. The children who had drank the Elixir suffered from the symptoms of kidney failure: convulsions, vomiting, extreme abdominal pain, nausea, stupor, and inability to pass urine, and for between seven and twenty-one days, "*they suffered intense and unrelenting pain.*"[27] Just as was the case with the publication of *the Jungle* in 1906, previously formenting discontent amongst consumers with their perceived lack of regulatory oversight of the food and pharmaceuticals industry was

19 *United States v. Johnson*, 221 U.S. 488 (1911),
20 https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law
21 *United States v. Ninety-Five Barrels Alleged Apple Cider Vinegar*, 265 U.S. 438 (1924). For those interested, the apple cider vinegar was 'alleged' only because it was made from dried apples not wet ones.
22 https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law
23 Hutt, Barton, Daemmrich, and Radin (2007) at pg. 15
24 https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law
25 Hutt, Barton, Daemmrich, and Radin (2007) at pg. 18
26 Ballentine, Carol, 'Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident' DA Consumer magazine (June 1981) at Pg 1
27 Ibid

given a focal point by the sulfanilimide disaster. Consumers immediately pressured Congress to act. It was the FDCA 1938 – signed into law by President Roosevelt (this time Franklin, not Theodore) on 24 June 1938 - which is still today the cornerstone of US regulation of the pharmaceutical sector. The FDCA 1938 replaced the FFDA 1906. The FDCA - according to its official title - gave *"authority to the (FDA) to oversee the safety of food, drugs, medical devices, and cosmetics."* Most importantly, the FDCA mandated a pre-market review of the safety of all new drugs, which began the modern licensing system in the US, some time before this was introduced anywhere in Europe. At this stage, however, there was no requirement of premarket review for both safety and efficacy and the system as it is known today – encompassing phase I-IV clinical trials – was not created until the Kefauver-Harris amendments of 1962. The US did now have a pre-market safety testing requirement (even though it was weak by todays standard), something which enabled it to prevent the Thalidomide disaster many years later.

Under the FDCA 1938, the FDA was given authority to approve pharmaceutical products for marketing, which meant that it could effectively exercise control over the information contained on the label and any other information disseminated for marketing purposes. This responsibility was placed with the FDA's Division of Drug Marketing, Advertising and Communications.[28] Now, through control over what claims may appear on the product label, indirect control was being exercised by the FDA regarding what uses (indications) the product could be advertised for. Mandatory 'use-instructions' labelling of pharmaceutical products also followed from the FDCA, as did – eventually – the mandatory prescription system. As to how the latter came about, according to Marks the FDCA 1938 gave the FDA authority,[29] *"for the first time in its 32-year history, to keep "unsafe" or untested products off the market"* and *"most of the FDA's new powers rested in its authority to regulate what manufacturers said about their products."* Given this new situation, US Pharmaceutical Industry (USPI) manufacturers were worried about the costs of compliance and demanded that the FDA be clear on what it would seek in terms of use-instructions labelling.

By December 1938, the FDA proposed regulations stipulating that: *"the labeling must include a full and complete description of the conditions, with their symptoms, for which the preparation is indicated, and a statement of the treatment thereof in such detail that every consumer may determine the proper course of self-medication."* By 1938, the practice of doctors writing prescriptions was already commonplace. But it was not yet the case that a pharmacist (or a 'retail druggist' to use the US term) was prohibited from selling certain products without prescription. Congress had already given the FDA authority (before the FDCA) to exempt products sold on prescription by a doctor from stating the ingredients and quantity on the label, and USPI now wished to extend that exemption also to use-instructions. The FDA bowed to industry and doctors' demands for this prescription labelling exemption from use-instructions. The effect, some argue, was to create the modern mandatory prescriptions system because now under these regulations, pharmacists could not sell an unlabelled product except on prescription, thus creating the Prescription-Only (PO) sale classification category. According to Temin, *"regulations issued by the FDA in December 1938*

28 Boden WE, Diamond GA. DTCA for PTCA: Crossing the line in consumer health education? *N Engl J Med.* 2008;358(21):2197–2200

29 Marks, Harry M. "Revisiting" the origins of compulsory drug prescriptions"." American Journal of Public Health 85, no. 1 (1995): 109-115 at 110.

arbitrarily created a new class of drugs 'that cannot legally be sold without a prescription.' Prior to these regulations, consumers could purchase any nonnarcotic drug they desired with or without a prescription, as they pleased."

These regulations (in December 1938) stated that pharmaceutical companies could substitute *"at their discretion"* the phrase: *"'Caution: To be used only by or on the prescription of a physician [or dentist or veterinarian]'"* in place *of "the detailed instructions for use required by the FDCA for non-prescription products."*[30] The 1938 prescription labelling regulations did not work well (see Chapter Four for more detail) and in *"the spring of 1944, the FDA issued new regulations limiting the use of prescription labeling to drugs that because of [their] toxicity or other potentiality for harmful effect [are] not generally recognized among experts [qualified] by scientific training and experience to evaluate [their] safety and efficacy, as safe and efficacious for use except by or under the supervision of a physician, dentist or veterinarian."*[31] Over the intervening 15 years squabbles between the FDA, industry, doctors, and pharmacists arose over who exactly would decide on whether a product fitted this definition. By 1951, at the time of the Durham-Humphrey amendments, USPI sought to keep the prescription labelling system, with industry actors deciding whether a product should be placed in the PO category, and subject to the prescription labelling exemption (rather than the FDA deciding this). Thus, according to Marks, *"in 1951, drug firms sought to continue, not to end, prescription labeling… they merely wished to preserve the status quo, in which individual companies had the discretion to decide which drugs deserved prescription labeling and the FDA had the burden of proving them wrong."*[32] Therefore the 1944 prescriptions regulations became law. Pharmaceutical firms remained the actor which decided which products met these criteria and if the FDA wished to challenge this it had to do so through the courts.

1.2.2 1938-1962: FDA Beginning to Tackle Industry with Congressional Oversight

From the passage of the FDCA 1938 onwards, armed with pre-market safety testing and mandatory labelling for pharmaceutical products, the FDA had teeth but not yet a high public profile. In the intervening 24 years – with the assistance of (and/or at the behest of) Congress - it began to exert real pressure on industry. By 1962 it had secured itself both more powers and an indisputably higher public profile. Throughout the first seven years of this period, industry became particularly powerful - during the second world war. Scientific advancements made in the private sector during this period resulted in the FDA no longer acting to assist industry but instead playing catch-up and exercising restraint upon industry. Representative of this transition is the 1943 SCOTUS decision in *United States v Dotterweich*[33] which established (near) strict criminal liability of any person who stands *"in a responsible relationship"* to a violation of food and drugs law, which the court said was due to *"the*

30 Ibid.
31 Ibid at 111.
32 Ibid at 112.
33 United States v Dotterweich [320 US 277 (1943)]

importance of food and drugs and the fact that they touch the lives of every citizen".[34] The third stage was fully underway in the 1950s, when it became clear that industry's own command of science, and its innovation, had outpaced government efforts to assist.[35] Now it was believed in Congress that it was important to ensure that the risks of innovation in the food industry were not passed on to consumers, with impunity for producers. One concern was the use of chemical preservatives in food.[36] And, for example, the Keefe Committee was set up in Congress in the 1950s to investigate this.[37]

The most significant Congressional investigation of the second half of the 20th Century into USPI was to come between 1959 and 1962 under Senator Estes Kefauver. Kefauver[38] is key to understanding why the FDA behaves the way it does today. Together with the actions of the FDA in relation to thalidomide, it was his Congressional hearings which thrust the FDA into the public spotlight and made it the champion of US consumers.

The Kefauver Hearings 1959-1963

Between 1959-1963 there were 17 (continuous) months of Committee hearings in the Senate Antitrust and Monopoly Subcommittee, chaired by Kefauver. These were known as the Kefauver hearings. At these, officers from the FDA were frequently obliged to be present and answer questions. Kefauver was not attacking the FDA, but USPI. Of the FDA, Kefauver was critical only insofar as he perceived lax oversight. In the hearings, Kefauver brought the same tactics as he had in his famed, 1950-1951 hearings regarding organised crime. In the 1959-1963 hearings, he was also appealing specifically to his liberal (economically minded) consumer support base.[39] According to Greene, prices and false claims of efficacy were of paramount concern to Kefauver and his base,[40] *"the escalating expense of lifesaving prescription drugs was illustrating that the free-market approach to medical innovation had costs as well as benefits."* This concern, Greene points out, was partly due to the (private) advances in science which had led to the creation of many new pharmaceutical products on the market. Thus *"the American pharmaceutical industry had come to play a dominant role in… the rising politics of consumerism."* Kefauver considered the average US consumer to be *"captive"* to this industry and that oversight was needed to prevent *"price-gouging"* and *"dubious claims of efficacy."*[41]

34 Hutt, Barton, Daemmrich, and Radin (2007) at pg. 20

35 See Temin, Peter. "The origin of compulsory drug prescriptions." *The Journal of Law and Economics* 22, no. 1 (1979): 91-105.

36 Hutt, Barton, Daemmrich, and Radin (2007) at pg. 21

37 Maltzman, Forrest. *Competing principals: Committees, parties, and the organization of Congress*. University of Michigan Press, 1998.

38 *Estes Kefauver, a Biography* by Charles L. Fontenoy. (Olympic Marketing, 1980.ISBN 978-0195014815) see also *Kefauver: A Political Biography* by Joseph Bruce Gorman. (Oxford University Press, 1971.)

39 Specifically, the "new consumer movement"– all that was left of consumer activists after the McCarthyist era of the 1950s had stripped away most of its more radical elements. This left only those liberal minded consumer activists who sought fair prices and fair quality rather than any more ambitious or arguably communist objective. See Glickman, Lawrence B. *Buying power: A history of consumer activism in America*. University of Chicago Press, 2009. And Glickman, Lawrence B. "" Buy for the Sake of the Slave": Abolitionism and the Origins of American Consumer Activism." *American Quarterly* 56, no. 4 (2004): 889-912.

40 Greene JA, Podolsky SH. Reform, regulation, and pharmaceuticals--the Kefauver-Harris Amendments at 50. *N Engl J Med*. 2012;367(16):1481-1483. doi:10.1056/NEJMp1210007

41 Greene and Podolsky (2012)

The hearings unveiled collusion between US doctors and USPI which shocked consumers. The American Medical Association ('AMA') Journal made millions of dollars in product advertising, and thus doctors were unlikely to challenge efficacy claims made therein.[42] In addition, Kefauver showed that the USPI heavily advertised more expensive originator products where doctors could prescribe generic products much cheaper.[43] Advertising and intellectual property protections also led to an abundance of 'me-too' products on the market: protected by patents but with little therapeutic advantage over existing products off-patent.[44] By the conclusion of the hearings, Kefauver presented legislative proposals which included compulsory premarket licensing authority for the FDA on criteria of both safety and efficacy. Due to stiff resistance and the accusation that Kefauver was *"expanding the power of government excessively, interfering with the freedom of doctors and patients, and threatening the viability of the pharmaceutical industry"*[45] it did not seem likely that those legislative proposals would be passed. By June 1962, he had lost the support of the Kennedy administration for the proposals.[46]

Thalidomide, FDA Heroism, and the New Drug Amendments of 1962

By the end of 1961, however reports began to emerge from outside the US relating to the Thalidomide disaster. Kevadon was the name given to Thalidomide in the US by the William S. Merrill Company[47] which sought to market it as a sedative. The scale of the harm in Europe (particularly the UK and Germany) became clear from 1962 onwards, at the height of the Kefauver hearings which already had the rapt attention of US consumers. The drug never passed the pre-market safety testing requirement in the US mandated by the FDCA 1938. Only circa 20,000 people used it on an experimental basis and 17 cases of birth deformities were recorded.[48] The non-approval of Thalidomide by the FDA was ensured by the Frances Kelsey – the same scientist who, in 1937, had helped to identify diethylene glycol as the toxic component in Elixir Sulfanilimide.[49] She *"refused to approve the drug application because of insufficient safety data"* pointing out that *"the submitted evidence (was) more anecdotal than clinical."*[50]

It was this moment in history - between 1961 and 1962, when the news of the Thalidomide disaster in Europe broke and the FDA's actions in preventing it to occur in the US became

42 https://en.wikipedia.org/wiki/Estes_Kefauver

43 Gorman (1971).

44 *"The marketing of new drugs that were no improvements on drugs already on the market, but nevertheless heralded as dramatic breakthroughs without proper concern for either effectiveness or safety"* Gorman (1971).

45 Greene and Podolsky (2012) The AMA was opposed to regulation based on efficacy, arguing that *"the only possible final determination as to the efficacy and ultimate use of a drug is the extensive clinical use of that drug by large numbers of the medical profession over a long period of time."* Others were fiercely opposed to the limitation on the grant of patents proposed by Kefauver where new products had little original therapeutic benefit.

46 Gorman (1971).

47 https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development

48 Braun W (2015-12-29). "Thalidomide: The Connection Between a Statue in Trafalgar Square, a 1960s Children's Show Host and the Abortion Debate". Huffington Post.

49 Frances Oldham Kelsey MD. See: permanent.access.gpo.gov/lps1609/www.fda.gov/fdac/features/2001/201_kelsey.html

50 https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development

known – which is most crucial to understanding why the FDA has behaved the way it does for the past 60 years. According to the FDA history, *"by 1962, the devastation caused by this drug in other countries had become big news in the United States. Thousands of children had been born with shortened, missing or flipper-like arms and legs."*[51]

Carpenter argues[52] that this moment above all cemented the FDA's reputation for consumer protection which he says helps to explain its approach – particularly to licensing – since 1962. Of great importance is the fact the news of both the disaster and the heroism came during the Kefauver hearings - at which time USPI and the FDA were in the public spotlight. As with the revelations made in *the Jungle*, there was a grassroots political reaction amongst US consumers. Kefauver then made a renewed attempt to introduce his legislation that would provide for premarket licensing authority for the FDA based on both safety and efficacy. His bill was re-introduced and this time passed unanimously in both houses, after which Kennedy signed it in to law.[53] The most important element in the Act was the requirement for testing of both safety and efficacy prior to a market access license being granted for a product.[54] Clearly Kefauver's original aims had been truth-in-labelling (i.e. efficacy) more than safety,[55] and the thalidomide disaster concerned safety rather than efficacy. However, by ensuring the legislation he reintroduced included "*provisions drafted by FDA specifically designed to prevent a disaster like thalidomide"* the New Drug Amendments (to the FDCA) of 1962 – the 'Kefauver-Harris Amendments' – created the US licensing system as it is known today. According to Greene, *"…these market-making and -unmaking powers were also tied to a new structure of knowledge generation: the orderly sequence of phase 1, phase 2, and phase 3 trials now seen as a natural part of any pharmaceutical life cycle."*

In addition, on advertising, the 1962 amendments gave the FDA express authority to regulate prescription drug labelling and advertising.[56] Regulations promulgated in 1969 by the FDA pursuant to the 1962 amendments stipulated that in the case of prescription drugs these adverts: 1) *"must not be false or misleading"*; 2) must present a *"fair balance"* of information describing both risks and benefits of the product; 3) must include facts *"material"* to the uses for which the product is being advertised and;[57] 4) must include, *"a brief summary"* that mentions every risk which is described in the product label as mandated by the FDA in its licensing decision.[58] At this stage (in 1962) broadcast or print advertisement direct to the

51 Ibid.

52 Carpenter, Daniel P. "The political economy of FDA drug review: processing, politics, and lessons for policy." *Health Affairs* 23, no. 1 (2004): 52-63 at page 59.

53 https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development

54 According to Greene and Podolsky (2012), *"The amendments granted the FDA the power to demand proof of efficacy — in the form of "adequate and well-controlled investigations"— before approving a new drug for the U.S. market. They also led to a retrospective review of all drugs approved between 1938 and 1962 (the Drug Efficacy Study Implementation program), which by the early 1970s had categorized approximately 600 medicines as "ineffective" and forced their removal from the market.*

55 Swann says, *"Kefauver's interest at the time was in drug pricing and marketing, believing that patients were paying too much and being misled by extravagant advertising claims. Kefauver introduced legislation to enforce truth in labeling and marketing."* https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development

56 Greene JA, Kesselheim AS. Pharmaceutical marketing and the new social media. *N Engl J Med.*

57 Ventola (2011)

58 Boden and Diamond (2008)

consumer was not common, although it was not prohibited by any specific regulation and was thus, by default, permitted under the first Amendment to the US Constitution. This would not become commonplace, however, until the 1980s.[59] In the 1950s and 1960s from the time of the introduction of mandatory prescription labelling, the practice of USPI was to advertise products directly to US doctors in what was known as 'detailing'. Detailing arguably had both educational and promotional elements. The 1969 regulations were directed at the detailing, rather than at DTCA, although in 1985 they were confirmed to extend also to (and to be sufficient in the case of) DTCA.

1.2.3 1962-1985: Champion of Consumers, Drugs Lag, and Political Pressure

Official FDA historian John Swann remarks that prior to the Kefauver hearings and thalidomide tragedy the *"FDA was not an unknown entity but after 1962, members of the public really started taking notice and having expectations that the government will protect them."*[60] He says that after these developments, "*the FDA's tenure as an obscure agency (would) never return"*[61] From 1962 onwards the FDA has been regularly in the Capitol Hill limelight, at the demand of the liberal consumer activist interest group which was Kefauver's support base. Not least because – owing to the Thalidomide disaster - Senator Hubert Humphrey and others established *"a pattern of additional congressional investigations and hearings"*[62] which was to continue indefinitely. According to Hutt, Daemmrich and Radin, *"all who have served at the FDA subsequently have spent a lot of time testifying on Capitol Hill and the FDA has received daily coverage by the news media."* Later, when discussing the fundamental characteristics of the FDA, I call this 'direct-to-consumer accountability.'

For reasons explained more fully in Chapter Two, the result of this direct-to-consumer accountability was long licensing approval times. Between 1962 and 1971 the US experienced a time lag in new drug approvals compared with its counterpart European agencies.[63] Compared with the UK agency, for example, during this period four times more new drugs became exclusively available in the UK as became so in the US. Twice as many new drugs were introduced in the UK than in the US.[64] However, in the 1980s the FDA showed itself to be accountable (and thus responsive) to consumers not just in exercising licensing caution generally, but also in speeding up the approval of entirely new drugs. In the 1980s, the

59 See Ventola (2011

60 https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development

61 Hutt, Barton, Daemmrich, and Radin (2007) at pg. 20

62 Greene and Podolsky (2012)

63 See Henninger, Daniel (2002). "Drug Lag". In David R. Henderson (ed.). Concise Encyclopedia of Economics (1st ed.). Library of Economics and Liberty. OCLC 317650570, 50016270, 163149563

64 Wardell, William M. "The drug lag revisited: comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976." Clinical Pharmacology & Therapeutics 24, no. 5 (1978): 499-524. See also Bakke, Olav M., William M. Wardell, and Louis Lasagna. "Drug discontinuations in the United Kingdom and the United States, 1964 to 1983: issues of safety." Clinical Pharmacology & Therapeutics 35, no. 5 (1984): 559-567.

Acquired Immunodeficiency Syndrome ('AIDS') crisis struck and the FDA faced pressure from patient interest groups such as 'The AIDS Coalition to Unleash Power' ('ACT-UP') which used the media to gain wider public support for their cause of expediting approvals of drugs to treat AIDS, in particular Azidotymidine.[65] In 1992, the FDA bowed to this pressure and introduced the 'subpart H' accelerated approval procedures[66] aimed to expedite drug delivery and cut costs for drugs treating serious and life-threatening illnesses and conditions.[67] This episode was part of a wider movement between 1972 and 1992 where widespread discontent was expressed with the length of FDA approval times.[68] During this period, the FDA had its budget cut by Congress and saw increased applications for approval from industry.[69]

As this stage of the FDA's history ended in the 1980s, the issue of advertising became more prominent. Possibly because the FDA was being so slow on licensing times throughout the 1970s, and because the FDA was so responsive to consumers throughout the whole period, USPI itself began to appeal directly to consumers. The first ever print example of DTCA was run by Merck in 1981[70] for Pneeumovax (an antipneumoccocal vaccine)[71] and Boots[72] – a pharmaceuticals retailer – began the trend of broadcast advertisement *"which promoted the lower price of its prescription brand of ibuprofen (Rufen), compared with Motrin (McNeil Consumer), in 1983."*[73] At this stage DTCA was permitted, save for the restrictions which the FDA could place on permissible advertising claims through the licensing process (approved indications) and the 1969 regulations regarding broadcast DTCA.[74] There was a significant increase in the volume of DTCA during the 1980s[75] due in part – argues Ventola – to a *"cultural shift"* which caused consumers to start actively participating in their healthcare decision making[76] and because of shifts in the US *"political climate"* which became generally more favourable to USPI .[77] Between 1983 and 1985 *"FDA Commissioner Arthur Hayes asked the pharmaceutical industry to observe a voluntary moratorium while the agency studied the*

65 See Vogel, D. (1989). AIDS and the Politics of Drug Lag. Public Interest, (96), 73. See also Griffin, Mary T. "AIDS drugs and the pharmaceutical industry: a need for reform." Am. JL & Med. 17 (1991): 363 and Relihan, Julie C. "Expediting FDA Approval of AIDS Drugs: An International Approach." BU Int'l LJ 13 (1995): 229 and Dunbar, Mary M. "Shaking up the status quo: how AIDS activists have challenged drug development and approval procedures." Food Drug Cosm. LJ 46 (1991): 673.

66 See https:// www.accessdata.fda.gov

67 See https://www.pharmamedtechbi.com/~/media

68 See Olson, Mary. "Substitution in regulatory agencies: FDA enforcement alternatives." The Journal of Law, Economics, and Organization 12, no. 2 (1996): 376-407.

69 Ibid.

70 Greene and Herzberg (2010) at 794.

71 Ventola (2011) at 699.

72 Abel GA, Penson RT, Joffe S, et al. Direct-to-consumer advertising in oncology. *Oncologist.* 2006;11(2):217–226.

73 Ventola (2011) at 704.

74 Frosch DL, Grande D, Tarn DM, Kravitz RL. A decade of controversy: Balancing policy with evidence in the regulation of prescription drug advertising. *Am J Public Health.* 2010;100(1):24–32.

75 Ventola (2011) at 704

76 Delbaere M, Smith MC. Health care knowledge and consumer learning: The case of direct-to-consumer advertising. *Health Mark Q.* 2006;23(3):9–29.

77 Shaw A. Direct-to-consumer advertising of pharmaceuticals: DTC regulation. *ProQuest.* Mar, 2008. Available at: www.csa.com/discoveryguides/direct/review3.php. Accessed July 28, 2011.

issue"[78] of broadcast DTCA. This voluntary moratorium was – in my view – the last act of the 'consumer champion' stage of the FDA's history.

1.2.4 Neoliberal Reforms and Faster Licensing Times: 1985 Onwards

Since 1985 the relationship between the FDA, industry, and consumers has been rebalanced. The first example of such a reform resulted from consumer and political pressure over drugs prices which caused pressures on the Federal and State budgets because of the introduction of limited socialised healthcare in the 1960s. To increase competition from generic products in the pharmaceuticals market, Congress enacted the Hatch-Waxman Act of 1985. Hatch Waxman amended the FDCA 1938 to do several things. The first and most important was to incentivise and facilitate the entry of generics on to the market by creating a new process for the approval of generic products: the Abbreviated New Drug Application ('ANDA')[79] which required generics manufacturers to show only 1) information on how it would manufacture the drug, 2) quality assurance and 3) bioequivalence.[80] This process provides a simple and quick way for generics to gain a market access license and prevents the FDA from asking for more from the generic manufacturer. Secondly, it provided generics manufacturers with a safe harbour from intellectual property infringement lawsuits (the 'research exemption') during the time in which it prepared its ANDA. Then, to protect innovation, it: 1) extended the term of patents given to originator products to cover the period that the originator spent under regulatory review by the FDA before receiving a market access license; and 2) gave an additional period of market exclusivity to originator drugs (five years) where these were a new chemical entity (i.e., they represented genuine innovation). Interestingly, Hatch-Waxman was a mixed bag. In providing for ANDAs in the case of generic drugs, it championed consumers in seeking to lower drug prices. However, it was very much a neoliberal, market-oriented reform which also extended patents for new drugs.

At the same time, in 1985, *"the FDA published a notice in the* Federal Register *claiming regulatory jurisdiction over DTCA and stating that prior standards of "fair balance" and "brief summary" that had been established for advertising to health care providers were sufficient to protect American consumers against deceptive or misleading claims."* And, according to Ventola, this led to an *"onslaught"*[81] of print DTCA. Broadcast DTCA was difficult to achieve due to the "*need to include complete information about risks from the package insert to satisfy the "fair balance" and "brief summary" regulatory requirements could be satisfied with small type in a product claim print ad. However, the cost of purchasing enough time to include this information in product claim broadcast ads was prohibitive."*[82] In 1995, this time accommodating industry, the FDA held a public hearing to discuss regulation of broadcast DTCA. In 1997 it issued draft guidance and in 1999 final regulations which allowed broadcast DTCA *to include only "major risks" and to provide guidance to viewers on where else to seek*

78 Ventola (2011) at 704.
79 Section 505(j) of the Act, codified as 21 U.S.C. § 355(j).
80 Showing that the generic drug operates the same in humans as does the originator drug.
81 Ventola (2011) at 704.
82 Greene and Herzberg (2010) at 802. Ventola (2011) at 704.

the full "brief summary" information.[83] *In 2004 the FDA further relaxed regulations for print DTCA permitting*[84] *merely a "simplified brief summary"*[85] *instead of complete prescribing information"*[86] A key part of the FDA's approach to the regulation of advertising of pharmaceutical products during this period has been forced by the US courts. The US Court of Appeals in *Pearson v Shalala*[87] in 1999 held that the FDA was subject to the First Amendment and thus there were limits upon how the FDA could restrict advertising, and a similar ruling was made by SCOTUS in *Thompson v Western States Medical Center* in 2002.[88] According to Ventola,[89] and others, in 1980 total USPI spending on DTCA was 12m USD, in 1990 47m USD and in 1995 340m USD, *"representing a nearly 3,000% increase in expenditures during a 15-year period before broadcast ad regulations had even been relaxed."*[90] After the 1997 revised guidelines and 1999 regulations this spending trebled to 1.2bn in 1998, *"and nearly quadrupled again during the following decade, topping 5b USD in 2009."* In 2018 it was 6.5bn USD.[91]

Building upon the Hatch Waxman Act in 1985, in 1992 Congress passed the Prescription Drug User Fee Act ('PDUFA'),[92] lobbied for by industry, consumer groups and the FDA itself.[93] PDUFA enabled the FDA to charge fees for use of its process and the increase in resources contributed to faster approval times. Its *"most important provisions create (1) a system of per application "user fees" that fund increases in the reviewer staff…, and (2) an incentive structure whereby the legislation is renewed only if the FDA meets specified performance goals."* Since PDUFA *"the average review time for* (new drugs*) has greatly declined, to thirteen months in 2002."*[94] By 2017 the FDA was outperforming the EMA in respect of waiting times for approval of therapeutically novel drugs[95]. Carpenter says[96] this is partly due to PDUFA and partly due to higher staff numbers at the FDA in the 5 years leading up to PDUFA. This Act represents best the rebalancing of the FDA from its consumer champion role to a role in which it was required to be responsive both to industry and to consumers. This was, however, a rebalancing and not a swing. The FDA remained directly accountable to consumers (through the media) at the time of PDUFA – as was shown by the success of the AIDS activists in obtaining accelerated approval procedures – and long after.

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83 Abel, Penson and Joffe (2006)
84 Lee AL. Changing effects of direct-to-consumer broadcast drug information advertising sources on prescription drug requests. *Health Commun.* 2009;24:361–376
85 Shaw (2008)
86 Ventola (2011)
87 [164 F.3d 650 (D.C. Cir.1999)]
88 [535 US 357 (2002)]
89 Ventola (2011)
90 Greene and Herzberg (2010) at 803
91 https://www.statista.com/statistics/686906/pharma-ad-spend-usa/
92 UNITED STATES CONGRESS Prescription Drug User Fee Act 1992: An Act to amend the Federal Food, Drug, and Cosmetic Act to authorize human drug application, prescription drug establishment, and prescription drug product fees and for other purposes (106 Stat 4491)
93 See Olson Mary K. "Regulatory reform and bureaucratic responsiveness to firms: The impact of user fees in the FDA." Journal of Economics & Management Strategy 9, no. 3 (2000): 363-395.
94 Carpenter (2004) at pg. 59.
95 See Hatswell, Anthony J., Gianluca Baio, Jesse A. Berlin, Alar Irs, and Nick Freemantle. "Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999–2014." BMJ open 6, no. 6 (2016): e011666.
96 Carpenter (2004) at pg. 59.

The rebalancing has meant that ever since, the licensing process has been highly politicised. For example, between 1988 - when it was approved in France - and 2000 when it was finally approved by the FDA[97], for example, the abortifacient Mifepristone[98] was the subject of a politicised licensing process whereby both Congress and the President pressured the agency at various times to abandon or speed up the approval of the drug.[99] The period since has seen many new powers given to, or taken away from, the FDA by Congress and/or the courts according to the political situation at the time, and this has always taken place under the watch of consumers.[100] In 1994 the Dietary Supplement Health and Education Act ('DSHEA 1994') established a regime for dietary supplements which applied also to most herbal remedies (thus bringing these under the FDA's regulatory remit). In 1994 the FDA also announced that it would consider regulating nicotine in cigarettes as a drug in response to the Citizen's Petition by the 'Coalition on Smoking OR Health" (a consumer interest group). However, in 2000 SCOTUS ruled in *Food and Drug Administration v. Brown & Williamson Tobacco Corp. et al*[101] that the FDA did not have authority to regulate tobacco as a drug.

Then, in 2009 the Family Smoking Prevention and Tobacco Control Act *"gave the FDA authority to regulate the manufacture, distribution, and marketing of tobacco products to protect public health"*[102] and the FDA Center for Tobacco Products was established with the FDA banning flavoured cigarettes. In 1997 PDUFA was reauthorised under the Food and Drug Administration Modernization Act which further reformed agency practices, including acceleration of the review of medical devices and further regulation of off-label promotion of pharmaceutical products. A scandal in 2012 involving an outbreak of meningitis linked to *"a contaminated compounded drug product"* killed 64 people and made 751 people ill. In response, Congress enacted the 2013 Drug Quality and Security Act ensuring greater regulatory oversight of facilities creating compounded drugs. During the Coronavirus pandemic of 2020-2021 the FDA has been drawn into further political discussions regarding the speed of approval of vaccines as well as safety oversight. In relation to this, [103] and to the opioid epidemic[104] the FDA has continued to be responsive to political pressure, particularly that coming via Congress, from consumers.[105]

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97 See Noah, Lars. "A Miscarriage in the Drug Approval Process: Mifepristone Embroils the FDA in Abortion Politics." Wake Forest L. Rev. 36 (2001): 571.

98 https://www.fda.gov/Drugs/DrugSafety/ucm111323.htm

99 See Noah (2001).

100 https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law

101 529 U.S. 120 (more)120 S. Ct. 1291; 146 L. Ed. 2d 121

102 https://www.fda.gov/about-fda/fda-history/milestones-us-food-and-drug-law

103 https://www.fda.gov/media/137005/download

104 https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-opioid-misuse-and-abuse

105 For example, *"on February 4, 2016, FDA leaders, in response to the opioid abuse epidemic, called for a far-reaching action plan to reassess the agency's approach to opioid medications. The plan will focus on policies aimed at reversing the epidemic, while still providing patients in pain access to effective relief."* And *"On February 4, (2916) FDA released five postmarketing requirements announced on September 13, 2013, and replaced them with 11 PMRs because the 10 postmarketing observational studies and one clinical trial include refined measures for assessing the known serious risks of misuse, abuse, addiction, overdose, and death."* Also, *"On March 24, (2016) FDA issued a draft guidance titled "General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products." This guidance recommends studies a generic applicant should conduct so FDA can evaluate the abuse deterrence of certain generic opioid drug products and help ensure that generic versions of approved opioids with abuse-deterrent formulations (ADFs) are no less abuse-deterrent than the brand-named drug."*

1.3 Overview, History and Analysis of Pharmaceutical Regulation in Europe

To describe the European system of pharmaceutical regulation it is necessary to first consider the NAs and then the EMA, because the European system is based on an interaction between all of these.

1.3.1 History of Regulation at the EU Member State Level up to the 1980s

I give the UK and Germany as examples of the system in the EUMS prior to the 1980s. Prior to the Pharmacy Act of 1868 the sale of drugs in the UK was regulated through guilds and other trade associations (grocers, then apothecaries). The Pharmaceutical Society of Great Britain was founded in 1841 and the Pharmacy Act *"limited the sale of poisons and dangerous drugs to qualified pharmacists and druggists."*[1] Apart from this there was little or no product regulation except in the case of narcotics such as cocaine and heroin - through the 1908 Poisons and Pharmacy Act and the 1920 Dangerous Drugs Act.[2] In Germany there was no separate drugs law at all until 1961 (West Germany).[3] Germany introduced its Medicines Act in 1961 but, like the 1868 UK Act it did not contain any obligation to test the efficacy and safety of drugs. It did, however, provide for registration of drugs (and side effects).[4] The reason was to keep the German pharmaceutical industry internationally competitive. It is coincidental that the German Medicines Act of 1961 came into force around the same time as the Thalidomide disaster. The approach of that Act was the standard across the EUMS at the time (immediately prior to Thalidomide) with no premarket testing requirement.

Thalidomide was first marketed in West Germany in 1957[5] and between 5000 and 7000 children in Germany were afflicted with a 50% survival rate. According to Lembit and Santoso, *"the role of this disaster in shaping the medicines regulatory systems is not hard to underestimate"* across the whole of Europe. *"As a result the whole regulatory system was reshaped in the UK where a Committee on the Safety of Drugs was started in 1963 followed by a voluntary adverse drug reaction reporting system (Yellow Card Scheme) in 1964."*[6] In Germany, as a result of Thalidomide, the Medicines Act of 1961, *"was changed a total of 17*

1 https://en.wikipedia.org/wiki/Pharmacy_in_the_United_Kingdom
2 https://en.wikipedia.org/wiki/Drug_policy_of_the_United_Kingdom
3 https://second.wiki/wiki/arzneimittelgesetz_deutschland
4 O'Keefe, Daniel F., and Rainer G. Czeniek. "A Study of the Drug Laws of the Federal Republic of Germany." *Food Drug Cosm. LJ* 32 (1977): 488.
5 Stephens, T and R Brynner, Dark Remedy: The Impact of Thalidomide and its Revival as a Vital Medicine (Massachusetts: Perseus Pub., 2001).
6 Rägo, Lembit, and Budiono Santoso. "Drug regulation: history, present and future." *Drug benefits and risks: international textbook of clinical pharmacology* 2 (2008): 65-77.

times by 1971, but a fundamental reform and thus a new overall concept were necessary."[7] By 1965 the (then) European Communities ('EC') laid down a guideline for the requirements for the approval of pharmaceutical products in the EUMS[8] in Directive 65/65 EC. By 1976 Germany had introduced an entirely new Medicines Act providing for premarket safety and efficacy testing. Similarly, in the UK, the changes implemented from 1963 onwards culminated in the Medicines Act 1968 which is a similar instrument to the German Medicines Act 1976, both being derived from the guideline in Directive 65/65 EC. Other EUMS governments moved quickly, after Thalidomide, to introduce or reform their regulatory systems. On one hand this was a reaction to Thalidomide, however, because the harmonisation of the internal market in pharmaceuticals was also envisaged by the EC at the same time, it is probably true to say that Thalidomide expedited this rather than causing it.[9]

1.3.2 Development of the National Agencies in the EUMS

Now, every EUMS has an agency at the national level regulating (at least) market access licensing for medicines. However, these were not established immediately post-Thalidomide. It was some decades later, in the 1980s, that agencies – separate from health ministries - began to emerge. Some of these are shown in Table 3**Table *3*** and the dates of establishment for some are given in the footnotes, below.

7 https://second.wiki/wiki/arzneimittelgesetz_deutschland

8 Directive 65/65/EEC of the Council of January 26, 1965 for the harmonization of legal and administrative regulations on medicinal specialties

9 Whilst the thalidomide disaster caused the most widespread harm - and is attributed with the development of modern licensing systems in the EUMS - other scandals related to other drugs undoubtedly contributed throughout the middle of the 20th Centruy, for example: Diethylstilbestrol (DES) and Bendectin. Due to differences in marketing and sales in the US and the EU, respectively, the extent to which these scandals entered the political rhetoric of policymakers in the two jurisdictions also differed. The thalidomide scandal had a much larger impact on the political world in Europe than it did in the US, precisely because the extent of the disaster in Europe was much greater.

Table 3 The NAs in14 Sampled EUMS

EUMS	Agency
Sweden	Medical Products Agency ('MPA')[10]
UK	Medicines and Healthcare Products Regulatory Agency ('MHRA')[11]
	Previously: Medicines Control Agency ('MCA')
Netherlands	Medicines Evaluation Board ('MEB')[12]
Germany	Federal Institute for Drugs and Medical Devices ('BfArM')[13]
Denmark	Danish Medicines Agency ('DMA')[14]
Finland	Finnish Medicines Agency ('FMA')[15]
Ireland	Health Products Regulatory Authority ('HPRA')[16]
Austria	Federal Office for Safety in Health Care ('BASG')[17]
Belgium	Federal Agency for Medicines and Health Products ('FAMHP')[18]
Italy	Italian Medicines Agency ('AIFA')[19]
Greece	National Organisation for Medicines ('NOM')[20]
Portugal	Infarmed
Spain	Agency of Medicines and Medicinal Products ('AEMPS')[21]
France	Agence Nationale de Sécurité du Médicament et des produits de santé ('ANSM')[22]
	Previously: Agence Francaise de Sécurité Sanitaire des produits de santé ('AFSSaPS')

Whilst licensing of pharmaceutical products (originally drugs) had been in place across Europe from the time of EU Directives in the 1960s and 1970s, 'agencification' came later. Some of the NA's listed above were created before the creation of the EMA in 1995, and others were

10 https://www.lakemedelsverket.se/en: in existence (in its current form) since 1990 and a government body under the Swedish Ministry of Health and Social Affairs.
11 Initially the Medicines Control Agency established in 1989
https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency: changing its name to the MHRA in 2003, an executive agency of the Department of Health and Social Care.
12 https://english.cbg-meb.nl: which falls under the Ministry of Health, Welfare and Sport.
13 https://www.bfarm.de/EN/Home/_node.html: which operates under the Federal Ministry of Health.
14 https://laegemiddelstyrelsen.dk/en: under the Danish Ministry of Health and Prevention.
15 https://www.fimea.fi/web/en: operating under the Finnish Ministry of Social Affairs and Health
16 https://www.hpra.ie/
17 https://www.basg.gv.at/en/about-us: *"As of January 2, 2006, the BASG commenced its work as the national authority for medicines, medical devices, blood and tissue together with the Austrian Medicines and Medical Devices Agency, a business division of the Austrian Agency for Health and FoodSafety (AGES MEA, until January 1, 2012 AGES PharmMed); prior to this, it was spun off from the Federal Ministry of Health and Women's Affairs"*
18 https://www.famhp.be/en/famhp *"The Federal Agency for Medicines and Health Products (FAMHP) was established by the law of 20 July 2006"*
19 https://www.aifa.gov.it/en/web/guest/home: *"The Italian Medicines Agency - AIFA is a public body operating according to the principles of autonomy, transparency and efficiency, under the direction of the Ministry of Health and the supervision of the Ministry of Health and the Ministry of Economy. AIFA cooperates with the Regions, the Italian National Institute of Health, Scientific Institutes for Research, Hospitalisation and Health Care, patient associations, physicians and learned societies, the world of production and distribution."*
20 https://www.eof.gr/web/guest;jsessionid=e1262afcd689413d3ee8a55a9a7e
21 https://www.aemps.gob.es/
22 https://ansm.sante.fr/ The French Agence Nationale de Sécurité du Médicament et des produits de santé which replaced the Agence Francaise de Sécurité Sanitaire des produits de santé in 2012 (the latter dated from 1998 and was preceded by another agency which predated the creation of the EMA in 1995).

only created as a response to the creation of the EMA. One example[23] is found in the UK developments: the UK Medicines Act 1968[24] required the licensing of medicines and ability to remove medicines from the market. Between 1971 and 1989 this role was undertaken in-house at the UK Health Ministry by the Medicines Division of the Department of Health and Social Security. In 1989 this became an agency separate from but underneath the same department – the MCA – with the mission statement: *"to promote and safeguard public health through ensuring appropriate standards of safety, quality and efficacy for all medicines on the UK market."*[25]

1.3.3 The Development of the European Medicines Agency and the EU-Wide Approach

The EMA (then the 'EMEA' the European Medicines Evaluation Agency) was created in 1995, and the NAs continue to play a pivotal role, with the EMA, in the process of licensing pharmaceutical products.[26] In the case of the NAs, as set out above, these were often established as divisions *within* EUMS government health ministries pursuant to EC Directives requiring premarket approval for medicines. The mission statement of these government departments – in the 1960s-1970s - was more focused on consumer protection than on assistance to industry. However, when these department divisions were agencified, the mission statement was different. Whilst the agencies were clearly charged with consumer protection the real reason for their establishment in the 1980s and 1990s (and beyond) was to assist industry and depoliticise the issue of pharmaceutical products market approval. In the case of the EMA, the reason for its creation was the achievement of a single European market in pharmaceuticals: a goal which benefits industry primarily and consumers less directly. Protection of consumers was already being catered for by the agencies or government department divisions created pursuant to or sometime after the 1965 Directive. The specific reason for creating the forerunner agency to the EMA (the EMEA) was stated in the preamble to Council Regulation (EEC) No 2309/93 of 22 July 1993.[27] This preamble stresses scientific expertise and regulatory harmonisation above consumer protection.[28]

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23 Going Forward, by 'agencification' I mean the removal of licensing and other functions from being functions undertaken in-house at EUMS Health Ministries, and delegation of these to subordinate (but separate) regulatory agencies.

24 Which contained elements required by Directive 75/318/EEC

25 https://publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf

26 See Mossialos, Elias, and Adam Oliver. "An overview of pharmaceutical policy in four countries: France, Germany, the Netherlands and the United Kingdom." The International journal of health planning and management 20, no. 4 (2005): 291-306.

27 Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Product

28 Preamble to Council Regulation (EEC) No 2309/93 of 22 July 1993 *"…only after a single scientific evaluation of the highest possible standard of the quality, safety or efficacy of technologically advanced medicinal products… should a marketing authorization be granted by the Community by a rapid procedure ensuring close cooperation between the Commission and Member States… whereas, furthermore, in order to achieve the effective*

The EMEA was set up partly with funding from the EU, and partly with assistance from the EU pharmaceutical industry ('EUPI'). The aim was to harmonise but not replace the work of the existing NAs and/or health ministries. The reason for doing so was to alleviate the cost to pharmaceutical firms of obtaining market approval (licenses) in multiple different EUMS. It was also an aim to tackle the problem of national protectionism in pharmaceuticals approval. The EMEA was renamed the EMA in 2004 after Regulation (EC) No 726/2004, which made some changes to the way the agency operated and prepared for the further expansion of the EU. It replaced the old system in which the EMEA operated as a framework for two Commission Committees: the Committee for Proprietary Medicinal Products ('CPMP'), and the Committee for Veterinary Medicinal Products. As such, much like some EUMS had already moved their licensing functions 'out-of-house' from ministries to (subordinate) agencies, so too the EMEA – an *in-house* entity at the Commission – was agencified to become the EMA. It was at this point (2004) that the EMA was located in London, moving to Amsterdam in March 2019 following the UK's decision to leave the EU.

According to its website now, the mission of the EMA is *"to foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health in the European Union."*[29] It operates within the European Legal Framework for Pharmaceuticals which is, *"is aimed at ensuring a high level of protection of public health. It is based on the principle that the placing of a medicine on the market is subject to the granting of a by the competent authorities."*[30] The crucial aspects of that legal framework are found in several instruments. The 2001 Human and Veterinary Medicinal Products Directives[31] which *"provide the legal framework for the authorisation, manufacture and distribution of medicines in the EU."* The 2004 Regulation which established a centralised procedure for authorising human and veterinary medicinal products and established the EMA.[32] Council Regulation (EC) No 297/95[33] (which introduced user fees) and the pharmacovigilance fee regulation (Regulation (EU) No 658/2014) as well as Commission Regulation(EC) No 2049/2005.[34] Standards and a

harmonization of the administrative decisions taken by Member States in relation to individual medicinal products which are presented for authorization in accordance with decentralized procedures, it is necessary to provide the Community with the means of resolving disagreements between Member States about the quality, safety and efficacy of medicinal products;… Whereas it is therefore necessary to establish a European Agency for the Evaluation of Medicinal Products ('the Agency');… Whereas the primary task of the Agency should be to provide scientific advice of the highest possible quality to the Community institutions and the Member States for the exercise of the powers conferred upon them by Community legislation in the field of medicinal products in relation to the authorization and supervision of medicinal products;…"

29 https://www.ema.europa.eu/en/about-us/what-we-do

30 https://www.ema.europa.eu/en/about-us/what-we-do/legal-framework

31 Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products and DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use

32 Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency

33 Council Regulation (EC) No 297/95 of 10 February 1995 on fees payable to the European Agency for the Evaluation of Medicinal Products

34 COMMISSION REGULATION (EC) No 2049/2005 of 15 December 2005 laying down, pursuant to Regulation (EC) No 726/2004 of the European Parliament and of the Council, rules regarding the payment of fees to, and the receipt of administrative assistance from, the European Medicines Agency by micro, small and medium-sized enterprises.

legal framework were set for clinical trials by Directive 2001/20/EC.[35] Provision was made for handling of post authorisation variations to terms of marketing authorisations by Commission Regulation 1234/2008[36] and Commission Regulation 712/2012.[37] Commission Regulation (EC) 2141/96,[38] and Directive 2011/62/EU[39] concerned falsified medicines, and Regulation (EC) 658/2007[40] provided for an EU penalties regime in respect of failure to comply with the 2004 Regulation. In addition, there is the traditional herbal medicines Directive 2004/24/EC,[41] Regulation (EC) 1901/2006[42] on paediatric medicines, Regulation (EC) No 1394/2007[43] and the legal framework for orphan medicines found in Regulation (EC) No 141/2000.[44] Finally, a package of pharmacovigilance legislation was introduced in 2010 including Regulation 1235/2010[45] and Directives 2010/84/EU[46] and Directive 2012/26/EU.[47]

The original mission statement of the EMEA[48]/EMA is more closely tied to the mission statements for the (original, agencified) NAs in the 1980s, 1990s, and beyond, born out of neoliberalism and a desire to be more accommodating to industry. This is shown by the

35 DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

36 COMMISSION REGULATION (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

37 COMMISSION REGULATION (EU) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

38 Commission Regulation (EC) No 2141/96 of 7 November 1996 concerning the examination of an application for the transfer of a marketing authorization for a medicinal product falling within the scope of Council Regulation (EC) No 2309/93

39 Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products

40 Commission Regulation (EC) No 658/2007 of 14 June 2007 concerning financial penalties for infringement of certain obligations in connection with marketing authorisations granted under Regulation (EC) No 726/2004 of the European Parliament and of the Council

41 DIRECTIVE 2004/24/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

42 Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004

43 REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004

44 Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products

45 REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products

46 DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use

47 DIRECTIVE 2012/26/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance

48 As it was formerly known

circumstances of its original creation as the EMEA, the preamble to the 1993 regulation, and the current mission statement given on the EMA website. These indicate that - notwithstanding that the overall aim of the EU legal framework on pharmaceuticals being to ensure a high level of protection of human health – the purpose of establishing the EMA was to assist industry and harmonise the internal market in pharmaceuticals.

1.3.4 The EMA and the Centralised Procedure

The EMA currently undertakes several major tasks:[49] 1) facilitating development and access to medicines; 2) evaluating applications for marketing authorisation; 3) monitoring the safety of medicines over their life cycle (pharmacovigilance); and 4) providing information to healthcare professionals and patients.

Under 2) above, both a centralised and a decentralised market approvals procedure exist.[50] In the latter case a system of mutual recognition is in place whereby all EUMS must accept the determination made by the agency of one EUMS. In the former, all EUMS must accept the approval issued by the Commission which is in turn based upon an opinion from the EMA. The centralised procedure is mandatory for biotechnology and other high-tech products, as well as drugs for specified diseases such as cancer, AIDS, and diabetes. In practice this means that most therapeutically novel drugs in the EU are granted approval through the centralised procedure,[51] however, there are nuances in this process. The EMA Committee on Medical Products for Human Use ('CMPH') relies on a network of experts chosen from the NAs. In reality, the expert evaluation is done at these agencies where they act as rapporteurs.[52]

On the functioning of the centralised procedure (according to Gehring)[53] once a pharmaceutical company producer has submitted its application to the EMA, the CMPH *"elaborates"* a scientific opinion on the product, and this is done through the 'rapporteur' system (see below). Using the scientific opinion, the Commission makes a decision proposal, which is then passed back to the CMPH which takes a decision. On the CMPH all EUMS are represented through a nominations system. Where there is a conflict between the CMPH and the Commission the decision is referred to the Council. The decision, once taken, is formally a decision of the Commission and thus the Commission and not the EMA is legally accountable

49 https://www.ema.europa.eu/en/about-us/what-we-do
50 https://www.ema.europa.eu/
51 Ibid.
52 See Mossialos (2005).
53 Gehring, Thomas, and Sebastian Krapohl. "Supranational regulatory agencies between independence and control: the EMEA and the authorization of pharmaceuticals in the European Single Market." Journal of European Public Policy 14, no. 2 (2007): 208-226.

for it.[54] According to Curto[55] the scientific committees, including the CMPH , are all composed of members who are appointed by the NAs for three-year renewable periods. In terms of the rapporteur system for scientific assessment (marketing approvals – licensing), the CMPH nominates one member to lead each scientific assessment as the rapporteur, and another member to act as co-rapporteur (an independent control). The selected members use the facilities of their 'home' NA to undertake the assessment. The EMA pays the selected members' NA for the scientific assessment work undertaken out of the user fees which it receives from industry. Industry actors (sponsoring firms) are not allowed to choose a rapporteur, they can easily influence the decision of which NA will act as rapporteur by, for example, their choice for the setting of clinical trials. In making decisions on its scientific recommendations the CMPH acts by consensus – where no full consensus is reached a majority position may be taken but dissenting opinions are published.[56]

The EMA Structure and Organisation

The EMA has its own budget, employees, and director. It had 103 employees in 1995, by 2017 had 775 and by 2021 it had 897.[57] In 2015 it had a budget of 304m EUR. In 2020 its budget was 358.1m EUR. Its current Executive Director (at the time of writing) is Emer Cooke from Ireland, and its management board chairperson is Christa Wirthumer-Hoche from Austria. The EMA budget comes mostly from industry paid user fees: 83% in 2015[58] compared to 45% for the FDA. In 2015 around 40% of its total expenditure was payments to the NAs for undertaking scientific assessments under the rapporteur system. Its staff have overwhelmingly scientific backgrounds and earn bureaucratic rather than political salaries averaging around 134,000 EUR per year in 2017. It also has a secretariat, a management board, seven scientific committees and several scientific working parties. The scientific committees are: (1) Human medicinal products (CMPH); (2) Veterinary medicinal products; (3) Herbal medicinal products; (4) Orphan drugs; (5) Paediatrics; (6) Advanced therapies; and (7) Pharmacovigilance risk assessment. The secretariat is organised into five units: the directorate, Human Medicines Development and Evaluation, Patient Health Protection, Veterinary Medicines and Product Data Management and Information and Communications Technology and Administration.

The EMA management board exercises administrative oversight over the EMA. It governs the EMA and the EMA is, in theory, primarily accountable to it. It contains one representative

54 According to Gehring, paraphrasing Tsebelis *"the agency appears to enjoy a comparatively weak formal status within the procedure. Since it is merely assigned the task of evaluating applications for the authorization of pharmaceuticals and of recommending decisions, it might appear to be a somewhat oversized scientific advisory committee fulfilling the function of a conditional agenda-setter in collaboration with the Commission."* Gehring, Thomas, and Sebastian Krapohl. "Supranational regulatory agencies between independence and control: the EMEA and the authorization of pharmaceuticals in the European Single Market." Journal of European Public Policy 14, no. 2 (2007): 208-226. Tsebelis, George. "The power of the European Parliament as a conditional agenda setter." *American Political Science Review* (1994): 128-142.

55 Curto, Alessandro, Katelijne van de Vooren, and Livio Garattini. "Market approval for drugs in the EU: time to change direction?." (2017): 933-936.

56 According to Barbieri, *"the Commission receives the final technical decision of the EMA on the approval of medicines, it verifies the fairness of the administrative procedures and gives formal authorisation to the commercialisation of the products."* Barbieri, Dario, and Edoardo Ongaro. "EU agencies: what is common and what is distinctive compared with national-level public agencies." *International Review of Administrative Sciences* 74, no. 3 (2008): 395-420 at pg. 398.

57 https://en.wikipedia.org/wiki/European_Medicines_Agency

58 Curto, van de Vooren and Garattini (2017).

from each of the EUMS, two from the Commission, two from the European Parliament ('EP'), two representatives from patient organisations, one representative from doctors' organisations and one representative from veterinarian organisations as well as one non-voting observer each for the three European Economic Area ('EEA') countries: Iceland, Liechtenstein, and Norway. It approves the budget and plans and selects the Executive Director. The Executive Director in turn proposes the budget and the annual working program. According to Barbieri[59] the EMA was originally structured underneath the Directorate General ('DG') Enterprise and Industry of the Commission.[60] In 2009 the DG Health and Food Safety[61] took charge of the EMA and it has remained under this DG ever since.[62]

1.3.5 Relationship between the EMA and the NAs in the Centralised Procedure

According to the EMA website[63] and other sources[64] *"the EMA works closely with the national competent authorities"* of the EUMS. It also states that *"the national competent authorities (the NAs)… supply thousands of European experts who serve as members of the Agency's scientific committees, working parties or in assessment teams supporting their members."* In addition, there also exists the 'Heads of Medicines Agencies Board' ('HMA'), separate from but closely related to the EMA which *"is a network of the heads of the (NAs which)… works to foster an effective and efficient European medicines regulatory system."* According to the HMA website[65] *"the HMA cooperates with the EMA and the European Commission in the operation of the European medicines regulatory network and it is a unique model for cooperation and worksharing on statutory as well as voluntary regulatory activities."* The HMA *"addresses key strategic issues for the network, such as exchange of information, IT developments and sharing of best practices; focuses on the development, coordination and consistency of the European medicines regulatory system; ensures the most effective and efficient use of resources across the network. This includes developing and overseeing arrangements for work-sharing; and coordinates the mutual recognition and decentralised procedures."*

It is argued here that the EMA –in the operation of the centralised licensing procedure (the only procedure I look at in detail) - *is* the NAs. The members of the CMPH are recruited from the NAs, although they act on that committee in a personal capacity rather than strictly as

59 Barbieri and Ongaro (2008).
60 https://www.outsourcing-pharma.com/Article/2014/09/17/Moving-EMA-to-DG-Enterprise-will-increase-risk-to-patients-says-NGO
61 Until 2014 known as the DG for Health and Consumers (DG 'SANCO').
62 Despite suggestions in 2014 by EC President Elect Jean Claude Juncker it should move back to DG Enterprise and Industry. Prior to the introduction of the management board the EMA (EMEA) was governed by the old 'comitology' process at the Commission.
63 https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human
64https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf
65 https://www.hma.eu/

representatives of the NAs. Also considering the input of the HMA board, the influence of the NAs is very strong within the EMA and the centralised procedure. When the comitology procedure was ended and a management board for the EMA was introduced, this was done for the purpose of diminishing partisan EUMS interests which had dominated decision making at the CMPH. Arguably, however, the effect was to transfer this influence from the ministers of the EUMS, to their NAs which – ostensibly – operate at arms-length from their health ministries, but which in reality are closely tied to them.

So to what extent is decision making at the EMA (CMPH) now separate from the NAs and the health ministries of the EUMS? According to Gehring and Kraphol[66] the rapporteur system, in which scientific opinions are elaborated by an institutionalised network of experts from the EUMS NAs *"implies that a draft opinion is scrutinised from the perspective of a variety of national regulatory cultures before being adopted, or amended, so that decisions agreed upon within the (CMPH) are acceptable from the perspectives of at least the majority of domestic regulatory agencies."* To be clear, in the rapporteur system, whilst it is the individual member of the CMPH (and the additional control co-rapporteur) who are assigned the task of the scientific evaluation, they may and are expected to use their own NA to process the (on average) 250,000 pages of the submitted dossier on a licensing application. The NAs are then renumerated for use of these resources out of the EMA budget which – as stated above – comes in 4/5 from user fees paid by industry. In reality[67] therefore, the centralised system is composed of the NA's[68] working together with – in the case of any one given application – one NA taking the lead.[69] In this case, the role of EMA itself does not seem to add much to the role of the rapporteur NA.

It is certain NA's - including the Swedish, German, (formerly) UK, Dutch and French agencies – which do most of the work as rapporteur agencies for the EMA. The most successful of those agencies have been criticised for their taking of user fees from industry.[70] They take these both at the national level for national licensing and by payment from the EMA at the European level for their efforts as rapporteurs. The partisan interests of the EUMS under the comitology procedure have thus been replaced potentially by the financial or bureaucratic interests of the NAs (and their officers) since the introduction of the management board. In addition, given that the NAs in the EUMS are directly accountable to the health ministry in each case, the influence of EUMS ministers over the European pharmaceuticals regulatory system may not have changed a great deal at all, since the adoption of a management board. Furthermore, the opportunities presented at the national EUMS level for industry capture of agencies is not greatly insulated against at the EMA where the centralised system is used. Whilst sponsoring firms cannot pick a rapporteur NA they can tacitly influence the CMPH

66 Gehring and Krapohl (2007).

67 Dehousse, Renaud. "Regulation by networks in the European Community: the role of European agencies." *Journal of European public policy* 4, no. 2 (1997): 246-261.

68 Eberlein, Burkard, and Edgar Grande. "Beyond delegation: transnational regulatory regimes and the EU regulatory state." *Journal of European Public Policy* 12, no. 1 (2005): 89-112.

69 Majone, Giandomenico. "The agency model: The growth of regulation and regulatory institutions in the European Union." *Eipascope* 1997, no. 3 (1997): 1-6.

70 See for the Swedish agency: https://www.riksrevisionen.se/download/ 18.78ae827d1605526e94b2dbf8/ 1518435509241/ RiR_2016_9_LAKEM_ANPASSAD.pdf And for the UK agency: https://publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf and for the Austrian agency https://www.rechnungshof.gv.at/rh/home/home/Bundesamt_Sicherheit_Gesundheitswesen_AGES.pdf

choice of rapporteur by e.g. the location of the clinical trials which form the basis of the dossier submitted to the EMA. I build upon these points below in Section 1.5 Key Characteristics of the National Agencies in the EUMS and Section 1.6 Key Characteristics of the European Medicines Agency1.6 Key Characteristics of the European Medicines Agency where I consider key characteristics of the NAs and the EMA. First, I do this for the FDA.

1.4 Key Characteristics of the Food and Drug Administration

In this Section I build upon the factual and historical information provided above in Section 1.2 Overview, History and Analysis of Pharmaceutical Regulation in the US and develop the analytical points first raised there. In the following sections I seek to characterise the FDA, the NAs, and the EMA, respectively. I am characterising their behaviour as agencies, by drawing upon the information set out in the sections above. The purpose of doing this is to provide a reference in Chapters Two, Three and Four, where I discuss the behaviour of these agencies in relation to private interest explanations for regulatory divergence. These characterisations further become relevant in Chapters Five and Six, where I say that the behaviour and practices of the agencies disclose institutions and institutional logics present in those agencies which can be analysed using typologies or dimensions of culture. To summarise, the three key characteristics of the FDA which I have identified are set out below in Table 4.

Table 4 Key Characteristics of the FDA

FDA
'Direct to Consumer Accountability'
Relative Resistance to Industry Influence
Politicised Science

1.4.1 Direct to Consumer Accountability

Busuioc and Groenleer adopt a definition of accountability taken from Bovens,[1] *"a relationship between an actor and a forum, in which the actor has the obligation to explain and justify his or her conduct, the forum can pose questions and pass judgment, and the actor may face consequences."* In this case the forum is Congress and the actor is the FDA. But, Congress represents (and is itself accountable to) a much wider forum – all US consumers. The media interest in Congressional hearings which involve the FDA effectively makes the entire body of US consumers the forum whilst Congressmen act as their mouthpiece.[2] Busuioc

1 Bovens, Mark. "Analysing and assessing accountability: A conceptual framework 1." *European law journal* 13, no. 4 (2007): 447-468 at 450

2 When I say 'direct to consumer accountability' I mean the opposite of accountability to a specific superior. Say that the President were the forum, and that the President privately held the FDA accountable and she, in turn, was accountable to all US consumers. That would not be 'direct to consumer accountability' for the FDA. What makes it *direct*, is the transparency and the media coverage. Congress knows that viewers watch not only the responses of the FDA but also the questions asked by the Congressmen, and so Congress asks the same questions asked by the media reflecting the views of consumers.

and Groenleer further distinguish *de jure* and *de facto* accountability[3] *"De jure accountability refers to accountability arrangements as provided for by formal design. De facto accountability refers to practices of accountability and more explicitly, to how the various formal arrangements provided by design operate and are used in practice in the interaction between the actor and the forum, below or above formal requirements."*[4] *De jure* accountability is best exemplified by the rules of procedure governing the Congressional hearings, but direct-to-consumer accountability for the FDA exists *de facto* because (and arguably *mainly*) *because* of media coverage of the Congressional hearings and US consumer interest in those hearings. Below I consider various aspects of de jure accountability of the FDA to the US branches of government before turning finally to de facto direct-to-consumer accountability resulting from media coverage and consumer interest.

FDA Accountability to the Executive

Like the NAs and the EMA, the FDA is not a *fully* independent, autonomous agency like the Central Intelligence Agency ('CIA'),[5] the Environmental Protection Agency ('EPA'), the Federal Communications Commission ('FCC'), and the Federal Trade Commission ('FTC').[6] It is attached to the Department of Health and Human Services ('HHS') - a cabinet level executive branch of the US government. The decisions of the FDA can legally be overridden by the secretary of HHS, a presidential appointee, concerning rulemaking and pharmaceutical product licensing. In addition, the President has authority to block regulations and guidance. The President (and Senate, together) appoints and confirms the FDA commissioner and can remove them. However, having said this, US agencies generally enjoy a higher degree of independence from the US executive than do EU agencies from the EU Commission.[7] In addition to this, the US has the Office of Information and Regulatory Affairs ('OIRA') which is a division within the Office of Management and Budget which itself is within the Executive Office of the President. OIRA was established by executive order (legally, a creature of the executive)[8] and exercises regulatory oversight of draft regulations and guidance. [9]

FDA Accountability to the Legislature

The accountability of the FDA to Congress has been described in detail above. Apart from the very public congressional hearings which regularly hold the FDA to account, in addition Congress provides the FDA with funding by setting the agency's budget (in addition to user fees) and, through legislation, can set the objective legal standards for its decision making,

3 Busuioc, Madalina, and Martijn LP Groenleer. "The theory and practice of EU agency autonomy and accountability: Early day expectations, today's realities and future perspectives." *in: M. Everson, C. Monda and E. Vos (eds.), European Agencies in between Institutions and Member States, Alphen aan den Rijn: Kluwer Law International, Forthcoming* (2013).

4 Busuioc and Groenleer (2013)

5 Central Intelligence Agency (CIA), Environmental Protection Agency (EPA), Federal Communications Commission (FCC) and Federal Trade Commission (FTC).

6 See Breger, Marshall J.; Edles, Gary J. (2015). *Independent Agencies in the United States: Law, Structure, and Politics*. Oxford: Oxford University Press. *ISBN 9780199812127*.

7 Even though they are frequently held to account in a number of ways by the Executive (and the legislature) and control can be exercised, to some extent on an ongoing basis. See Geradin, Damien. "The development of European regulatory agencies: what the EU should learn from American experience." Col. J. Eur. L. 11 (2004): 1.

8 Executive Order 12866 of September 30, 1993.

9 See Wiener, Jonathan B., and Alberto Alemanno. "Comparing regulatory oversight bodies across the Atlantic: The office of information and regulatory affairs in the US and the Impact Assessment Board in the EU." (2010).

enforceable through the courts. This includes the Administrative Procedures Act which prescribes transparent procedures applicable to all US agencies. It can also pass legislation which directly changes the work of the agency. The FDA is empowered by Congress to make secondary legislation (regulations) as set forth in the primary legislation of the FDCA 1938. These regulations have the full force of law. Albeit they are reviewable by OIRA, and Congress retains the power to change the primary legislation and the courts can determine whether the making of the secondary legislation falls outside the exact powers conferred on the FDA by the primary legislation - the FDCA 1932 (as amended from time to time). The FDA therefore has discretionary powers under the enabling legislation, unlike the EMA.

Whilst the EMA and its accountability to various actors is considered at length below, it helps to point out, now, the contrast between the EU and the US on the issue of the power to make secondary legislation. In EU law, the 'Meroni doctrine' which arose in response to the perceived democratic deficit states that the community institutions cannot delegate the powers conferred upon them by the treaty to bodies having their own legal personality except in so far as this is *"limited to implementing powers clearly defined and entirely supervised by the delegating institution on the basis of specific and objective criteria."* In other words, discretionary powers cannot be delegated *"involving a margin of political judgment"* without amendment of the Treaty. This decision has been referred to for decades since 1958 relegating EU agencies (once they arose from the 1990s onwards) to *"the status of internal bodies in the institutional architecture."* This effectively gives the EMA a much weaker (secondary) law-making status vis a vis the Council and the EP than does the FDA vis a vis Congress. The Meroni doctrine also effectively empowers the Court of Justice of the European Union ('CJEU') to substantively review the decision-making processes of the EMA against objective standards. As argued by Gehring and Kraphol this means that the non-scientific actors involved in the EMA's decision making find they have no room for strategic maneuverer and the outcome is precisely what was envisaged by the Meroni doctrine: removing any element of politics from the EMA's decision making. By being permitted to promulgate regulations including discretionary powers conferred on it, the FDA is expressly opened to politicised decision making. It should be noted that the Meroni doctrine is viewed by many as weakened in recent decades since the process of agencification began.[10]

FDA Accountability to the Courts

In addition, the US courts monitor the actions of the FDA and serve as a check on the agency's authority. In the US, legal standards relating to both procedural and substantive aspects of agency decision making are spelled out in legal rules[11] that are accessible to the public.

10 See: Judgment of the Court of 13 June 1958. Meroni & Co., Industrie Metallurgiche, SpA v High Authority of the European Coal and Steel Community. Case 9-56 and judgment of the Court of 13 June 1958. Meroni & Co., Industrie Metallurgiche, società in accomandita semplice v High Authority of the European Coal and Steel Community. Case 10-56. Renaud Dehousse: *European governance in search of legitimacy: the need for a process-based approach*. In "Governance in the EU". Ed. European Commission, Luxembourg, 2001, p. 185-205 https://www.jeanmonnetprogram.org/archive/papers/01/010301-04.html. Gehring, Thomas, and Sebastian Krapohl. "Supranational regulatory agencies between independence and control: the EMEA and the authorization of pharmaceuticals in the European Single Market." Journal of European Public Policy 14, no. 2 (2007): 208-226. Chamon, Merijn. "The empowerment of agencies under the Meroni doctrine and article 114 Tfeu: comment on United Kingdom v. Parliament and Council (short-selling) and the proposed single resolution mechanism." *European Law Review* 39, no. 3 (2014): 380-403.

11 The Administrative Procedure Act, Pub.L. 79–404, 60 Stat. 237, enacted June 11, 1946.

Moreover, the US courts take a relatively relaxed approach to standing requirements. The result is that both industry actors and members of the public have the capacity to challenge US regulatory agencies through the US courts, and the courts have shown that they are prepared to quash agency decisions.[12] As the agency is already subject to being overridden by the secretary of the HHS and the President directly, the Courts act as backup mechanism where the President/HSS has failed to act or agrees with the agency.[13]

FDA De Facto Direct to Consumer Accountability through the Media via Congress

The FDA is very sensitive to media coverage. According to Carpenter*, "FDA officials want good press (or no bad press) in the news media but also want to preserve a reputation for scientific rigor among academics and medical professionals."* Both are important.[14]

Carpenter argues that the FDA's primary goal has always been – and remains – to keep US consumers satisfied by generally exercising caution in licensing. This is something which saves its officials from negative coverage following Congressional hearings. Indeed, the FDA seems to have achieved this well since the 1960s when it was given licensing powers, and Carpenter remarked in 2004 that "*…as gauged by public opinion polls, the FDA remains one of the most popular agencies in government, regularly securing 70 percent or greater "approval" of its performance among sampled respondents."* In a dilemma for the FDA, however, disease-specific consumer groups also make use of media coverage to advance their own agenda, one often opposite to the main body of US consumers seeking caution. This was the case with AIDS activists in the 1980s. In 2000 Carpenter found more than 3,100 of these disease-specific groups present and politically active in the US and noted that these exploded in number in the 1970s and 1980s. These groups – being smaller and better organised, with a narrower agenda – are often able to obtain media attention in different ways. For example, by protest marches and media appearances on a specific issue at a specific moment in time (e.g., where a new drug is under review, and it is felt that this is taking too long). Carpenter argues that the success of these disease specific groups is contingent upon their ability to gain media coverage of the plight of those suffering without access to drugs, and thus often they will be more successful when the disease in question has qualities which capture widespread public sympathy. He points out the difference between asthma and arthritis. The former causes a

12 See Busuoic, Madalina. "Accountability, control and independence: the case of European agencies." European Law Journal 15, no. 5 (2009): 599-615.

13 Part of the reason why they are able to quash the decisions is because those decisions are openly political in some respects, and because the FDA has power to exercise its own discretion. In addition, many judges in the US are elected, so the Courts too can represent 'indirect' to consumer accountability, albeit that this normally has to take the form of a legal challenge based on the formal legal accountability mechanisms outlined above: i.e. failure to adhere to the Administrative Procedures Act, failure to exercise discretion reasonably, or acting ultra vires – i.e. outside of the powers conferred on it by the FDCA 1938.

14 Carpenter, Daniel P. "Groups, the media, agency waiting costs, and FDA drug approval." American Journal of Political Science (2002). This direct-to-consumer accountability interacts with the mechanisms of 'indirect' to consumer accountability above, which I have explained are ways in which ordinary consumers (and to a lesser extent industry) can seek to pressure the FDA. They can do it by pressuring Congressmen who in turn hold hearings, or reduce the FDA budget etc. Or they can pressure the President, who can review the decisions, block them, or remove (with the Senate) the head of the FDA. Where all else fails – i.e., Congress or the President won't act, then Consumers (or industry) can use the courts, but then they stick to the formal legal accountability mechanisms (i.e. a strict legal basis for the challenge) instead of a broad political one.

death rate nine time higher than the latter yet the media – according to his analysis – mentions arthritis nearly twice as often as it does asthma.[15]

The tactics of the AIDS activists in the 1980s were sufficient to win widespread public attention and support using the media and, in turn, to force the hand of the FDA to introduce expedited approval. Where these groups can succeed in doing this, the FDA is responsive.[16] An additional complicating factor is and was that during the 1960s-1980s when the relationship of the FDA was most opposed to industry, and when its budget (albeit limited) was funded by Congress and not yet by industry user-fees, USPI began to work with the disease specific consumer groups in order to seek expedited approval of certain products. Carpenter says,[17] "*Firms themselves have in the past six to eight years created, fostered, and subsidized a number of patient advocacy groups; and… firms regularly seek alliances with patient advocates in pressing the case for priority status, accelerated approval, or simply approval before the FDA. The second of these is a much more common, and much more successful, strategy. Put differently, politically strategic pharmaceutical firms know that industry lobbying is less successful than patient advocacy, and their regulatory behavior adapts to this fact."* Completing his analysis of the responsiveness of the FDA to consumers Carpenter conducted an empirical duration analysis of drug review times using a measure of the wealth of disease specific advocacy groups, a measure of the amount of news coverage that the disease in question received as well as a set of controls, as explanatory variables, concluding that "*there is considerable evidence—from anecdote, from factual inspection of the FDA's behavior, and from statistical analyses of drug review times—that the political organization and newsworthiness of patients is negatively associated with drug review times (that is, it causes these review times to get shorter).*"

1.4.2 Relative Resistance to Industry Influence

Having identified that the FDA is primarily accountable to US consumers, I have also noted how industry may exert influence through consumers. This might happen through sponsorship of, or alliance with, disease specific advocacy groups, although Carpenter notes[18] that in the US it is much more common for ad-hoc networking to take place between industry and such consumer groups, rather than these groups being a front for industry lobbying.[19] In addition to this, since the enactment of PDUFA in 1992, user fees have considerably reduced review times. Carpenter states that this has led to a decrease in new drug licensing times by setting, *"an incentive structure whereby the legislation is renewed only if the FDA meets specified performance goals."*[20] In this sense, PDUFA seems to have made the FDA more responsive to industry. But does this mean that the FDA has become more responsive to

15 Carpenter (2004) at pg. 56.

16 Certainly, the incentives of the FDA have been changed so that it has become more concerned about the negative coverage that would follow from Type II errors, rebalancing this with its already present fear of negative coverage from Type I errors. See Chapter Two for more detail.

17 Carpenter (2004) at pg. 56-59.

18 Carpenter (2004) at pg. 56.

19 As has been argued to be the case in the EU and in Australia.

20 Carpenter (2004) at pg. 59

industry *than* to consumers towards and since the turn of the century? It is difficult to argue that this is the case because the essential accountability structure described above has not changed. It is not true to say that the FDA in now 'in the pocket' of USPI since PDUFA. Barber[21] notes, for example, that industry lobbying efforts (directly, or through networking with disease specific advocacy groups) tend to lead *either* to a shorter review time, or to a broader range of indications[22] being licensed for the sponsored product. I.e., it appears that even where PDUFA forces the FDA to meet more stringent performance standards in review times, the agency's instinct to avoid negative coverage for the wider consumer group (demanding caution) means that it will limit the approved range of indications correspondingly, thus retaining its tendency to be cautious overall.

Moreover, USPI in its lobbying efforts does not seem to either heavily target the FDA directly or to focus on the issue of licensing times. A study undertaken by Wouters[23] in 2018 concludes that USPI directs most of its efforts at the State (rather than Federal) level and at legislatures (rather than agencies). USPI itself – through its lobby the Pharmaceutical Research and Manufacturers of America ('PhRMA') - did not spend as much on lobbying between 1999 and 2018 (422m USD) as did US doctors through the AMA (462m USD) or US hospitals through the American Hospital Association ('AHA') (426m). The sum expended was mainly spent on campaign contributions to State and Federal legislature electoral candidates: *"Federal campaign contributions were targeted at senior legislators serving on congressional committees that draft health care bills and at presidential candidates from both major political parties. At the state level, the industry focused its efforts on opposing major drug cost-containment measures."* Whilst it is clear, therefore, that USPI seeks to influence legislative outcomes, the focus appears to be more upon state level cost containment measures (for example generic substitution) rather than upon review times for licensing. Potentially, it is the case that USPI cannot influence the FDA to both expedite review times and expand the scope of indications for sponsored drugs, and its best efforts to do so are found in networking (only) with disease specific advocacy groups. Thus, combining these findings with the observations made about direct-to-consumer accountability - resistance to industry influence is a key characteristic of the FDA, at least relative to the NAs and EMA.

1.4.3 Politicised Science

Both resulting from and causing direct-to-consumer accountability is the fact that the FDA is a highly politicised agency. Clearly it does not reject science, and it has a world-leading scientific reputation to uphold. However, relative to the approach of the EMA and the NAs in Europe, the FDA does not exclude politics in favour of science. Direct to consumer accountability leaves the FDA in a position where it cannot avoid political scrutiny and thus

21 Barber IV, Benjamin, and Luis Diestre. "Pushing for speed or scope? Pharmaceutical lobbying and Food and Drug Administration drug review." *Strategic Management Journal* 40, no. 8 (2019): 1194-1218.

22 Diseases for which the product may be marketed to treat

23 Wouters, Olivier J. "Lobbying expenditures and campaign contributions by the pharmaceutical and health product industry in the United States, 1999-2018." *JAMA internal medicine* 180, no. 5 (2020): 688-697

cannot avoid its decision making becoming the subject of political debate. The effect of this is seen in aspects of the history of the FDA and US pharmaceuticals regulation set out above.

Transparency and Public Participation

The scholarly consensus is that US agencies are receptive to the views of consumers and public participation is greater overall compared to in European agencies (generally).[24] This makes the FDA decision-making process accessible to ordinary consumers. How does this interact with the role of science at the FDA? Firstly, the more 'voice' is given to consumers, the less 'voice' is available for experts. Again, the scholarly consensus is that US regulatory agencies rely less upon the appraisals of experts than agencies in the EU.[25] Conversely, it is observed the FDA involves US consumers in decision-making on an ad-hoc basis, and that it does so regularly, and takes that input seriously. Whereas European agencies (including the EMA) involve consumers in decision making in a highly structured way, provided for in laws and rules of procedure, with the result that consumer views have less impact. I develop this point further below in Section 1.6 Key Characteristics of the European Medicines Agency.

Qualitative v Quantitative Risk Assessment

Comparing the approach of the EMA to the FDA in decision-making, Angelis and Phillips[26] comment in 2021 upon the recent move to introduce a quantitative benefit-risk framework developed by the FDA, *"intended to improve the clarity and consistency in communicating the reasoning behind the FDA's decisions"* the use of which is, however, restricted *"within the current* (benefit-risk framework) *that is purely qualitative."* They point out that *"by contrast, European regulators and researchers have been long exploring the use of quantitative decision analysis approaches for evaluating drug benefit–risk balance."*[27] Quantitative measures for decision making are less open to politicisation than are qualitative measures. Qualitative factors allow ethical or political viewpoints to affect the decision making of committees at the FDA, because, *"in contrast to quantitative decision analysis, qualitative approaches do not allow for the quantification of values, uncertainties and trade-offs, nor their aggregation."*[28] By restricting itself to a qualitative framework, the FDA ensures that its analyses lead it towards an (albeit limited) number of different potential actions, and the choice between those actions is a political choice to be made. Where a purely quantitative framework is used for analysis and decision-making – argue Angelis and Philips – often there is only one possible 'correct' decision that could be made following analysis.

24 See Hofstede, Geert. Culture's consequences: International differences in work-related values. Vol. 5. Sage, 1984. See also, Mostert, Erik. "The challenge of public participation." Water policy 5, no. 2 (2003): 179-197.
25 See Wiener, Jonathan B., and Alberto Alemanno. "Comparing regulatory oversight bodies across the Atlantic: The office of information and regulatory affairs in the US and the Impact Assessment Board in the EU." (2010).
26 Angelis, Aris, and Lawrence D. Phillips. "Advancing structured decision-making in drug regulation at the FDA and EMA." *British Journal of Clinical Pharmacology* 87, no. 2 (2021): 395-405.
27 Ibid.
28 Angelis and Phillips (2021) at 396.

Science v Politics or Science and Politics

Recently in 2016, under the Trump administration, the 21st Century Cures Act was signed into law, which[29] *"encouraged greater use by the FDA of "real-world" evidence not obtained through randomized controlled trials."* This is a departure from scientific convention which could lead to the FDA process becoming more political and less scientific: because adherence to certain conventions is what defines the scientific method. The 21st Century Cures Act *"prompted concerns"* amongst some in the US that the FDA was moving even further away from a scientific paradigm for decision making. However, it is not assumed here that a pharmaceuticals regulatory agency should or could be 100% scientific in its approach. It may well be that the EMA and the NAs are unduly apolitical. Commenting upon scrutiny of the FDA during the COVID 19 pandemic, and suggestions that it be made a fully independent agency in order to avoid political influence, Lynch et al[30] observe the unavoidably political nature of the FDA's position, they say: *"…calls to 'follow the science' and avoid 'politicizing' the FDA are rooted in legitimate concerns, but in the context of this pandemic, the relationship among science, values and politics has often been oversimplified."* They argue that the FDA cannot make decisions *"on the basis of science alone"* and politics has a role to play. Moreover, they recognise what I have stated above, that by granting pre-eminence to the role of science, that would come at the cost of democratic accountability.[31]

The FDA as Institutionally Political

I say that the politicisation of science is a key institutional feature of the FDA and that it results from direct to consumer accountability. Direct to consumer accountability means that use of purely quantitative criteria for decision making at the FDA would make that decision making process politically inaccessible to consumers. This is something which the FDA does not want. Direct to consumer accountability means the FDA not only seeks to avoid negative media coverage, but actively seeks positive media coverage. Consumers would not watch the FDA congressional hearings nor would broadcast media report these if the discussions were entirely scientific, quantitative, and technical. The FDA commissioner would not be able to develop a strong public personality if s/he were to adopt a purely scientific approach in his/her responses to Congressional questions. Richard Cooper argues[32] that the agency's enabling legislation requires FDA personnel *"to apply science, ethics, and/or economics as they understand them."* He argues that personal, and possibly ideologically laden views of science, ethics and/or economics are liable to influence the decision making of FDA officials in the same way as *"ideology, bureaucratic politics, or even personal ambition"*. It also follows from this that where the FDA may be swayed by public commentators in the academic and scientific community, the agency will be most responsive to those scientists who are most well-known and highly regarded by consumers (not necessarily by other scientists). Thus Carpenter[33] quotes Alison Lawton, a long-time FDA observer, who says, *"the FDA is very*

29 Schwartz, Jason L. "Real-world evidence, public participation, and the FDA." *Hastings Center Report* 47, no. 6 (2017): 7-8 at pg. 7.

30 Lynch, Holly Fernandez, Steven Joffe, and Matthew S. McCoy. "The limits of acceptable political influence over the FDA." *Nature medicine* 27, no. 2 (2021): 188-190.

31 Lynch, Joffe, and McCoy (2021) at pg. 189.

32 Cooper, Richard M. "Science, Ethics and Economics in FDA Decision-Making: The Legal Framework." *Food & Drug LJ* 61 (2006): 799.

33 Carpenter (2004) at pg. 54.

responsive to what I would call 'opinion leaders' in the scientific and medical communities. It cares very much about what these people think as to how the agency is doing."[34]

Summary and Conclusions: FDA

The key, unique aspect of the FDA as an organisation, it is submitted, is direct to consumer accountability, which takes place through the media. This implies both that consumers are interested in what the FDA does, and that the FDA wants to avoid negative media coverage and seeks positive media coverage. Direct to consumer accountability interacts with mechanisms of 'indirect' to consumer accountability through the actions of Congress, the Executive and (to a lesser extent) the Courts, which in turn act at the prompting of (normally) consumers. Instances of these indirect to consumer accountability mechanisms also represent the major opportunities for the FDA to receive positive media coverage. Thus, in order to ensure it can receive positive feedback (i.e., that consumers remain engaged) transparency and public participation are ensured by the FDA. This includes the use of an accessible (qualitative) language of decision making and account-giving.

The existence of direct to consumer accountability has the result that the FDA is relatively resistant to industry influence when compared with the NAs and the EMA. Key to understanding this is to acknowledge that in the absence of direct to consumer accountability, industry capture would occur by default. I expand on this more below in relation to the EMA and the NAs. The fact of user fees (which exist for many NAs, for the EMA as well as for the FDA), added to the fact that it is industry which collects and presents the scientific data relevant for licensing decisions, results in a situation whereby if there were no incentives set to be cautious (because of direct to consumer accountability) then the agency would always accommodate industry by default. This happens even where the agency decision making is undertaken according to only scientific and quantitative criteria. Instead, for the FDA, direct to consumer accountability means that the FDA is first and foremost responsive to consumers. Moreover, if industry wishes to influence pharmaceutical regulation it finds it difficult to do this directly by pressuring the FDA but must instead ally with disease specific consumer groups, or lobby State and Federal legislatures for changes to primary legislation. Finally, the institutional politicisation of science at the FDA enables direct-to-consumer accountability – by making decision making accessible to consumers - and thus avoids industry capture by default.

34 Alison Lawton, vice-president for regulatory affairs, Genzyme Corporation, interview, 11 June 2003.

1.5 Key Characteristics of the National Agencies in the EUMS

The NAs, I say, have three characteristics which distinguish them from the FDA. In addition, below, where I consider the EU level, one of those characteristics is enhanced further. The first characteristic is what I call 'double insulation'. The creation of the NAs allowed the EUMS health ministers to avoid accountability to domestic consumers for assisting their *national* pharmaceutical industries, particularly if a product safety scandal emerged. These health ministers were insulated in two ways. The first is that they could claim that agency bureaucrats, not the ministry itself (and, due to the convention of ministerial responsibility, themselves as the embodiment of that ministry) had been at fault if a safety scandal occurred. The second is that – if the bureaucrats were not demonstrably at fault – the health ministers could say that the disaster leading to the scandal was unavoidable, because all decision making at the agency had been based on science alone, and not politics. Thus, the minister was double-insulated from accountability.[1] The second characteristic – which applies to both the EU level and the EUMS level – is 'capture by default'. Given the ability to charge user-fees, and the fact that the NA and industry between themselves decide on the required scientific data. And, given that industry actors are left to collect that data, then – in the absence of FDA style direct to consumer accountability – the NAs will always accommodate industry 'by default' in their licensing processes. The third characteristic enables the first and makes inevitable the second due to removing the probability of direct to consumer accountability; and it is that (for both the NAs and the EMA) 'science excludes politics': the agencies actively present their decision-making as apolitical. The key characteristics are set out in Table 5 **Key Characteristics of the NAs** below.

Table 5 Key Characteristics of the NAs

NAs
'Double Insulation'
Capture by Default
Science Excludes Politics

1.5.1 Double Insulation

Between the introduction of compulsory premarket licensing in the EUMS and the creation of separate agencies with legal personalities and governance systems, health ministers in the EUMS faced a number of different imperatives which pulled them in different directions on issues of product licensing and price regulation. They had to ensure the safety of all products

1 When I return to the EU level element below, double insulation becomes treble insulation, because now the Minister could blame the EU as well as blaming the NA and science itself.

and therefore should favour slow, cautious licensing. However, they must also ensure the quick availability of new pharmaceutical products to assist consumers suffering from diseases who were being treated under socialised healthcare, and so they should expedite licensing occasionally. Then, they had to assist the national pharmaceutical industry which provided employment and tax revenue, and so they needed to keep the licensing system low-risk for those firms. They also needed to lower the cost of pharmaceutical products to the public purse by keeping the licensing process low-cost for industry users. They needed to (partly) fund the administration of the licensing process directly out of the public purse, which set incentives to keep the process fast.[2] However, if fast licensing resulted in products being licensed which caused injuries to consumers, then the public purse would bear the cost of this through providing treatment to the injured, particularly in the context of European socialised healthcare.

The ministers had to justify outcomes to consumers (voters) in political terms, in parliaments, under scrutiny from opposing political parties. The questions put to them in the legislature would be political in nature and would have to be answered in qualitative political language. Under the convention of (individual) ministerial responsibility found in the UK – and even more stringent legislature-executive accountability mechanisms in the other EUMS political systems[3] - ministers (or the government as a whole) bore personal responsibility to the legislature for the actions of their entire department including all civil servants. This meant that in the eyes of ordinary consumers, the minister had direct oversight of everything that happened within his or her department, including the licensing of medicines. Because, in addition, health ministers in the EUMS were often in charge of socialised healthcare systems providing medical care to consumers: in the eyes of consumers, the issue of licensing pharmaceutical products, purchasing them, and providing them to consumers as part of treatment were indistinguishable from each other and, any adverse health outcome (or disaster, or scandal) would ultimately be placed at the feet of the minister. The minister (or government) could not – under parliamentary and constitutional convention - try to place the blame upon civil servants or employed scientists working for the department.

2 Goodman, Clifford. "Medical technology assessment directory: A pilot reference to organizations, assessments, and information resources." (1988).

3 https://en.wikipedia.org/wiki/Individual_ministerial_responsibility: "Individual ministerial responsibility is a constitutional convention in governments using the Westminster System that a cabinet minister bears the ultimate responsibility for the actions of their ministry or department…. This means that a Parliamentary motion for a vote of no confidence is not in order should the actions of an organ of government fail in the proper discharge of its responsibilities. Where there is ministerial responsibility, the accountable minister is expected to take the blame and ultimately resign." Note that this is a feature of the Westminster model of government, and is found most strongly in the UK, Canada, Australia, and New Zealand, but not in the United States. It is a feature of monarchical-cabinet governments, where much of the constitution rests on unwritten conventions. https://www.cbc.ca/news2/background/groupaction/v2fullreport/CISPAA_Vol1_4.pdf. I argue in Chapter Six that relatively individualistic cultures place more focus on personal fault and blame, including in the case of ministers, and thus they are less likely to hold a minister accountable for the actions of a whole department, as the embodiment of that department. By contrast, in relatively hierarchical cultures, the minister is more likely to have to accept responsibility for the whole department, and resign. The UK convention, therefore, is hierarchical relative to the US approach. By contrast, the Continental European approach more often forces the resignation of the whole government based upon the failings of a department underneath one minister, an even more centralised, and hierarchical approach, which is even further removed from the personal fault of a particular minister.

The removal of pharmaceutical product licensing from the ministry itself and the placement of that responsibility within a *separate* agency underneath the ministry would assist the pharmaceutical industry. It would allow the agency to have a close relationship with industry in a way which would not be acceptable in the eyes of consumers if it were between the minister (ministry) and industry directly. The minister could still influence the actions of the agency directly and would still be responsible to Parliament for the actions of the agency. He was, however, further removed from those decisions now than he was before, in the eyes of consumers.[4] This new system enabled the agency (under the minister) to take licensing decisions which balanced the interests of public safety and the interests of the pharmaceutical sector. Prior to this system, the minister was always tempted to satisfy the public first, to keep his job. So now, there was double insulation for the minister if things went wrong: through the existence of the agency itself, and through pleading 'science'. The minister was still responsible, in formal legal terms, but might even keep his job if the public believed that either the agency was at fault or that the disaster or scandal were unavoidable because the relevant decision really was taken under science.

1.5.2 Science Excludes Politics

A key tactic for *achieving* effective double insulation for the health ministers in the EUMS has been to ensure that the use of science at the NAs excludes any room for politics. If the NAs were to appear politicised to EUMS consumers, then those consumers would deny the minister the opportunity to evade political questions by reference to scientific expertise. Agencies and ministries - particularly in the northern EU Member States (hereafter 'NEUMS') - have tried very hard to depoliticise the system of pharmaceuticals regulation. Abraham and Lewis argue that the UK, Swedish, Dutch, and German agencies have been (up to 1998) four of the most successful in this endeavour.[5] They (Abraham and Lewis) describe extensive efforts made at these agencies to separate scientific/technical advisory functions from executive functions. This is mostly done for the sake of appearances in the eyes of consumers, as the executive committee (deciding on the license) will generally always act on the advice of the advisory committee. The old UK agency (the MCA) completely separated these two committees: 1) the Committee on the Safety of Medicines ('UKCSM') and 2) the executive committee of the MCA itself. Yet, the authors observe, the MCA decision never went against the advice of the UKCSM. Moreover, the MCA put heavy emphasis on the input of independent (external) experts to judge the safety and efficacy of products. Similarly in Sweden, the advisory committee is the Board of Drugs ('SVBOD') but the director of the Swedish MPA always took the executive decision on licensing which never contradicted the advice of the SVBOD.

4 This also made it easier for the minister to plead a technical, scientific justification for decisions, and to nominate the appearance of agency scientists or bureaucrats at parliamentary committee hearings instead of himself. The scientists and bureaucrats were permitted to give an impenetrable, technical answer to questions in circumstances where the minister could not.

5 Lewis, Graham, and John Abraham. "Making harmonisation work: the politics of scientific expertise in European medicines regulation." *Science and Public Policy* 25, no. 3 (1998): 155-169 at pg. 165.

This emphasis on the formal separation of advisory and executive functions, and the (British) reliance on external expertise, both serve to make the licensing process appear apolitical in the eyes of EUMS consumers. Consumers do not then form the impression that the minister (or industry actors) influenced the scientific advice or interpretation of the scientific data.

One might argue that it is only through maintaining an agency which – when (rarely) scrutinised - shows impeccable adherence to science, that both the agency and the minister (or perhaps even the government) can survive politically following a safety scandal. In France, for example, after the *Mediator*[6] and *Poly Implant Prothèse*[7] scandals the French health minister wound up AFSSaPS and replaced it with ANSM following a government led inquiry: something which would be unlikely to happen with the FDA given its 115-year history, and the high regard in which US consumers hold it.

1.5.3 Capture by Default

Whilst significant efforts have been made to formally separate decision making and advisory functions, and to ensure that the work of the NAs appears to be done only in accordance with science, there is industry capture 'by default'. This is because there is a lack of direct to consumer accountability, and because the data provided as the basis for scientific opinions (informing licensing decisions) comes from industry. In addition, user fees paid by industry to the NAs ensure that the NAs work to accommodate industry in the licensing process. The most 'successful' NEUMS NAs generally make large sums from user fees, something criticised in reports regarding the Swedish MPA,[8] the UK MHRA[9] and the Austrian BASG.[10]

Capture by default is assisted greatly by a lack of direct to consumer accountability. That is caused by 1) a lack of transparency and public participation in the decision-making processes of the NAs; and 2) a lack of media coverage of the NAs and their operations, which is mutually reinforcing with a lack of consumer interest in what the NAs are doing (EUMS consumers direct their attention towards the health ministers, and with regard to different issues instead). On the first point, a 2005 report from the UK House of Commons Health Committee[11] and a 2016 report from the Swedish National Audit Office[12] criticised the MHRA and the MPA, respectively, for a lack of transparency. Arthur Daemmrich, comparing the German agency with the FDA,[13] also points to different levels of external political surveillance, higher in the US both from the government and from consumers. The *"more opaque"* German

6 See https://www.bbc.com/news/world-europe-56562909
7 See https://www.imarcresearch.com/blog/pip-breast-implant-scandal
8 https://www.riksrevisionen.se/download/18.78ae827d1605526e94b2dbf8/1518435509241/RiR_2016_9_LAKEM_ANPASSAD.pdf
9 https://publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf
10 https://www.rechnungshof.gv.at/rh/home/home/Bundesamt_Sicherheit_Gesundheitswesen_AGES.pdf
11 https://publications.parliament.uk/pa/cm200405/cmselect/cmhealth/42/42.pdf
12https://www.riksrevisionen.se/download/18.78ae827d1605526e94b2dbf8/1518435509241/RiR_2016_9_LAKEM_ANPASSAD.pdf
13 See Daemmrich, Arthur, and Georg Krücken. "Risk versus risk: decision-making dilemmas of drug regulation in the United States and Germany." Science as Culture 9, no. 4 (2000): 505-534.

institutional structure, he argues, shields the agency from outside criticism. On the second point, in a state with socialised healthcare the health minister become a natural focal point for consumer concerns, and newspapers will sell more copies if they run a front-page picture of a familiar minister than of the unknown director or head of an administrative agency.[14] Moreover, where healthcare decisions are highly decentralised, this can make it difficult for consumer activists to make their voices heard.[15] This is in part due to the limited resources that consumers have to advance their lobbying interests. It makes sense then that consumers in the EUMS will target the obvious candidate – their health ministers - rather than the NAs, and far less the EMA.[16]As a result of the absence of direct to consumer accountability, the NAs are closer to industry, and more accommodating of industry than is the FDA in the US.

Finally, whilst all decisions of the NAs are presented to consumers as based upon (only) science, it is EUPI which ''does the science". None of the NAs have the funding or resources to carry out their own clinical trials. The NAs generally advise industry actors on what data is required, and industry actors return with that data. So long as the submitted dossier meets academic scientific conventions – then the NAs will interpret that data in the way which the sponsoring firm seeks.[17] None of the NAs – unlike the FDA – have the resources to *independently* verify the clinical trials results nor to analyse the data provided to them in any detail. As such, Wiktorowicz et al state that the NAs *"focus on a small… number of critical variables"*[18] compared to the FDA, and require only summaries of randomized controlled trials from industry before making decisions.

Summary and Conclusions: NAs

In conclusion, the NAs have been established in the EUMS (particularly in the NEUMS) to depoliticise the issue of pharmaceutical product licensing and lift political pressure on ministers from both industry and the electorate. That political pressure is partly a result of socialised healthcare systems being the norm in the EUMS. For the same reasons, the NAs lack direct to consumer accountability because they are relatively opaque in their operations, are not the subject of consumer or media attention, and have low levels of public participation in decision-making relative to the FDA. The NA's provide health ministers with the opportunity to avoid taking personal responsibility in the case of safety disasters, as they may simply

14 In the US, without socialised healthcare this is very different. The consumer paid their insurer, the insurer paid for the drug which was produced by a pharmaceutical company. The drug was prescribed by a doctor not employed by the US state. It is difficult to see where the cabinet minister really becomes blameworthy in this connection. Kefauver in 1959-1962 ensured that in this situation the finger of US consumers would be pointed in blame at the pharmaceutical sector, with a corresponding expectation on the commissioner of the FDA personally to protect the public against this.

15 Baggott, Rob, and Rudolf Forster. "Health consumer and patients' organizations in Europe: towards a comparative analysis." *Health expectations* 11, no. 1 (2008): 85-94 at pg. 86.

16 To do so is cheaper and, where the obvious candidate is the minister, generally he or she can affect things domestically wherever the problem has arisen: particularly where his or her department oversees the whole system of socialised healthcare. It is likely then that Europeans will continue to blame the minister, and that the minister will always look for ways to absolve himself from blame using 1) science; 2) where that fails, the agency (e.g. scrapping AFFSAPS) and/or 3) Europe, on which point I expand in the next section.

17 Moreover, because the NAs generally charge user fees, they are effectively being paid by industry to tell industry what is required so that industry can come back with a dossier which will always be rubber stamped by a formally separate but in reality unitary decision maker with the advisory committee.

18 Wiktorowicz, Mary, Kathy Moscou, and Joel Lexchin. "Transnational pharmacogovernance: emergent patterns in the jazz of pharmaceutical policy convergence." *Globalization and health* 14, no. 1 (2018): 1-20 at pg. 5

blame the agency and wind it down - something which could not occur in the US given the affinity between US consumers and the FDA. The NAs assist industry and take user fees for doing so, both of which suit the interest of the health ministers, whilst these can appear to be politically removed from this process. Double insulation from accountability is ensured by designing the agencies so that all decision making appears to consumers to be scientific and politically neutral. The result of this organisational design and the lack of direct to consumer accountability is that industry capture of the agency occurs by default.

Now I turn to the EU level, the EMA and the centralised procedure to show how the objectives of certain health ministers are secured even further by the existence of the EMA and the centralised licensing system – a situation which I call here, 'treble insulation'.

1.6 Key Characteristics of the European Medicines Agency

The key characteristic here is treble insulation. The other two have already been raised in the context of the NAs and will be explained in the context of the EMA more briefly below. Treble insulation refers both to 1) the fact that the EUMS health ministers are further insulated from accountability to their domestic consumers as a result of the centralised procedure, by being able to blame the Commission which 'formally' took the decision; and 2) the fact that the EMA appears to be accountable to no one, in reality, except itself (meaning the CMPH). These characteristics are set out below in Table 6 **Key Characteristics of the EMA**

Table 6 Key Characteristics of the EMA

EMA
'Treble Insulation'
Capture by Default
Science Excludes Politics

1.6.1 Treble Insulation

To assert this characteristic requires me to undertake a detailed analysis of the accountability of the EMA to various actors. At first glance it may seem that the EMA should be most accountable to the Commission (being underneath the Commission). However, its scientific approach means that the most significant accountability mechanism to be found at the EMA is the accountability of a rapporteur NA (represented by its CMPH member) to the other members of the CMPH standing committee. The scientific approach means that neither the Commission nor the Council is likely to ignore a scientific opinion from the CMPH. The EUMS governments represented in the EMA Management Board will find it difficult; a) to understand the scientific advice; or, b) to disagree with their own NA representative on the CMPH who has already endorsed the opinion. The EP has little interest in reviewing, or technical competence to review, that opinion and objective decision-making standards - which the CJEU may hold the EMA to - tend to reinforce the scientific approach of the CMPH. Thus, 'indirect' accountability to EU consumers which might have taken place via the EP, the EUMS governments (represented in the management board) or through the courts is lost to the characteristic of 'science excludes politics.'

As there is not a high level of media coverage of, nor a substantial direct consumer interest in the EMA's scientific decision-making, there is no direct to consumer accountability of the sort found in relation to the FDA in the US. Involvement of EU consumers in the decision-making process of the EMA is superficial, orchestrated top-down by the EU itself rather than a result of grassroots consumer activism and is preoccupied with ensuring that consumer groups involved in decision-making are not mere 'fronts' for EUPI. The effect of the technical, scientific approach at the EMA is that the NAs have all the *de facto* decision-making power

and the centralised system for licensing merely amounts to the actions of one rapporteur NA lightly 'peer-reviewed' by the other 27 (now 26) NAs in the CMPh standing Committee. That NA is normally one of the NEUMS NAs and most frequently the Dutch MEB, the UK MHRA, the Swedish MPA, the French ANSM, the Austrian BASG, or the German BfArM. These agencies are all executive or administrative agencies underneath the health ministries in each of these EUMS, and therefore there is ample opportunity for the health ministers in each EUMS to assist national pharmaceutical industry actors through use of their own NA acting as rapporteur for the CMPH. Now, however, if something were to go wrong from a safety perspective after a license has been granted by the Commission (EMA) using the centralised procedure, not only can the health minister claim that the harm was unavoidable as the decision was made on the basis of science only, and alternatively blame the rapporteur NA if there is scope to do so (double insulation); now, he can also blame the EU Commission, which formally made the decision (treble insulation).

The EU Commission and Council

In theory, the accountability of the EMA as an agency to the Commission and the EUMS governments is high and should be higher than that of the accountability of the FDA to HHS and the President given the existence of the *Meroni* doctrine in the EU.[1] Prior to the EU 'agencification' process, the comitology procedure[2] ruled Commission decision-making within the various DGs. Thus, before the creation of the EMEA in 1995, the partisan interests of the EUMS governments[3] in Community pharmaceuticals policy – as expressed in committee - were strong, and the process was less scientific and more overtly political.[4] Barbieri and Ongaro state that prior to the creation of the EMEA in 1995 *"the communitarian pharmaceutical policy was poorly regulated at the central level and the role of the member states was prominent, due to the nature of the comitology process"*.[5] One of the aims stated in the preamble to Council Regulation (EEC) No 2309/93 of 22 July 1993[6] was that, "*it is necessary to provide the Community with the means of resolving disagreements between Member States about the quality, safety and efficacy of medicinal products"* i.e. to diminish the influence of the EUMS governments through the comitology procedure. The *"structural disaggregation"* of the EMEA from DG Enterprise and Industry in 1995 (i.e. creation of the separate agency with its own management board) assisted in this.[7]

Scholten points out that the formal position of EU agencies as they originated in establishments within the Commission - such as the EMA in its existence prior to 1995 as the

1 Contrasted with the ability of the FDA to make its own secondary legislation under the FDA which indicates it has a higher level of autonomy than does the EMA from the Commission See Busuoic (2009). See Buess, Michael. "European Union agencies and their management boards: an assessment of accountability and demoi-cratic legitimacy." Journal of European Public Policy 22, no. 1 (2015): 94-111.

2 See Busuoic (2009).

3 See Buess (2015).

4 See Busuoic (2009).

5 See Barbieri and Ongaro (2008).

6 Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

7 See Barbieri and Ongaro (2008).

comitology CPMP within DG Enterprise and Industry[8] - was simply to assist the Commission by gathering information.[9] Then, at some point they were endowed with *"decision making and supervisory"* powers but still lacked formal autonomy from the Commission. According to Makhasvili and Stephenson[10] EU agencies were established at this stage to bring about their independence in a way which protected them in their decision making from *"political pressure, vested interests and political short-termism"* The latter was widely recognised by the 1990s to be the result of the comitology system. Busuioc and Groenleer argue[11] that during the 1990s-2000s agencies were established in the EU and welcomed as a way of solving several of the EU's problems. For example, they could *"increase the EU's effectiveness by providing high-quality expertise and problem-solving capacity, no longer relying on national institutes, centres of agencies"*.[12]

Barbieri and Ongaro say[13] that EU agencies generally *"have no actual difference in terms of their managerial autonomy from what would be achievable by internally decentralized units of the European Commission"*.[14] It is true that the EMA as created, and today, does not seem to be particularly independent from the Commission in formal legal terms.[15] As the EMA and the centralised licensing procedure stand, the Commission has ultimate decision-making authority. In the event of a conflict between the Commission and the CMPH, it is the Council which will make the decision *"enabling this institution to further restrict the decision-making autonomy of the EMA".[16]* When the Commission disagrees with the EMA and overturns the scientific opinion of the CMPH it must *"justify the deviation, and provide a good argument for the decision."*[17] Gehring and Kraphol point out, however, that, apart from the formal decision-making authority of the Commission, *"the (EMA) dominates the authorisation procedure, while political control is almost negligible in practice."*[18] They say the EMA acts as an *"agenda-setter"*[19] for the decision making stages which follow and, as noted above, it is practically impossible for the other actors involved to ignore the scientific opinion of the CMPH (the rapporteur, which is in practice one NA).

In addition, because sponsoring firms must make their application for a license directly to the EMA not to the Commission, *"the EMA cannot be sidestepped"* unlike some other scientific

8 The name was changed in 2004 to CMPH: the CPMP existed within the Commission before the creation of the EMEA in 1995.

9 Scholten, Miroslava. *The political accountability of EU and US independent regulatory agencies*. Martinus Nijhoff Publishers, 2014.

10 Makhashvili, Levan, and Paul Stephenson. "Differentiating agency independence: perceptions from inside the European Medicines Agency (EMA)." *Journal of Contemporary European Research* 9, no. 1 (2013): 4-23.

11 Busuioc and Groenleer (2013)

12 Ibid.

13 Barbieri and Ongaro (2008).

14 See also Levy, Roger. "Critical success factors in public management reform: the case of the European Commission." *International Review of Administrative Sciences* 69, no. 4 (2003): 553-566.

15 Which is due to the *Meroni* doctrine: it cannot be.

16 Makhashvili and Stephenson (2013).

17 Krapohl, Sebastian. "Credible commitment in non-independent regulatory agencies: A comparative analysis of the European agencies for pharmaceuticals and foodstuffs." *European Law Journal* 10, no. 5 (2004): 518-538 at 532

18 Gehring and Krapohl (2007).

19 Ibid

committees in the EU, where the Commission sets the agenda.[20] Gehring and Kraphol argue this means that the scientific opinions of the EMA *"inevitably set the agenda for subsequent decision stages"*. Another avenue of potential influence by the Commission over the EMA is found in the fact that the Commission provides a portion of the budget for the EMA.[21] But the influence of the Commission is substantially diminished by the fact that the EMA can charge user fees, accounting for a much larger proportion of its budget.[22] Another is that the EU equivalent of the US regulatory oversight board, in the EU the 'Regulatory Scrutiny Board'[23] exists as a part of the Commission. However, it cannot review acts or secondary legislation made by the EMA because the EMA has no authority to make these. It is limited only to scrutinising legislative acts of the Commission which might impact the operation of the EMA. The EMA is not strongly accountable to the Commission.

EMA Management Board

After the creation of the EM(E)A, the comitology procedure for accountability to the EUMS governments was replaced with a management board upon which all the EUMS are represented. Makhashvili and Stephenson say *"the* [management board] *generally monopolises decision-making and ultimately controls many aspects of the agency's functioning. As a result, the member states are arguably the actors most influential on the EMA itself…"*.[24] The management board of the EMA, they argue, has been, *"seen to choose to protect the interests of national offices, rather than 'protecting the efficiency and financial health of the agency which it steers.'"*[25] On the other hand, Gehring and Kraphol argue that *"decisions adopted within the EMEA will usually be difficult for the member states to challenge for scientific reasons"* through the management board *"because their own expert administrations"* represented on the CMPH *"are closely involved in their elaboration and will not complain about a particular decision, unless it is considered as grossly unconvincing by an outvoted representative."*[26] Thus whilst the EUMS should wield partisan influence through the management board, they are not likely to do so in practice.

Busuioc and Groenleer consider the interrelationship between the management boards and the executive directors of EU agencies. In doing so, they consider the effectiveness of management boards as an accountability forum (i.e., a principal) generally to their agencies, including in the specific case of the EMA.[27] The Executive Director is supervised by the Management Board. She oversees the operation and functioning of the EMA: for which she plans, organises, staffs, directs, coordinates and budgets. Importantly *"while they act under the supervision of management boards, agency heads are outside the reach of traditional controls that were relevant before delegation within the Member States, the Commission or*

20 Krapohl, Sebestian. "Risk regulation in the EU between interests and expertise: the case of BSE." Journal of European Public Policy 10, no. 2 (2003): 189-207.
21 Busuoic (2009).
22 Makhashvili and Stephenson (2013).
23 https://ec.europa.eu/info/publications/meetings-regulatory-scrutiny-board_en
24 Makhashvili and Stephenson (2013).
25 See also See also Busuioc, Elena Madalina. *The accountability of European agencies: legal provisions and ongoing practices*. Uitgeverij Eburon, 2010.
26 Gehring and Krapohl (2007).
27 Busuioc, Madalina, and Martijn Groenleer. "Wielders of supranational power? The administrative behaviour of the heads of European Union agencies." *The agency phenomenon in the European Union* (2012): 128-151.

the Council."[28] Executive directors have been viewed with suspicion by some scholars who argue that they lack sufficient accountability to any forum,[29] which is troubling given that the role of the head of an agency is particularly expedient for the unilateral development of power at that agency[30] and for changing agency behaviour.[31] Busuoic and Groenleer use survey evidence to investigate the relationship between management boards and executive directors. They find that (generally) the management board exercises stricter supervision over executive directors than do the Commission, the Council, or the EP. Executive directors are generally appointed for five years but the average tenure of the executive directors in their empirical study was nine years.[32]

The first executive director of the EMA came from the Commission, and there was no evidence of the politicisation of the director's appointment. In fact, the arrival of the executive director from the Commission, secure in the knowledge that he could return to the previous (lower) position at the Commission once finished, *"made it easier for the director to come to agreement on such matters as the budget"*[33] which supports the view that the EMA (in particular) is a scientific and depoliticised agency. It also supports the view that the executive director of the EMA has a lower public profile than the FDA commissioner who is a high profile and highly political appointment by the US President and Senate. The appointment of the executive director of the EMA is less politically salient than the Commissioner of the FDA partly because the executive director of the EMA does not have real scope to influence the adoption of the scientific opinion following scientific assessment by a rapporteur NA (when it comes to licensing). It was discussed above how, by contrast, FDA officers including the Commissioner are required and expected to politicise the scientific processes at the US agency. Busoic and Groenleer confirm *"the… (EMA) directors have no direct influence over the opinions being issued, relying on networks of experts in the member states."*

Surveys undertaken by Busoic and Groenleer[34] have indicated that – particularly at the EMA – there are some difficulties in the management board exercising meaningful oversight. This suggests that *within* the EMA the CMPH enjoys a high level of autonomy from the management board, and thus relatively little accountability to the EUMS governments or the Commission relative to 1) other EU agencies and 2) the FDA. The surveys indicated that at the most technically complex agencies – for example, the EU Aviation Safety Authority ('EASA') – members of the management board are not sufficiently immersed in the material being discussed to exercise effective oversight. The director of the EASA stated, *"I think that the vast majority of the members of the board do not have time enough to go in detail and to be sufficiently informed about the agency. They know of course the agency but not sufficiently in*

28 Ibid.

29 Everson, Michelle. "The legacy of the market citizen." (1995): 73-89. And Curtin D. 2007. Holding (Quasi-Autonomous EU Administrative Actors to Public Account. European Law Journal 13: 532-41 and Vos E. 2000. Reforming the European Commission: What Role to Play for EU Agencies? Common Market Law Review 37: 1113-34

30 Kaufman H. 1981. The Administrative Behavior of Federal Bureau Chiefs. Washington D.C.: The Brookings Institution

31 Wood BD, Waterman RW. 1991. The Dynamics of Political Control of the Bureaucracy. American Political Science Review 85: 801-28

32 Busuioc and Groenleer (2012).

33 Ibid.

34 Ibid.

detail and maybe they don't read sufficiently all the documents we send to them and it doesn't appear that they make a reflection on those documents."[35] Of the EMA Management Board, *"whereas some members were very professional and well prepared for the discussions in the meetings, "there are some of them they are more or less coming here not to put their EMEA hat but just to sit and watch…"* Most respondents felt that there were too many people on the board in order to have *"efficient discussions"*. The executive director of the EMA said, *"the board and the construction of this kind of board does not help an executive director and does not help the agency in a professional way to steer the organization."* Busoic and Groenleer highlight that this was such a problem at the EMA that steps were taken to encourage the management board members to participate more actively.[36] They conclude overall that *"management boards often seem to display serious weaknesses in monitoring the work of the directors, thus potentially allowing agency directors to wield supranational power"* and in their view *"asymmetries of information represent the biggest threat in a delegation process."* I add that in the case of the most technically complex agencies such as the EMA, those asymmetries of information are likely to be most serious, of all EU agencies, and this may account for the particularly serious problems found at the EMA management board disclosed in the survey responses.[37]

The scientific approach of the technically complex EMA ensures that EUMS government oversight *through* the management board remains difficult. The EUMS government's influence in decision-making is likely to come through the representatives of the NAs on the CMPH standing Committee instead. Given that the NAs are executive agencies underneath the health ministries in each of the EUMS, this influence is likely to manifest but will not be overtly political in nature. What remains after management board input is relegated to weak oversight, is a CMPH composed of nominees from the NAs, which select one of their number – a rapporteur NA – to undertake an assessment. CMPH oversight of this amounts to a 'peer-review' of the scientific analysis. Groenleer thus argues[38] that the NAs hold considerable sway

35 Busuioc and Groenleer (2012). *"This was confirmed by another respondent, a member of the board, who perceived the situation as being in stark contrast with his own experience at the national level agency where the board "works together very well and everybody is prepared and knows what's going on. It's not like that at all. And I'm sure some people come to the meetings who haven't read the papers and don't really understand the issues to be honest."*

36 Ibid. *"This appears to have been quite problematic for EMEA given that actual remedial measures were instituted in an attempt to tackle the issue. As the director explained, "I have my board; some of them are frustrated also. And for the moment, we have put together a little working group in the board in order to look at the rules and responsibility of the board and how the board could participate in a more active way.(…)"… It is hard to assess the reasons behind the lack of participation, which could range from lack of interest in the workings of the agency to lack of preparation, as discussed above or even lack of time and resources. In fact, respondents have made reference to all these reasons as possible explanations for some of the delegations' non -engagement in debates."…*

37 Busuioc and Groenleer (2012). See also Kassim, Hussein, and Anand Menon. "The principal-agent approach and the study of the European Union: promise unfulfilled?." *Journal of European Public Policy* 10, no. 1 (2003): 121-139 and Kiewiet, D. Roderick, and Mathew D. McCubbins. *The logic of delegation*. University of Chicago Press, 1991. And Lupia, Arthur, and Mathew D. McCubbins. "Representation or abdication? How citizens use institutions to help delegation succeed." *European Journal of Political Research* 37, no. 3 (2000): 291-307. And McCubbins, Mathew D., Roger G. Noll, and Barry R. Weingast. "Administrative procedures as instruments of political control." *Journal of Law, Economics, & Organization* 3, no. 2 (1987): 243-277 and Moe, Terry M. "Power and political institutions." *Perspectives on politics* (2005): 215-233.

38 Groenleer, Martijn. The autonomy of European Union agencies: A comparative study of institutional development. Eburon Uitgeverij BV, 2009. At 166

over the EMA and the centralised licensing procedure, possibly more so than the Commission, the Council, the EUMS governments represented in the management board, the European Parliament, or the Executive Director. In his view, too, this is due to the issue of the pharmaceutical self-assessment (the rapporteur system for the centralised licensing procedure), where the NAs "*can broker their preferences through (the HMA).*"[39]

European Parliament

Turning to the EP, in formal accountability terms it exercises the same types of oversight mechanism that Congress does over the FDA.[40] The EP is represented on the EMA management board and its representatives there give feedback. The executive director of the EMA reports compulsorily to the EP specialised Committee; and that Committee also visits the EMA every two years and can monitor the EMA website. It can advise against the appointment of an executive director.[41] It can work with the European Ombudsman to supervise administrative procedures and conduct.[42] These formal accountability mechanisms (to the EP and other actors), note Busuioc and Groenleer, not only match well with what is found for the NAs at the EUMS level, but *"the sheer magnitude of these procedures at the European level and the number of forums involved, compared to the administrative capacity of some of the agencies, the level of accountability obligations to which EU agencies are subject is likely unparalleled in similar bodies at the national level."*[43] Quite unlike what results from congressional oversight of the FDA through its system of public hearings, in the view of Busuoic and Groenleer the abundance of formal accountability mechanisms under which the EMA operates may result in *"accountability overloads"* which may reduce the effectiveness of EP specialised committee oversight of the EMA. They say *"from an accountability perspective, overloads, just as deficits, are failures of accountability, the 'negative externalities' of accountability. In the case of agencies, accountability procedures already in place for the main EU institutions were simply transplanted without much forethought as to the extent to which they were compatible with these smaller scale executive organisms. This has resulted, as observed above, in overloads and overlaps that affect the 'health' of the overall accountability system."* Their empirical analysis showed that the EP underused the many accountability mechanisms available to it.[44]

As with the oversight of the management board, this partly results from the technically complex nature of the work done at the EMA. Busuoic and Groenleer say, *"while some EP committees demonstrate interest and are involved with the agencies within their remit, others display a low level of involvement and low attendance during hearing meetings."*[45] In the case of the EP, *"Political accountability practices (vis-à-vis the EP or the Council) tend to be less intensive, incident-driven, focused on a limited number of issues and guided by political priorities and political saliency."* Thus, what piques the interest of political observers will

39 Makhashvili and Stephenson (2013).

40 Ibid.

41 Andoura, S., & Timmerman, P. (2008). Governance of the EU: The Reform Debate on European Agencies Reignited. EPIN Working Papers No. 19, October 2008 at pg. 14

42 Keleman, Daniel R. "The politics of 'eurocratic' structure and the new European agencies." *West European Politics* 25, no. 4 (2002): 93-118 at pg. 100.

43 Busuioc and Groenleer (2013).

44 See also Busuioc, Elena Madalina. *The accountability of European agencies: legal provisions and ongoing practices*. Uitgeverij Eburon, 2010.

45 Busuioc and Groenleer (2013).

prompt the mobilisation of the formal accountability mechanisms. However, due to the technical nature of the EMA's work, and the purely scientific way in which it is presented by the CMPH, there is little available to pique the interest. Even where EUMS governments or (less likely) EU consumers disagree with a Commission (EMA) licensing decision (for example), the reasoning for that decision is found in the scientific opinion of the CMPH (in turn, really, the scientific analysis of one rapporteur NA). Thus, it is very difficult to disagree with using the language of politics. That is one reason for a lack of EP oversight.

The second is the problem of accountability overloads, and these two work together. Essentially, the EP thinks that the management board has a handle on the technical aspects and thus they can monitor this. Many on the management board believe the EP specialised committee is acting as a failsafe mechanism to cover any of the technical details which the management board has missed. Both the EP and the management board are sure that the Commission and Council exercise some additional oversight anyway when the formal decision is made or will, at least, take responsibility for it. And, all potential accountability principals ultimately trust that the CMPH – composed of scientists – fully understand the technical details.[46] Real (de facto) accountability of the CMPH to the EP is lost to the EP's belief that some other institution has it covered, and that the CMPH monitors itself anyway. Busuioc and Groenleer argue that… *"to improve political accountability, better de facto involvement of these forums would need to be generated by raising awareness of agencies, (the impact of) their work and their profiles within the EP's committees (as well as the Council's structures) in order to stimulate the better use of existing accountability arrangements."*[47] Mahkashvili and Stephenson echo this[48] citing Koppell[49] and his term 'multiple accountabilities disorder' they argue that it relates not just to EP and Commission oversight of the EMA's activities but also to the management board's oversight.

Court of Justice of the European Union

According to Makhasvili the CJEU *"monitors the actions and decisions of the EMA and, at the request of EU institutions or citizens, can further scrutinise its functioning"* which means[50] that it is possible for citizens to *"to take a case to the ECJ against the EMA's 'decisions'."*[51]

Whilst there is the formal possibility of judicial review of the EMAs decisions for many interested parties, the nature of CJEU review is limited to ensuring that the decision has been made in accordance with scientific conventions. Gehring and Kraphol[52] consider the accountability of the EMA through substantive (legal) decision criteria and judicial oversight.

46 Which, of course, they do, but that rather overlooks the point that the data for a licensing decision comes from the applicant industry actor and is only considered in detail by the rapporteur and co rapporteur NA.

47 Busuioic and Groenleer say, Instead, *"In terms of institutional design, we find that agencies' accountability obligations are not usually linked or tailored to agencies specificities, administrative capacity, and accountability arrangements already in place…. A possible explanation for this is that, in reaction to agencies' perceived 'independence' (i.e. unqualified autonomy) and increased calls for enhanced agency accountability, the 'knee-jerk' institutional response was to simply add on accountability arrangements, irrespective of agencies' formal and/or actual autonomy."* Busuioc and Groenleer (2013).

48 Makhashvili and Stephenson (2013).

49 Koppell, Jonathan GS. "Pathologies of accountability: ICANN and the challenge of "multiple accountabilities disorder"." *Public administration review* 65, no. 1 (2005): 94-108.

50 Keleman (2002).

51 Makhashvili and Stephenson (2013).

52 Gehring and Krapohl (2007).

They argue that judicial oversight actually focuses and strengthens the scientific imperative in EMA decision making. The *Meroni* doctrine prohibits granting significant political decision-making discretion to EU agencies and the result of this is that the EMA is bound to substantive legal decision criteria in the decisions it makes. The CJEU can only review acts of the EMA for compliance with those criteria. These are found in Regulation 726/ 2004[53] which established the centralised procedure. The broadest criteria are that *"authorization decisions shall exclusively rely on the evaluation of the safety, efficacy and quality of a pharmaceutical product."*

These criteria are supplemented by detailed criteria in the 'Community Code Relating to Medicinal Products for Human Use.' That is now found in Directive 2001/83/EC[54] which contains detailed standards relating to the clinical trials which must be undertaken for all products before a licensing decision may be made. In addition, the code expressly states that *"non-scientific factors like the economic well-being of the pharmaceutical industry or financial constraints of domestic healthcare systems shall be ignored."* In other words, the decision on licensing must be made based on the scientific opinion of the CMPH alone. Again, the position of the CMPH and the rapporteur NA is strengthened by these substantive decision criteria because the criteria do not allow for any challenge other than failure to adhere to scientific convention. Whilst there have not been a great number of cases brought before the CJEU concerning authorisation decision of the EMA, specifically[55] one example given by Gehring and Kraphol[56] is case C-39/03 P (24 June 2003) concerning the EMA's authorisation of anoretics (anti-obesity drugs). Here the CJEU went into great detail on the substance of the scientific opinion produced by the committee, checking it for adherence to the standards set by Regulation 2309/93 (726/2004) and Directive 2001/83/EC. The CJEU did not and does not supplant the expert view of the CMPH scientists with that of its own, but merely considers compliance with the legal standards. Here the CJEU demonstrated that it would not decline to check adherence to the *standards*, merely because this involved consideration of the technically complex *opinion*. Its oversight of the EMA's compliance with legal standards (in this case regarding transparency) can more recently be seen in cases C-175/18 P and C-178/18 P.[57]

If the CMPH, in turn, produces an opinion which in any way can be characterised as incorporating *non-scientific* factors then this is likely to be challenged via judicial review before the CJEU by EUMS governments, by the management board, by the Commission (which may disagree with the opinion), by the wider CMPH committee (aside from the rapporteur and co-rapporteur NA representatives) and by consumers (if the CJEU's strict standing rules permit this). Gehring and Kraphol argue that this further incentivises the CMPH

53 Council Regulation (EEC) No 2309/93 of 22 July 1993 laying down Community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Agency for the Evaluation of Medicinal Products

54 DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use

55 The CJEU has, in recent years, exercised oversight over other aspects of the authorisation process, not just the decision itself, for example in 2020 ruling on the issue of disclosure of documents to the public: See C-175/18 P and C-178/18 P

56 Gehring and Krapohl (2007) at pg.218

57 https://www.roschier.com/newsroom/the-cjeu-rules-on-access-to-documents-submitted-when-applying-for-marketing-authorization/

to stick to a rigidly scientific approach. In ensuring this, the CMPH also limits *"the room for manoeuvre of the non-scientific actors involved in the European authorization of pharmaceuticals, namely the Commission and (the other NAs represented on the) CMPH*." Thus, the imperative on all of the actors involved in the licensing process is bound to the scientific approach and since applicant pharmaceutical firms as well as other interested parties may seek judicial review it, "*is hardly conceivable that these actors deviate from a scientifically sound opinion of the (CMPH rapporteur)… without eventually being called back by the European courts."* This means that the EUMS governments and the Commission are *"restricted to tacit oversight of whether the criteria are sincerely applied by the agency."* [58]

Consumers

I turn now to the relationship between the EMA and EU consumers, and the potential accountability of the EMA *to* EU consumers. I conclude below that there is no direct to consumer accountability of the type found between the FDA and US consumers. To develop the argument fully, I first consider the public profile of the EMA, then I consider the historic problem of the democratic deficit in the EU, then I consider how the EU as a whole has sought to reach out to consumers to close the democratic deficit. I then consider how this problem was framed anew with the creation of the NAs and the wider EU agencification process from the 1980s onwards. Finally, I consider specifically how, at the EMA, attempts have been made to involve consumers in the decision-making process, concluding that EMA accountability to consumers via these methods has a very different quality to the media-enabled direct to consumer accountability in the US.

The Media, Pluralism, Focal Points, and Consumer Attention

The FDA is over 100 years old and appears regularly in the US media. Even if EU consumers were interested in what the EMA is doing, the EMA is never likely to be a focal point for consumer discontent or fear regarding pharmaceutical products. It exists in a different country to most EU consumers. There is no popular European media broadcaster producing news bulletins from a European angle which can match the viewing figures for major news broadcasters found in the EUMS domestic news media markets or the US nationwide media

58 Gehring also argues that because they have created substantively binding general rules which will apply to all future cases, the Commission, Council and EP have bound themselves against advancing *"parochial"* (i.e. partisan, tied to support of industry or a particular firm or national pharmaceutical sector) interests in any specific case. As a result, he argues, capture of the licensing system by any one specific interest – including by industry - becomes less likely. I argue below, however, that capture occurs 'by default', that in the absence of direct to consumer accountability, the EMA and the centralised procedure are structurally accommodating of industry. Gehring concludes, *"the authorization process is not integrated by the bargaining power of non-scientific actors any more, but by scientific reasoning within the limits of mandatory European law… Legally enforceable substantive decision criteria increase the power of the scientific expert committee vis-a`-vis the non-scientific actors, as long as it sticks to its mandate."* These criteria (and the possibility of judicial review) *"can be exploited best by the actors who are specialized in scientific expertise, whereas they deprive the non-scientific actors of their bargaining power."* The primary scientific actors in the process are the scientists staffing the NAs and, in any given case, is one rapporteur NA. Again, therefore, this de jure accountability mechanism makes that NA and the CMPH accountable to no one except themselves and their own scientific standards. Gehring and Krapohl (2007). See also Gehring, T. (2004) 'The consequences of delegation to independent agencies: separation of powers, discursive governance and the regulation of telecommunications in Germany', European Journal of Political Research 43(4): 677 – 98. See also Joerges, Christian, and Jürgen Neyer. "From intergovernmental bargaining to deliberative political processes: the constitutionalisation of comitology." *European law journal* 3, no. 3 (1997): 273-299.

market.[59] The lack of a focal point problem is exacerbated by the multiplicity of official languages at the EU. It is simpler for news outlets is to frame the issue – and thus report it – not as an 'EU' story but as a domestic story, given that relatively few EU acts have immediate direct effect within the EUMS but require some implementation by the EUMS governments instead. Focal points matter to the broadcast (news) media because media outlets compete for the attention of viewers. Even in Europe where state subsidised media is commonplace, in many EUMS these compete with private commercial enterprises in the 'attention' economy.

The dissatisfaction of EU consumers also needs a clear focal point. This is particularly so, given that consumers are such a widespread and disparate group ,that to have any hope of organising and placing pressure it needs to be clear 'where' they should 'meet' and 'whom' they should place pressure on. As the provision of healthcare is invariably state coordinated across all EUMS, and thus is a key political issue at every election, the obvious focal point for EU consumers is their national health ministers and health ministries, and the default channel of expression is established political parties in domestic political accountability fora.

I argue in Chapter Two that EU/EUMS consumers exhibit a relative preference – versus US consumers – for expressing discontent through these established structures in the context of the corporatist/neo-corporatist political systems which still represent the norm in most EUMS. By contrast, in the US political system the media is almost entirely privately owned and levels of competition in the news media market are high – with no state funded broadcaster crowding out the smallest players. The result is a pluralistic media – lots of different broadcasters, some larger, some smaller – reporting the same facts from very different (and relatively less balanced, in any one case) angles. In addition to a relatively more pluralistic media, the political system too is relatively more pluralistic. Here, it is relatively less common for consumers to be 'activist' only through established political parties. Instead, consumers often form an interest group of their own, harness the pluralistic media to advance their cause, and then network with the established political parties whilst remaining independent. This means that in the US there is a large number of groups potentially critical of a target, and they have the means to broadcast that criticism. Where a focal point exists – such as in the case of the FDA,[60] then the result is that the FDA receives a lot of media attention and has a much higher public profile than does the EMA or the NAs.

The Democratic Deficit and Attempts to Overcome It

I now consider the historic problem of the 'democratic deficit' in the EU. I do this because in the following paragraphs I argue that consumer participation in agency decision making in the EU is 'institutionalised' (installed from the top-down) rather than resulting from consumer activism (bottom-up), as it does relatively more in the US. The reasons for the institutionalisation of consumer participation in EU agencies are found in the original

59 National news broadcasters find it easier to have one correspondent in Brussels to report on all things EU-related rather than attending the offices of the EMA. Partly because the EU organs and agencies are so spatially dispersed, partly because the organisational structure is so complex (being a sui-generis supranational entity), and partly because the personal identity of the leadership of the EU is unclear to casual observers (because the question of leadership is context-specific), the EU itself, in the eyes of the ordinary EUMS consumer (of any EUMS) lacks a focal point. As Kissinger is alleged to have once asked, 'who do I call if I want to speak to Europe?'

60 Being a Federal agency which regulates for the entire nation, directly, without intermediation.

'democratic deficit' problem. The origins of this, argue[61] Arnull and Wincott, are to be found in the fact that, of the three communities established in the mid twentieth century, two were merely technical and had little impact on EU consumers: the European Coal and Steel Community, and Euratom. The third, the more ambitious European Economic Community, was never envisaged at that stage to become what it has become 70 years later. Arnull and Wincott claim that, considering this, and the fact that the *"pre-war spirit of deference to those in authority had not yet broken down"* EU consumers were happy to accept these *"grand schemes of civil servants and politicians"* without much push back. At this stage, for example, only a limited right of judicial review was made available to private parties before (what was then called) the European Court of Justice. Instead of a full Parliament, all which was seen as necessary was an assembly carrying out an advisory and supervisory function to the appointed Commission. Under this structure, the pushback from the European demos against the Commission was envisaged to come via the EUMS governments and from the Council which represented the EUMS citizens. These would have unlimited standing to challenge all community acts. This is the origin of the democratic deficit – at the time not viewed as a deficit at all. For the communities, as established, direct accountability to the wider European demos was neither necessary nor sought after.

Having been created this way, the EC became path dependent upon this accountability structure. Changes in technology and science, increased prosperity, successive expansions of the EC (later the EU) and the fact that war became a distant memory, led to a populace in western European EUMS who were relatively less willing than their parents to passively accept government.[62] In the new EUMS of eastern Europe the citizenry demanded that the EU work for them and deliver levels of prosperity found in the western EUMS. There was more critical scrutiny of public institutions, and people became more litigious. The difficulties attendant upon the ratification of the Maastricht treaty showed how EU consumers were no longer willing to accept the democratic deficit which had been a hallmark of the EC since its inception. Fisher doubts[63] whether the *'innovative governance'* structures which the EU has developed (in alternative) can ever match up to the direct representative democracy in line with *"conventional understandings of the constitutional state."* However, Maravcsik defends the status quo found in Europe, pointing to both direct and indirect mechanisms of democratic accountability.[64] Curtin[65] wonders how effective these really are, *"at the European level itself it is clear that although the European Parliament may indeed be directly connected to national voters through direct elections to the European Parliament these elections, apart from the low turnouts, are not focussed on European issues nor do they give a mandate at the European level to a 'government.'"*

In response to criticisms over the democratic deficit and legitimacy shortfall, the EU has been seeking – particularly since the 1960s and 1970s – to reach out directly to consumers. From

61 Arnull, Anthony, and Daniel Wincott, eds. *Accountability and legitimacy in the European Union*. Oxford University Press on Demand, 2002 at page 6

62 Arnull and Wincott (2002) at page 7

63 Fisher, Elizabeth. "The European Union in the age of accountability." (2004): 495-515

64 Moravcsik, Andrew. "Reassessing legitimacy in the European Union." *JCMS: journal of common market studies* 40, no. 4 (2002): 603-624.

65 Curtin, Deirdre. "Delegation to EU non-majoritarian agencies and emerging practices of public accountability." *Regulation Through Agencies In The EU, A New Paradigm Of European Governance* (2005): 88-119.

compensation for cancelled or delayed flights,[66] to a strict standard of liability for producers of defective products,[67] to limitations upon working hours[68] and consumer protections for distance selling.[69] Trumbull argues[70] that the governments of Germany and France from the 1960s onwards sought to please its 'consumer citizenry' and passed 'consumer-protection' legislation in both countries in support of expanded social and healthcare rights. Much of this legislation in these two EUMS came from their coordination as the two major actors at the EC intergovernmental level. Two major advantages of channelling these legal measures through the EC, were that 1) it brought Germany and France closer to each other on the horizontal level and 2) brought the EU organs and agencies closer to ordinary consumers across Germany and France on the vertical plane.

EU Consumers and EU Agencification

The democratic deficit problem described above became particularly troubling when – for reasons of facilitating governance – the EU began to create separate agencies with supervisory and advisory functions; from the 1990s onwards. Busuoic and Groenleer claim that the EU stood to benefit from agencification by way of a legitimacy boost in the eyes of consumers. The idea was that the expertise held in these agencies would be transparent, and that there would be a high level of public participation, in contrast to the *"opaque"* comitology system. It was believed that this would *"ensure interest group monitoring, as well as independence and from political and industry interference".*[71]

However, since their creation the agencies, including the EMA, have come under scrutiny. They are non-majoritarian and have thus been described as *"uncontrollable centres of arbitrary power"*.[72] Eventually the EP called for restraint on agencification.[73] At the same time, contrary to what was hoped for at the beginning of the process, interest groups have become unhappy about a lack of transparency and openness.[74] Some say it has become apparent over twenty years that *"the governance of these entities is not merely an administrative and technocratic matter… it is an inherently political issue that gives rise to fierce interinstitutional struggles and heavy contestation in terms of its political consequences for the distribution of resources and the balance of power in the EU. Ironically the EU's nonmajoritarian world is heavily politicised."*[75] If it is true that what happens at the EMA is unavoidably political, then some direct-to-consumer accountability[76] would ensure at least that the political views of consumers balanced out the political views of industry not just indirectly through the EUMS on an intergovernmental level, but directly and thus more presciently. However, the response

66 Regulation (EC) No 261/2004
67 Directive 85/374/EEC
68 Directive 2003/88/EC
69 Directive 97/7/EC of the European Parliament and of the Council of 20 May 1997 on the protection of consumers in respect of distance contracts
70 Trumbull, Gunnar. *Consumer capitalism: politics, product markets, and firm strategy in France and Germany*. Cornell University Press, 2006.
71 Busuioc and Groenleer (2013).
72 Everson, Michelle. "Independent agencies: hierarchy beaters?." *European Law Journal* 1, no. 2 (1995): 180-204 at 190
73 Busuioc and Groenleer (2013).
74 Busuioc, Madalina. *European agencies: Law and practices of accountability*. Oxford University Press, 2013.
75 Busuioc and Groenleer (2013).
76 Lynch, Joffe, and McCoy (2021)

of the EU to this problem has been to become even more technocratic-scientific and technically complex. Employing more formal accountability mechanisms which lead to accountability overloads and 'multiple accountability disorder'. Taken together with the agency's technocratic-scientific approach, this makes the decision-making behaviour of the agency inaccessible not only to consumers but also to the EP.

Institutionalisation of Consumer Participation at the EMA

It is my argument made here and in Chapter Two that a relatively 'passive' European 'consumer citizenry' does not pay so much attention to the EU and its agencies as do US consumers to their Federal agencies. Critics complain of a lack of transparency and public participation at the EU level, but a major component of this is the fact that not many EU consumers have an interest in looking, or participating. The EU nevertheless must respond to critics like Fisher, and Arnull and Wincott,[77] lest it lend ammunition to euro-sceptics across the EUMS. So, whilst in the US consumers fought for transparency, and demanded to participate, in the EU consumer participation and transparency was installed from above by the EU itself. At the EMA, in particular,[78]many initiatives have been undertaken[79] to satisfy observers that there is increased transparency and public participation in the organisation.

Initially lauded for its efforts to reach out to all stakeholders[80] from 2010 concerns were being raised[81] by many in science[82] and academia[83] leading to a resurgence of efforts at the EMA to increase transparency for the benefit of EU consumers.[84] One problem with potential reforms (public participation) lay in the fact that 'patient' consumer groups (representing healthcare consumers) at the EU level are not particularly common. Mahoney[85] analyses the decision of interest groups to join coalitions – for example, a coalition between a patient consumer group and another interest group such as doctors, seeking to combine resources to lobby for a specific legal reform – in the US and the EU. She finds that *"citizen groups in both systems see an advantage is banning together and, in the process, showing their solidarity and pooling their resources"* but overall European *"advocates are building formal coalitions at a much lower rate than their American counterpart"* and *"differences in the composition of the US and EU advocacy communities may also affect the propensity of EU groups to align, since larger pan-European federations don't see the same benefits as smaller specialized US groups"*. Kurzer notes that it is *"rare"* for European citizens to *"prevail over the elitist technical decision*

77 See above: Arnull and Wincott (2002): Fisher (2004)

78 Way, Dominic Hugo Patrick. "Transparency in risk regulation: The case of the European medicines agency." PhD diss., King's College London, 2017.

79 Bonini, Sergio, Hans-Georg Eichler, Noël Wathion, and Guido Rasi. "Transparency and the European Medicines Agency—sharing of clinical trial data." *New England Journal of Medicine* 371, no. 26 (2014): 2452-2455.

80 Abbasi, Kamran, and Andrew Herxheimer. "The European Medicines Evaluation Agency: open to criticism: Transparency must be coupled with greater rigour." (1998): 898-900.

81 Hampton, Tracy. "European drug agency under fire." *JAMA* 306, no. 6 (2011): 593-595.

82 Bouder, Frederic, Dominic Way, Ragnar Löfstedt, and Darrick Evensen. "Transparency in Europe: a quantitative study." *Risk Analysis* 35, no. 7 (2015): 1210-1229.

83 Löfstedt, Ragnar, and Frederic Bouder. "New transparency policies: risk communication's doom?." *Earthscan Risk in Society* (2014).

84 Way, Dominic, Frederic Bouder, Ragnar Löfstedt, and Darrick Evensen. "Medicines transparency at the European Medicines Agency (EMA) in the new information age: the perspectives of patients." *Journal of Risk Research* 19, no. 9 (2016): 1185-1215.

85 Mahoney, Christine. "Networking vs. allying: the decision of interest groups to join coalitions in the US and the EU." *Journal of European Public Policy* 14, no. 3 (2007): 366-383.

making procedures in Brussels" with the successful boycott of genetically modified crops being one exception to this rule.[86]

Writing about patient consumer groups specifically in the field of pharmaceutical regulation, Parker and Wells[87] note that many of these receive funding from the pharmaceutical industry – particularly those groups which seek for regulators to license products more quickly: *"HCO ('Healthcare Consumer Organisations') acceptance of pharmaceutical industry funding delivers a risk that HCOs will prioritise the interests of the funder over interests of the public, and sectorwide reliance on industry funds might mean than non-industry funded voices are drowned out. If there is a perception amongst health policy makers that HCOs are becoming mouthpieces for industry rather than providing a citizen's rights perspective on health services, they may stop listening to HCOs or stop inviting HCO involvement in policy."* This is seen as a major problem at the EU level. The reason for this is that – as stated above – there are not many patient consumer groups operating at the EU level. These are focused on the national EUMS level, at the health minsters, and via the established political parties. Because of this, and because the centralised procedure is seen to operate at the EU level (although in reality the rapporteur NA from one of the EUMS is most important in this process) it is more likely that the groups found at the EU level will be the disease-specific patient consumer groups, and these are the most susceptible to the receipt of pharmaceutical industry funding.[88]

Baggott and Forster[89] noted concerns about *"the representativeness and legitimacy of (health consumer and patients' organisations – HCPOs) in Europe, as well as questions regarding their independence "notably with regard to the drugs industry"*. They also state, *"the availability of political opportunity structures… (is)… an important factor."* Because where there are multiple decision-making entities which a patient consumer group could target in a decentralised system for the provision of healthcare, it is likely they will choose only one, whichever becomes their focal point, to avoid *"spreading their limited resources too thinly."* Thus, where health ministries (parents to the NAs) exist at the EUMS national level and political parties exist at that level, when a safety scandal arises in relation to a pharmaceutical product – most likely administered through a socialised healthcare system overseen by the same ministry – consumers if they organise in response will organise around the political parties and target the health ministry without giving much attention to the EU level. On the other hand, where a pharmaceutical firm (or industry) seeks to create a disease specific patient consumer group as a front to press for approval of a drug it sponsors, they will likely have the resources to reach out across the EU and bring these consumers together at the door of the EMA.

To tackle this latter problem, in recent years the EU and the EMA have enacted initiatives (top-down rather than bottom-up) to institutionalise patient consumer group involvement within the EMA decision-making process. One example is the installation of two patient

86 However, to do so, this consumer group required the assistance of some of the EUMS. Kurzer, Paulette, and Alice Cooper. "Consumer activism, EU institutions and global markets: The struggle over biotech foods." *Journal of Public Policy* (2007): 103-128.

87 Parker, Lisa, Anthony Brown, and Leanne Wells. "Building trust and transparency: health consumer organisation–pharmaceutical industry relationships." *Australian Health Review* (2020).

88 Lofgren, Hans. "Pharmaceuticals and the consumer movement: The ambivalences of 'patient power'." *Australian Health Review* 28, no. 2 (2004): 228-237.

89 Baggott, Rob, and Rudolf Forster. "Health consumer and patients' organizations in Europe: towards a comparative analysis." *Health expectations* 11, no. 1 (2008): 85-94.

consumer group representatives on the EMA management board. The surveys undertaken by Busuoic and Groenleer[90] would suggest that real opportunities for these representatives to contribute here are limited. DG Sanco established the 'Health Forum' where many patient consumer groups are represented[91] in order to *"improve the openness, transparency and responsiveness of EU decision-making"* and in addition to the Health Forum is the 'Open Forum' containing circa 400 organisations reported on behalf of by the Open Forum to the Commission. Then there is a 'Virtual Forum' where the Commission exchanges information with stakeholder groups. All three fora were created by the EU institutions, rather than being an initiative of patient consumer groups themselves.[92] Baggott also says that patient consumer groups are increasingly co-opted on to committees and working groups, including at the EMA.[93]

Despite this, it seems that ordinary officers at the EMA do not see much benefit in having consumers in the room for every decision, particularly where they are unwilling or unable to say much because the discussions under way are technically complex and based in science to the exclusion of politics. According to survey evidence from Tafuri et al[94] FDA officers still see consumer participation as more important than do their EMA counterparts: *"FDA respondents defined public hearings as an important instrument to guarantee transparency, especially in case of borderline applications or in case of rejected drug applications, because they give the opportunity to the agency to explain their position directly to the public."* On the other hand, *"more than half of the EMA respondents (four of seven) showed scepticism about the added value that patient advocacy groups could bring to the evaluation process and concern about their potential conflict of interest, and in general, did not seem to agree about establishing public hearings in the EU. In addition, they explained that an emotional involvement may 'distract' the assessor from the data of the application and affect the objectivity of the review process, which should only be science and evidence-driven."* Why do FDA officers welcome public participation whilst EMA officers are bemused by it? One reason is that the politicised science at the FDA means consumers can contribute in meaningful ways to discussions whereas they cannot at the EMA. Another is the incentive effects of direct to consumer accountability. The FDA respondents quoted above know that if they do not consult the public first, but then approve a drug in a *"borderline"* case, then they will face negative media coverage afterwards. By contrast if something goes wrong with the centralised licensing procedure at the EMA, the officers and the agency will not face such a backlash because consumers will first blame health ministers, and if the minister seeks to pass blame to the EMA then the EMA can plead that it did all decision-making under science.

Alongside the need to avoid accusations of opacity and democratic deficit, another imperative pressing on the EMA is the need to avoid accusations of collusion with industry. Thus, another reason why consumer participation has been institutionalised top-down is that unless the

90 Busuioc and Groenleer (2012).

91 These include the European Older Peoples Platform, the European Breast Cancer Coalition, Mental Health Europe, the European Organization for Rare Disorders, the European Patients Forum and the International Alliance of Patients Organizations.

92 Baggott and Forster (2008).

93 Ibid.

94 Tafuri, G., P. Stolk, F. Trotta, M. Putzeist, H. G. Leufkens, R. O. Laing, and M. De Allegri. "How do the EMA and FDA decide which anticancer drugs make it to the market? A comparative qualitative study on decision makers' views." *Annals of oncology* 25, no. 1 (2014): 265-269.

EMA exercises tight control over consumer participation it risks being seen to collude with industry through industry financed 'consumer' groups. As such, the EMA 'vets' the consumer groups which it permits to participate. Thus, the EMA *"has produced a set of guidelines on the representativeness and legitimacy of HCPOs, which include declarations about finances and conflicts of interest..."*[95] Moulon and Dedes[96] say, *"The criteria to be fulfilled by patients' and consumers' organizations involved in EMEA activities"* seek to *"ensure that these chosen organizations were legitimate representatives to speak on behalf of their members and that they were genuine and transparent in terms of funding and activities."*

Lofgren implies that this top-down institutionalisation of patient consumer involvement is likely to be ineffective for fostering a genuine dialogue between the agency and consumers generally:[97] the *"critical edge, and.. autonomy as civil society-based organisations"* is likely to be, *"weakened through co-option into government structures and dependence on the health professions"* in the same way as it is when they are captured by the pharmaceutical industry. EMA accountability to consumers via these methods does not have the quality that media scrutiny brings the politicised actions of the FDA. 'Grassroots' consumer activism in response to disasters and scandals, and resulting consumer vigilance in between these, results in real responsiveness of the FDA to consumers in order to seek positive media coverage. The instalment of consumers in the EU style is artifice and, whilst perhaps well intentioned for seeking to avoid industry influence via consumer group 'fronts,' it does not affect the underlying characteristic of capture-by-default. That characteristic could only be solved by US style direct to consumer accountability, which would require US style consumer activism. Passive EU consumers, however, have not been, and have not needed to be, this way in their relationships with the EU and/or its agencies to the same extent as consumers in the US. On this basis I argue there is little or no direct to consumer accountability for the EMA. What remains – without direct to consumer accountability - is just treble insulation for health ministers.

1.6.2 Science Excludes Politics

On 'science excludes politics': the basis of the *Meroni* doctrine was that no political discretion could be granted to EU agencies, and this has necessitated that the approach of the EMA be wholly and solely scientific. Building on the insights they have regarding binding decision standards enforced by the CJEU, Gehring and Kraphol argue[98] that *"the institutional arrangements in which the EM(A) is embedded"* mean that this oversight *"is compatible with*

95 Moulon, Isabelle, and Nikos Dedes. "The patients' and consumers' working party at the European Medicines Agency: a model of interaction between patients, consumers, and medicines regulatory authorities." *The Journal of ambulatory care management* 33, no. 3 (2010): 190-197…"

96 Ibid…*"Since the European Medicines Agency was created in 1995, it has engaged in dialogue with its various stakeholders, including patients and other representatives of civil society. The establishment of the Patients' and Consumers' Working Party represented a key step forward in the formalization of this interaction. The working party has played a crucial role in facilitating the integration of patients and consumers in various regulatory activities".*

97 Lofgren (2004)

98 Gehring and Krapohl (2007)

(the EMA's) quasi-independent action" because the former *"restricts the non-scientific actors involved in the authorization of pharmaceuticals more than the agency – as long as the agency adheres to its mandates of producing scientifically convincing decisions".* I.e. the effect of the binding decision standards is to diminish the effect of *Meroni* and grant the EMA 'quasi-independence.' This happens because the validity of its decision making is judged against scientific standards, and it is the NA representatives in the CMPH, not the other actors, which are scientists.

The rapporteur system excludes opportunities for opportunistic political manoeuvring[99] because a draft scientific opinion is considered by all the NAs from each of the EUMS before being finalised,[100] making it difficult for EUMS governments to disagree with, or for their representatives on the management board to dispute. Because the Commission is legally obliged to justify any deviation from the CMPH scientific opinion and must refer the matter back to EMA if it has scientific doubts, there are *"strong incentives"* for the Commission to accept the opinion as written by the EMA. And, as such, the Commission never allows politics to cause it to deviate from that opinion. Moreover the Commission could not dispute the scientific basis of the opinion because it lacks the *"scientific apparatus"* to do so. That scientific apparatus lies with the NAs which act as rapporteurs. Even the full CMPH standing committee cannot dispute the science contained in the draft opinion because to do so would require full independent analysis which the EMA would not provide financial compensation for (it compensates the rapporteur and co rapporteur out of user fees), although the co-rapporteur acts as a control for scientific standards.[101] In addition to the substantive decision standards enforceable by the CJEU upon an application for judicial review, the oversight mechanism discussed here *"provides a permanent incentive for the EM[E]A expert committee to elaborate convincing opinions against which no relevant actor can seriously mobilize the oversight system."*[102] Of the CMPH standing committee, its members know how important it is to create scientifically sound opinions to protect their reputation as a scientific body – impartial and apolitical.[103] I argue in Chapter Two that the desire of the CMPH to protect this reputation – in the eyes of industry, governments and the scientific community including all

99 Martijn L. P. Groenleer. (2014) Agency Autonomy Actually: Managerial Strategies, Legitimacy, and the Early Development of the European Union's Agencies for Drug and Food Safety Regulation. They specifically say that the *"multi-tiered oversight mechanism commits the EMEA, and all other actors involved-including the member states-to a rule-based decision-making process, which strictly limits the margin for opportunistic manoeuvre of all relevant actors."* Gehring and Krapohl (2007)

100 The rapporteur system implies that *"a draft opinion is scrutinized from the perspectives of a variety of different national regulatory cultures before being adopted or amended, so that decisions agreed upon within the committee are acceptable from the perspectives of at least a majority of domestic regulatory agencies."* Gehring and Krapohl (2007)

101 Gehring and Krapohl (2007) Explaining further, they say, *"according to the formal procedure, both the Commission and the member states represented in the Standing Committee can examine every authorization decision prior to its adoption. In practice, neither of the oversight actors has established the necessary scientific apparatus for doing so. Employment of their formally strong decision-making power will thus depend on external alert. A 'fire alarm' may be raised in particular by an applying pharmaceutical company or by an outvoted member of the EMEA expert committee. However, the far-reaching inactivity of this oversight system does not imply that it is irrelevant for the authorization procedure..."*ee also Pollack, Mark A. *The engines of European integration: delegation, agency, and agenda setting in the EU*. Oxford University Press, USA, 2003.

102 Gehring and Krapohl (2007)

103 Ibid

NAs, but *not necessarily* so much in the eyes of EU consumers - is key to its approach to licensing.

1.6.3 Capture by Default

Capture by default has already been described above in the NAs section, and I remarked there that it was attributable to the payment of user fees and the fact that the sponsoring (industry) firm provides the data. What capture by default really means here is that consumers are kept out of the process due to there being no direct to consumer accountability. This has the effect that, relative to the FDA, the EMA and the NAs are likely to accommodate industry a lot more often, to license products more quickly and to cooperate a lot more with industry (in the later stages) to ensure that a product which appears to have a positive risk-benefit profile will receive a license.

Table 7 The EMA and the NAs Key Characteristics

NAs/EMA
'Double' (NAs) and then 'Treble' (EMA) 'Insulation'
Capture by Default
Science Excludes Politics

Capture here, therefore, need not had negative connotations which recall the behaviour of the William S Merrel Company (marketing Thalidomide) to Frances Kelsey in 1961. It is not that industry directly pressures the EMA/NAs or their officers – strict rules limit the amount of interaction between the agencies and industry. However, in the absence of capture by consumers (as direct to consumer accountability might be described) capture by industry will result.[104] The key characteristics of the EMA and NAs are summarised in Table 7 above.

104 '*Capture by Consumers v Capture by Industry':* A point implicitly made in Chapter Two is that capture by consumers would lead to a preference for Type II errors over Type I errors, because consumers prefer caution and become activist in response to scandals and disasters. Behavioural science has shown that in their responses, ordinary (non-expert) consumers are likely subject to probability neglect and to system neglect. Capture by industry in the form of a politicised agency which actively sought to ignore science, in favour of industry demands, would lead to a preference for Type I errors over Type II errors. However, most pharmaceutical firms are already incentivised to produce safe products from a reputational perspective and in response to incentives set by the possibility of liability. Thus, firms which seek a license for a new product will likely already have established that the product is safe. Thus, if an agency wishes to minimise the sum of the cost of Type I and Type II errors then it should seek to accommodate industry as much as possible, and to work with the sponsoring firm to get the product to market. This is what the EMA (rapporteur NAs) effectively does by providing advice to industry and by accepting user fees. That is 'capture by default', but that is only relative capture by industry (not consumers) compared to the FDA capture by consumers. Which results from direct to consumer accountability.

1.7 Conclusions

In this Chapter I have provided a great deal of historical and factual information relating to the US and the European pharmaceutical regulatory systems. In Section 1.4 Key Characteristics of the Food and Drug Administration to Section 1.6 Key Characteristics of the European Medicines Agency I have drawn this information together with other primary (empirical) and secondary (analytic) evidence found in the literature regarding the FDA, the NAs and the EMA to argue for a 'characterisation' of these agencies encompassing some key characteristic about their behaviours and approaches.

The key characteristics of the FDA, the NAs and the EMA are set out again in Table 8 **The FDA, the EMA and the NAs Key Characteristics** below.

Table 8 The FDA, the EMA and the NAs Key Characteristics

FDA	NAs/EMA
'Direct to Consumer Accountability'	'Double' (NAs) and then 'Treble' (EMA) 'Insulation'
Relative Resistance to Industry Influence	Capture by Default
Politicised Science	Science Excludes Politics

In Chapters Two through Four I draw upon this characterisation when undertaking a private interest analysis of the regulatory divergence in each case. This is most useful in the case of licensing and DTCA in Chapter Two, however, due to the importance of the agencies in the regulatory systems it is also relevant for each of the other divergences. In Chapters Five and Six I return to these characterisations of the agencies as the basis for a cultural analysis of them. As such, the work undertaken in this Chapter remains relevant throughout the whole remainder of this thesis.

Chapter Two: Licensing and Direct to Consumer Advertising

2.1 Introduction

> *"A £100 reward will be paid by the Carbolic Smoke Ball Company to any person who contracts the increasing epidemic influenza colds, or any disease caused by taking cold, after having used the ball three times daily for two weeks, according to the printed directions supplied with each ball. £1000 is deposited with the Alliance Bank, Regent Street, showing our sincerity in the matter"*
>
> *The Pall Mall Gazette, London, 13 November, 1891*

Far from being sincere in the matter, the Carbolic Smoke Ball Company refused to pay out after poor Mrs Carlill purchased the device yet, despite using it as instructed for nearly two months, contracted flu on the remarkably specific date of 17 January 1892.[1]

Her plight gave rise to a familiar case in English contract law: *Louisa Carlill v Carbolic Smoke Ball Company* and – finding that the promise made in the *Pall Mall Gazette* was a serious one - the court granted compensation to the plaintiff. Most likely, the smoke ball was never an effective product. Perhaps it was not even safe. In 1891 there was no pre-market licensing requirement for pharmaceutical products. Coupled with few legal controls over advertising claims, this exposed consumers to financial and physical harm. Where an unsafe product reaches the market it will be more widely consumed, and thus cause more damage, if it has been advertised. Thus, regulators may wish to restrict advertising and be cautious in licensing where consumer protection is paramount. On the other hand, a safe product which is denied market access, or which is granted market access but cannot be advertised, is likely to be under-consumed: costing consumers the foregone health benefits of consumption.

In this Chapter I apply extant theories of regulation to seek explanation for regulatory divergence in the licensing of pharmaceutical products, and in direct to consumer advertising of prescription-only pharmaceutical products (DTCA), in the United States (US) and the European Union (EU). Approaches to regulating both diverge across these two jurisdictions. Here, I seek to explain these divergences using public and private interest approaches to regulation, as well as through considering institutional differences.

I begin in Section 2.2 Licensing and Direct to Consumer Advertisingby setting out the divergences, then in Section 2.3 Public Interest ApproachI ask which jurisdiction's regulatory positions is most readily justified by public interest theory. At this stage I identify an initial 'public interest puzzle' which is that each jurisdiction is inconsistent between its approaches to each area. In one area they regulate cautiously and in the other, permissively. Whilst it may be the case

1 Carlill v Carbolic Smoke Ball Company [1893] 1 QB 256 at p256 *"The plaintiff, a lady, on the faith of this advertisement, bought one of the balls at a chemist's, and used it as directed, three times a day, from November 20, 1891, to January 17, 1892, when she was attacked by influenza".*

that caution in one area makes up for a lack of caution in the other, this still does not fully explain why one jurisdiction has chosen a system configured towards caution in licensing and the other towards caution in advertising.

To seek further explanation, in Section 2.4 Private Interests, Groups, Organisations, and InstitutionsI look beyond the regulation itself and potential public interest justifications, towards the groups and organisations which brought the regulation into being, and their private interests. Here, I draw upon my characterisation of the US Food and Drug Administration (FDA), the EU European Medicines Agency (EMA) and the EU Member States' (EUMS) national agencies (NAs) which is set out in set out in the 1.7 Conclusions to Chapter One. I also draw upon a charaterisation developed in this Chapter in relation to doctors and consumers in the US and the EU. I find that an extended version of Daniel Carpenter's 'reputation' model of bureaucracy behaviour[2] aptly explains why the US has chosen its approach - and the EU its approach - to licensing. However, another puzzle – the 'private interest puzzle' - is then presented. The extended reputation model would suggest that the US would ban DTCA and the EU would permit it, yet the inverse is true. I turn finally to institutional analysis to resolve the private interest puzzle and I conclude that the legal institution of free speech protection in the US constrains the ability of the FDA to ban DTCA, whilst the institution of socialised healthcare in the EU constrains the ability of the EU Commission to lift the ban on DTCA.

2 See Carpenter, Daniel P. "Groups, the media, agency waiting costs, and FDA drug approval." American Journal of Political Science (2002): 490-505. Carpenter, Daniel P. "Protection without capture: Product approval by a politically responsive, learning regulator." American Political Science Review 98, no. 4 (2004): 613-631. Carpenter, Daniel P. "The political economy of FDA drug review: processing, politics, and lessons for policy." Health Affairs 23, no. 1 (2004): 52-63. Carpenter, Daniel Paul, Brian Feinstein, Colin Moore, Marc Turenne, Ian Yohai, and Evan James Zucker. "Why Do Bigger Firms Receive Faster Drug Approvals?" (2004). Carpenter, Daniel. "Reputation, Information and Confidence: The Political Economy of Pharmaceutical Regulation." Chapters (2010). Carpenter, Daniel P., and George A. Krause. "Reputation and public administration." Public administration review 72, no. 1 (2012): 26-32.

2.2 Licensing and Direct to Consumer Advertising

In this Section I set out the divergent approaches to licensing and DTCA before turning, in Section 2.3 Public Interest Approach to Section 2.4 Private Interests, Groups, Organisations, and Institutionsto seek an explanation using the extant theories of public interest and private interest as well as institutional analysis.

2.2.1 Licensing

A detailed history and overview of the regulation of advertising and licensing is given in Chapter One. The legal standard for licensing at both the FDA and EMA/NAs is based on a cost benefit analysis regarding the safety and efficacy of the product.[1] At the FDA most pharmaceutical products which are drugs are evaluated by the New Drugs Committee ('NDC') at the Center for Drug Evaluation and Research ('CDER'). The usual procedure is the New Drug Application ('NDA').[2] The NDC assesses a dossier of clinical trials data[3] provided by the sponsoring firm and asks: 1) whether the drug is safe and effective in its proposed use(s) and whether the benefits of the drug outweigh the risks; 2) whether the drug's proposed labelling (package insert) is appropriate, and what it should contain; and 3) whether the methods used in manufacturing the drug and controls used to maintain the drug's quality are adequate to preserve the drug's identity, strength, quality and purity.[4] If the NDA is approved, the product may be marketed in the US.

The Prescription Drug User Fee Act (PDUFA) and subsequent legislation[5] introduced expedited procedures. One is 'priority review'[6] and this designation means the FDA will aim to take

1 In both cases therefore the product would receive a license if the evidence submitted by the sponsoring firm – after analysis by the agency – proves the product to be safe and effective.

2 In addition to the standard procedure – NDA – there is the Investigational New Drug procedure ('IND') which applies to drugs to allow them to be transported within the US before clinical trials begin in anticipation of an NDA. There is also the 'Abbreviated New Drug Application' (ANDA) which applies to generic products. Here, generic products do not need to include preclinical (animal) and clinical human) data to establish safety and efficacy, the sponsor need only show that the product is bioequivalent to an originator product. Special procedures also apply to 'over-the-counter' products (i.e. those which will be made available on general sale (GSALE)) and to biologic products such as vaccines.

3 The dossier presented by the sponsoring firm to the FDA *"must contain data from specific technical viewpoints for review, including chemistry, pharmacology, medical, biopharmaceutics, and statistics."* See https://www.fda.gov/drugs/types-applications/new-drug-application-nda

4 See https://www.fda.gov/drugs/types-applications/new-drug-application-nda

5 Including a later Act – the Food and Drug Administration Modernization Act of 1997 ('FDAMA') – which introduced both performance targets and expedited review procedures.

6 Which applies where the product in question would be *"a significant improvement in the safety or effectiveness of the treatment, diagnosis or prevention of a serious or life-threatening disease"* See Reichert, Janice M., and

action on an application within six months compared to the ten months under standard review.[7] There is also 'fast track', 'breakthrough therapy' and 'accelerated approval.'[8] In each case the FDA will decide - upon application by the sponsoring firm - whether the product qualifies for an expedited designation, and the criteria for doing so are arguably open to politically motivated disagreement.

In the EU, the centralised procedure[9] is the means through which the *"great majority"* of new drug products marketed in the EU/EUMS are approved. According to Reichert and Healy the standard centralised procedure operates (as of 2001) as follows: six months prior to submission, notification of the intention to submit a product dossier is sent to the EMA. Next, the dossier is submitted and the EMA has 15 days to validate it and start the review process. Scientific review should be undertaken by the Committee on Medicinal Products for Human Use (CMPH) - the rapporteur and co-rapporteur - within 120 days. The 'clock' is then 'stopped' to allow time for the sponsoring firm to answer questions and/or address any issues raised by the CMPH. That 'clock-stop' time should not exceed 182 days. One the sponsoring firm has responded, the clock restarts. The CMPH then should give a final scientific opinion within 90 days. The EMA then has 30 days to finalise a report to the Commission.

The Commission is required to make its final decision public within 60 to 80 days after receipt of the report from the EMA/CMPH. The EMA also has expedited review procedures in including 'accelerated assessment' which reduces the timeframe for the CMPH to review an application under the centralised procedure. This procedure will be used where *"the CMPH*

Elaine M. Healy. "Biopharmaceuticals approved in the EU 1995–1999: a European Union–United States comparison." *European journal of pharmaceutics and biopharmaceutics* 51, no. 1 (2001): 1-7 at pg. 2

7 See https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/priority-review

8 Fast track is a designation which is *"designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose is to get important new drugs to the patient earlier."* If a drug receives a fast track designation the sponsoring firm will benefit from more regular meeting with the FDA to discuss the progress of the drug's development and licensing. It will be eligible for accelerated procedure and priority review and it may be eligible for 'rolling review' meaning that sections of the NDA can be sent to the FDA as and when they are completed. See https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track. Breakthrough therapy designation *"is a process designed to expedite the development and review of drugs that are intended to treat a serious condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)… A drug that receives Breakthrough Therapy designation is eligible for… All Fast Track designation features… Intensive guidance on an efficient drug development program, beginning as early as Phase 1… (and) Organizational commitment involving senior managers."* See https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy. Accelerated approval allows *"for serious conditions that filled an unmet medical need to be approved based on a surrogate endpoint."*

9 *"This procedure is compulsory for human medicines containing a new active substance to treat: HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune system dysfunctions and viral diseases; medicines derived from biotechnology processes, such as genetic engineering; advanced-therapy medicines such as gene-therapy, somatic cell-therapy or tissue-engineered medicines; and orphan medicines (for rare diseases). It is optional for other medicines which: contain a new active substance for indications other than those for which the centralised procedure is compulsory; that are a significant therapeutic, scientific, or technical innovation; and whose authorisation would be in the interest of public… health at EU level."* See https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines See also https://www.ema.europa.eu/en/documents/other/laboratory-patient-journey-centrally-authorised-medicine_en.pdf

decides the product is of major interest for public health and therapeutic innovation".[10] Whilst under the standard centralised procedure (not including clock-stop time) licensing can take up to 210 days, under the accelerated procedure this can be cut to 150 days.[11]

I consider two aspects of licensing. The first is times to approval ('TTAs') – the time it takes for the FDA and the EMA to approve a product application. The reason for comparing licensing times rather than overall licensing volume (i.e., the 'pass rate' of license applications) is that most products which end up marketed globally are granted a license by both agencies, and products which fail to be approved by one are generally denied a market-access license by both. The major difference between the agencies is therefore the time taken to consider license applications, which reflects - as argued in the literature set out below - different levels of caution at those agencies regarding potential safety concerns. The second aspect is a comparison of the frequency with and form in which products – once licensed – are subject to post-market safety measures ('PSMs').

Licensing TTAs

Between 1962 and 1976 the US experienced slower TTAs compared to the EU/EUMS.[12] Compared with the UK, for example, during this period four times more new drugs became exclusively available in the UK as in the US and overall, twice as many new drugs were introduced in the UK than in the US.[13] According to Wardell and others the drugs lag was caused by excessive FDA caution in licensing.[14] Daemmrich explains that by the 1980s the

10 See https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/accelerated-assessment

11 In addition, the CMPH, *"may recommend that the marketing authorization be granted `under exceptional circumstances', a designation which allows medicines to be approved when comprehensive data on quality, efficacy, and safety under normal conditions cannot be provided."* In this case what is granted is a conditional marketing authorisation. Reichert and Healy (2001) at pg. 2. See also https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/conditional-marketing-authorisation *"The EMA supports the development of medicines that address unmet medical needs. In the interest of public health, applicants may be granted a conditional marketing authorisation for such medicines on less comprehensive clinical data than normally required, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required. Medicines for human use are eligible if they are intended for treating, preventing or diagnosing seriously debilitating or life-threatening diseases. This includes orphan medicines .Its use is also intended for a public health emergency (e.g. a pandemic). For these medicines, less comprehensive pharmaceutical and non-clinical data may also be accepted."*

12 See Grabowski, H. G. Regulation and the international diffusion of pharmaceuticals. In The International Supply of Medicines—Implications of U.S. Regulatory Reform, edited by Helms, R. B. , pp. 5–36. American Enterprise Institute, Washington, D.C., 1980. See also Henninger, Daniel (2002). "Drug Lag". In David R. Henderson (ed.). Concise Encyclopedia of Economics (1st ed.). Library of Economics and Liberty. OCLC 317650570, 50016270, 163149563

13 Wardell, W. M. Introduction of new therapeutic drugs in the United States and Great Britain: An international comparison. Clin. Pharmacol. Ther. 14: 773–790, 1973. See also Wardell, W. M. Therapeutic implications of the drug lag. Clin. Pharmacol. Ther. 15: 73–96, 1974. Wardell, William M. "The drug lag revisited: comparison by therapeutic area of patterns of drugs marketed in the United States and Great Britain from 1972 through 1976." Clinical Pharmacology & Therapeutics 24, no. 5 (1978): 499-524. See also Bakke, Olav M., William M. Wardell, and Louis Lasagna. "Drug discontinuations in the United Kingdom and the United States, 1964 to 1983: issues of safety." Clinical Pharmacology & Therapeutics 35, no. 5 (1984): 559-567. See also Kaitin, K. The drug lag: An update of new drug introductions in the United States and in the United Kingdom, 1977 through 1987. Clin. Pharmacol. Ther. 46: 121–138, 1989 and Coppinger, P. L., Peck, C. C., Temple, R. J. Understanding comparisons of drug introductions between the United States and the United Kingdom. Clin. Pharm. Ther. 46: 139–145, 1989.

14 Daemmrich, Arthur. "Invisible monuments and the costs of pharmaceutical regulation: twenty-five years of drug lag debate." *Pharmacy in history* 45, no. 1 (2003): 3-17 at pg.3-4

FDA, *"relented and changed regulatory procedures. As a result, new drugs came on the market more quickly, ending the political saliency of comparisons with approval rates in other countries."* Considering the drugs lag in 1992 from an intra-European perspective, Andersson[15] found that the Swedish and Norwegian agencies up to this point had TTAs like the FDA but that the UK and West Germany had the quickest TTAs. These - and France - licensed the greatest number of new drugs out of the US and all EUMS. Since Congress enacted PDUFA, TTAs have changed at the FDA, although it is not the case that the FDA is now faster than the EMA/NAs. The FDA now licenses fast *and* slow relative to the NAs/EMA: it is inconsistent on TTAs. These depend upon the type of product seeking a license, which in turn determines whether the FDA will use its expedited procedures. I describe this here as a 'bifurcated' approach and I summarise it in Table 9 **Bifurcated TTAs at the FDA** below. I argue below that despite the bifurcation, the approach of the FDA relative to the EMA/NAs in general is still cautious due to the correlation of PSMs at the FDA with faster TTAs.

Table 9 Bifurcated TTAs at the FDA

TTAs	Types of Product	Procedure
Relatively fast compared to NAs/EMA	Products to treat 'media-friendly' diseases such as certain cancers and arthritis	Expedited
Relatively slow compared to NAs/EMA	All other products	Standard

Several studies conducted over the past decade indicate that the FDA now has quicker TTAs than the EMA for certain pharmaceutical products. Cassie et al note that median TTAs for new drugs at the FDA decreased by over half: from 33.6 months in 1979-1986 to 16.1 months in 1997-2002.[16] Cabiedes[17] considered licensing times for innovative pharmaceutical products between 1995 and 2003. The mean TTA in the US was longer - 18.2 months compared to the EU's 14.7 months. However, *"in both cases, the approval time for priority drugs* (expedited review) *authorised by the FDA was markedly shorter"* than for the EMA/NAs using their

15 Through a literature review. Andersson F. The Drug Lag Issue: The Debate Seen from an International Perspective. International Journal of Health Services. 1992;22(1):53-72. doi:10.2190/9Y32-X86Y-M3F0-JQFC at pg. 53-54. See also Ricardo-Campbell, R. Drug Lag: Federal Government Decision Making. Hoover Institution Studies 55. Hoover Institution Press, Stanford University, Stanford, Calif., 1976. See also: de Haen, P. The drug lag—Does it exist in Europe? Drug Intell. Clin. Pharm. 9: 144–150, 1975. Grabowski, H. G., Vernon, J. M. Innovation and invention—Consumer protection regulation in ethical drugs. Am. Econ. Rev. 67: 359–364, 1977. Hass, A. E. A Historical Look at Drug Introductions on a Five-Country Market—A Comparison of the United States and Four European Countries (1960–1981). Ope Study No. 60. Office of Planning and Evaluation, Food and Drug Administration, Washington, D.C., 1982. Berlin, H., Jönsson, B. International dissemination of new drugs: A comparative study of six countries. Managerial and Decision Economics 7: 235–242, 1986. Parker, J. Who has a lag? J. Soc. Admin. Pharm. 6: 138–152, 1989.

16 Frank, Cassie, David U. Himmelstein, Steffie Woolhandler, David H. Bor, Sidney M. Wolfe, Orlaith Heymann, Leah Zallman, and Karen E. Lasser. "Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals." *Health affairs* 33, no. 8 (2014): 1453-1459 at pg. 1454

17 Cabiedes Miragaya, Laura. "Authorisation and Withdrawal of Pharmaceutical Innovations in the European Union and in the United States (1995-2003)." *Documentos de trabajo (Universidad de Oviedo. Facultad de Ciencias Económicas)* (2005).

standard procedures. In 2017 Downing et al[18] looked at TTAs for 142 drugs approved by both the EMA and FDA between 2011 and 2016. The median TTA at the FDA was 303 days and at the EMA was 369 days. In a recent (2020) review Joppi et al[19] looked at review times at the FDA and the EMA for novel drugs between 2015 and 2017 and found that *"the median review time was longer at the EMA than FDA and was shorter for drugs undergoing FDA-expedited programmes compared to the same drugs approved by the EMA through the standard procedure."*

It is noted by many, therefore, that faster FDA TTAs are correlated with use of expedited procedures. Carpenter notes that[20] certain diseases are likely to receive more attention in media coverage than other diseases and suggests that volume of media coverage is correlated with use of expedited procedures by the FDA. He highlights cancer treatments as a clear example. Downing et al[21] found shorter TTAs at the FDA for cancer treatments, treatments for hematologic disease, and for orphan drugs, but not for other products. In relation to certain cancer drug approvals between 1999 and 2014, Hatswell at al[22] found that "*of the applications made to both agencies with a comparable data package, the FDA granted more approvals (43/44 vs 35/44) and took less time to review products (8.7 vs 15.5 months)."* Sifuentes notes[23] that *"approval time for oncology therapeutics* (at the EMA)... *is on average twice as long as in the US"* although a part of this difference is attributable to clock-stopping at the EMA and the time taken for formal approval to be given by the Commission, at the end of the process.

Roberts et al[24] found concurring results: reviewing oncology drug approval between 2003 and 2010 they found a median TTA for new cancer drugs at six months for the FDA, typically becoming available in the US before they do in the EU. Leo et al[25] considered approval times for breast cancer drugs between 1995 and 2018 and found that of the 17 approved by both the FDA and the EMA on average these became available 12 months earlier in the US than the EU. They point out major differences in the FDA and EMA use of expedited procedures for these drugs. The FDA granted expedited review to 19 out of 25 of its approved drugs yet the EMA granted priority review to none and the FDA granted four accelerated approvals (later revoking one). The EMA gave only two of the drugs which it considered, conditional approval. Looking just at the FDA and EMA approvals of a novel cancer drug (antineoplastic

18 Downing, N.S., Zhang, A.D. and Ross, J.S., 2017. Regulatory review of new therapeutic agents—FDA versus EMA, 2011–2015. *New England Journal of Medicine*, *376*(14), pp.1386-1387 at pg. 1387.

19 Joppi, Roberta, Vittorio Bertele, Tommaso Vannini, Silvio Garattini, and Rita Banzi. "Food and Drug Administration vs European Medicines Agency: Review times and clinical evidence on novel drugs at the time of approval." *British journal of clinical pharmacology* 86, no. 1 (2020): at pg. 170.

20 Carpenter (2004)

21 Downing, Zhang, and Ross (2017) at pg. 1387

22 Hatswell, Anthony J., Gianluca Baio, Jesse A. Berlin, Alar Irs, and Nick Freemantle. "Regulatory approval of pharmaceuticals without a randomised controlled study: analysis of EMA and FDA approvals 1999–2014." *BMJ open* 6, no. 6 (2016).

23 Sifuentes MM, Giuffrida A (2015) Drug Review Differences across the United States and the European Union. Pharmaceut Reg Affairs 4: e156. doi:10.4172/2167-7689.1000e156

24 Roberts, Samantha A., Jeff D. Allen, and Ellen V. Sigal. "Despite criticism of the FDA review process, new cancer drugs reach patients sooner in the United States than in Europe." *Health Affairs* 30, no. 7 (2011): 1375-1381 at pg. 1378.

25 Leo, Chandra P., Bettina Hentschel, Thomas D. Szucs, and Cornelia Leo. "FDA and EMA approvals of new breast cancer drugs—A comparative regulatory analysis." *Cancers* 12, no. 2 (2020): 437.

tyrosine kinase inhibitors) Shah et al[26] found that the FDA granted priority review to twelve of these whilst the EMA did not grant accelerated assessment to any. The average TTA at the FDA was thus 205.3 days, whereas at the EMA it 409.6 days. However, again, some of the difference was due to EMA clock-stopping and Commission formal approval time. Hence the difference in active review times (even taking in to account the fact that the FDA was using its expedited procedures) was 225.4 days at the EMA and 205.3 days at the FDA.

However, when the use of expedited procedures is discounted, and looking only at active review times, it seems that the EMA/NAs may remain the quicker agencies in TTAs. Looking at a selection of 27 biopharmaceutical products approved both by the EMA and the FDA between 1995 and 1999, Reichert and Healy found[27] that (discounting clock-stopping) the mean EMA approval time for these products was 48 days shorter (at 322 days) than at the FDA (360 days). More of these products received priority review at the FDA, and those that did received TTAs 32% faster than at the EMA. Where the EMA did use its expedited approval (exceptional circumstances) procedure, these products were only approved *"slightly faster on average"* than products reviewed using the standard EMA procedure. Most importantly, the FDA took 48% longer than the EMA, on average, where both used their standard procedures.

It is useful to turn briefly to international comparisons which go beyond the US and the EU in order to provide a broader perspective, and further insight in to what factors may account for differences in TTAs. Comparing drug approval times across all new drugs in the US, EU, and Japan between 1999 and 2007 Tsuji and Tsutani[28] found that there was a lag of only 2.7 months for the EU compared to the US whereas that between the US and EU (on one hand) and Japan (on the other), was much more significant. Looking specifically at cancer drugs, Samuel and Verma[29] found a more significant difference between the EMA and the FDA, which put the EMA on a par with the Canadian agency (Health Canada) at circa 6.5 months behind the FDA in TTAs. Their analysis confirmed that this was due to greater use of accelerated approval mechanisms at the FDA. Rawson[30] also considered differences between Canada, the EU and the US (between 1998 and 2018) and found that, "*approval times in Canada, Europe and the US have been consistent in the last decade."* In 2018 they were very similar to each other – consistent with the other studies considered here. Between 2002 and 2016 the median TTA at the FDA was 304 days, at the EMA 371 days and at Health Canada 364 days. This review did not discount clock stopping or differentiate between the agencies' use of expedited procedures. Importantly, it noted greater consistency in licensing times at the EMA over the 1998-2018 period than at the FDA, which saw a sharp difference in average TTAs before and after 2005. The FDA therefore has been less consistent than the EMA in its

26 Shah, Rashmi R., Samantha A. Roberts, and Devron R. Shah. "A fresh perspective on comparing the FDA and the CMPH/EMA: approval of antineoplastic tyrosine kinase inhibitors." *British journal of clinical pharmacology* 76, no. 3 (2013): 396-411 at 396.

27 Reichert and Healy (2001) at pg. 2

28 Tsuji, K., and K. Tsutani. "Approval of new drugs 1999–2007: comparison of the US, the EU and Japan situations." *Journal of clinical pharmacy and therapeutics* 35, no. 3 (2010): 289-301 at pg. 290.

29 Samuel, N., and S. Verma. "Cross-comparison of cancer drug approvals at three international regulatory agencies." *Current Oncology* 23, no. 5 (2016): e454.

30 Rawson, Nigel SB. "Canadian, European and United States new drug approval times now relatively similar." *Regulatory Toxicology and Pharmacology* 96 (2018): 121-126.

average licensing times in recent decades and less consistent *between* products in TTAs due to inconsistent use of its expedited procedures.[31]

I conclude as follows from this review of the literature concerning TTAs: 1) between the late 1960s and the early 1980s (at least) there was a pronounced drugs lag and average TTAs for the FDA were significantly longer than that for the NAs in the EUMS (particularly the UK and West Germany). 2) Since the 1990s-2000s both the FDA and the EMA are world leaders in TTAs for pharmaceutical product licensing generally. 3) The FDA makes greater use of its accelerated procedures than does the EMA, and it may do this more often in the case of certain types of product, such as drugs to treat cancer. 4) When the FDA uses its expedited procedures it more often achieves faster TTAs than the EMA does. 5) Some of the difference between the FDA expedited procedure TTAs and the EMA standard procedure TTAs results from the practice of stopping the clock at the EMA and for the additional time required at the end of the licensing process for the Commission to formally grant approval. 6) The FDA approach where it does not use its expedited procedure is still likely to result in longer TTAs than the standard approach adopted at the EMA, at least in terms of active review times. 7) Most importantly though, as set out in Chapter One, it has been found that where the FDA uses its expedited procedures to license with fast TTAs, its tendency is to restrict the approved indications in the license.[32] Pharmaceutical firms can thus obtain either 'speed' or 'scope' on an application. This means that the FDA's approach overall remains cautious compared to that at the EMA. That is because the latter has relatively consistent TTAs: not so frequently expedited and not observed to be 'offset' by a restriction upon approved indications, and which are nevertheless generally faster than the FDA's non expedited TTAs. The observation regarding 'speed v scope' is linked, also, to the use of PSMs at the FDA.

Licensing PSMs

PSMs increase in frequency with faster TTAs at the FDA,[33] thus reinforcing the point made above that where the FDA expedites review, it offsets this speed through the effect of some measure of caution, be that a restriction upon indications, or a PSM. Cassie et al note that *"drugs approved after* (PDUFA's) *passage were more likely to receive a new black-box warning or be withdrawn than drugs approved before its passage (26.7 per 100.0 drugs versus 21.2 per 100.0 drugs at up to sixteen years of follow-up)."*[34] At the EMA/NAs it seems that approval near the review deadline does not affect the likelihood that PSMs will follow later. Zeitoun et al found that, *"neither faster EMA regulatory review speed nor approval near regulatory*

31 See also Downing, Nicholas S., Jenerius A. Aminawung, Nilay D. Shah, Joel B. Braunstein, Harlan M. Krumholz, and Joseph S. Ross. "Regulatory review of novel therapeutics—comparison of three regulatory agencies." *New England Journal of Medicine* 366, no. 24 (2012): 2284-2293 at pg. 2284.

32 Barber IV, Benjamin, and Luis Diestre. "Pushing for speed or scope? Pharmaceutical lobbying and Food and Drug Administration drug review." Strategic Management Journal 40, no. 8 (2019): 1194-1218.

33 Abraham, John, and Courtney Davis. "A comparative analysis of drug safety withdrawals in the UK and the US (1971–1992): implications for current regulatory thinking and policy." *Social Science & Medicine* 61, no. 5 (2005): 881-892. Frank, Cassie, David U. Himmelstein, Steffie Woolhandler, David H. Bor, Sidney M. Wolfe, Orlaith Heymann, Leah Zallman, and Karen E. Lasser. "Era of faster FDA drug approval has also seen increased black-box warnings and market withdrawals." *Health affairs* 33, no. 8 (2014): 1453-1459 at pg. 1454

34 Cassie et al (2014) at pg. 1453.

deadlines was associated with greater likelihood of PMSEs among recently approved novel medicines."[35]

The FDA – relative to the international community as a whole – is reluctant to issue full market withdrawals of products. Ninan and Wertheimer show that between 1979 and 2012, of the 151 drugs on the UN Banned Drug list *"Only 67 % of the 151 drugs that were on the List were banned by the U.S, while internationally 79 % were banned."*[36] This is also true of the EMA, given that rates of withdrawal between the EMA and the FDA are very similar: between 1995 and 2003, *"2.2 % in the US and between 1.6 % and 2.7 % in the EU."* according to Cabiedes.[37] Compared to other agencies, the rate of withdrawal by both the FDA and the EMA seem low. Rawson found *"rates of drugs withdrawn for safety reasons were 1.4% in Canada, 0.9% in Europe and 0.8% in the United States."*[38] Both the EMA and the FDA extensively use warnings. Lasser et al[39] in 2002 say *"out of the 548 drugs that were approved in the U.S. between 1975-1999, fifty six (10.2 %) of them required a new black box warning or were withdrawn"*[40] and they elaborate, *"Five hundred forty-eight new chemical entities were approved from 1975-1999. Of these, 56 (10.2%) drugs acquired a new black box warning or were withdrawn from the market. In Kaplan-Meier analyses, new drugs had a 4% probability of being withdrawn from the market over the study period*". It was therefore much more common for the FDA to issue 'BlackBox Warnings' ('BBWs') than to withdraw. In the EU, Zeitoun et al[41] considered the frequency of EMA issuance of 'Dear Healthcare Provider Communications' ('DHPCs') for drugs it had approved between 2001 and 2010. They found that the issuance of a DHPC was much more likely than market withdrawal, *"among 161 eligible medicines, PSMs were identified for 49 (30.4%), 44 of which were DHPCs, five of which were withdrawals."*

The EMA/NAs generally warn healthcare professionals through non-public DHPCs rather than warning consumers directly. The FDA does the latter through BBWs. However, both the FDA and the EMA/NAs make use of DHPCs.[42] In the US, DHPCs may be issued by either the FDA or by the license holder, and the FDA has in the past few years issued guidance to industry to assist in making DHPCs more accessible, recognising that these letters are often published on the internet and read by consumer groups. In the EU, the EMA and/or the NAs may issue a DHPC (and the initiative to do so may also come from the license holder) and often the NAs will issue one based on the advice of the EMA. This may happen when the EMA or the NAs have suspended market authorisation pending further scientific investigation[43] or when

35 Zeitoun, J.-D., Lefèvre, Jé. H., Downing, N. S., Bergeron, H., and Ross, J. S. (2015) Regulatory review time and post-market safety events for novel medicines approved by the EMA between 2001 and 2010: a cross-sectional study. *Br J Clin Pharmacol*, 80: 716– 726. doi: 10.1111/bcp.12643 at pg. 716.

36 Ninan, Benson, and Albert I. Wertheimer. "Withdrawing drugs in the US versus other countries." (2012).

37 Cabiedes (2005).

38 Rawson (2018) at pg.126.

39 Lasser, Karen E., Paul D. Allen, Steffie J. Woolhandler, David U. Himmelstein, Sidney M. Wolfe, and David H. Bor. "Timing of new black box warnings and withdrawals for prescription medications." *Jama* 287, no. 17 (2002): 2215-2220.

40 As quoted in: Ninan and Wertheimer (2012).

41 Zeitoun et al (2015) at pg. 716.

42 The FDA updated its guidance on DHPCs in 2017 see https://www.fda.gov/regulatory-information/search-fda-guidance-documents/dear-health-care-provider-letters-improving-communication-important-safety-information

43 Sifuentes (2015)

either of these issues a full market withdrawal. As of 2014 only the UK, France, Spain, and the Netherlands made DHPCs publicly available, which comprised less than half of the EU population at the time.[44] An example of an EMA DHPC is shown below in Figure 2 **Example of EMA DHCP from October 2017**.[45]

<Date>

<Active substance, name of medicinal product and main message *(e.g. introduction of a warning or a contraindication)*>

Dear Healthcare professional,

<Name of marketing authorisation holder> in agreement with <the European Medicines Agency> and the <National Competent Authority > would like to inform you of the following:

Summary

Guidance: This section should be in bold/larger font size than the other sections of the DHPC and preferably in bullet points.

- <Brief description of the safety concern in the context of the therapeutic indication, recommendations for risk minimisation (e.g. ***contraindications, warnings, precautions of use)*** and, if applicable, switch to alternative treatment>
- <Recall information, if applicable, including level (pharmacy or patient) and date of recall>

Background on the safety concern

Guidance: This section may include the following information:

<Brief description of the therapeutic indication of the medicinal product>

<Important details about the safety concern (adverse reaction, seriousness, statement on the suspected causal relationship, and, if known, the pharmacodynamic mechanism, temporal relationship, positive re-challenge or de-challenge, risk factors)>

<An estimation of the frequency of the adverse reaction or reporting rates with estimated patient exposure>

<A statement indicating any association between the adverse reaction and off-label use, if applicable>

<If applicable, details on the recommendations for risk minimisation>

<A statement if the product information is to be or has been revised, including a description of the changes made or proposed> ***Guidance: No need however to include or attach the precise (translated) text of the product information which, at the time of dissemination of the DHPC may not be available as final approved translations)***

<Place of the risk in the context of the benefit>

<The reason for disseminating the DHPC at this point in time>

<Any evidence supporting the recommendation (e.g. include citation(s) of key study/ies)>

<A statement on any previous DHPCs related to the current safety concern that have recently been disseminated>

<Any schedule for follow-up action(s) by the marketing authorisation holder/competent authority, if applicable>

Call for reporting

<A reminder of the need and how to report adverse reactions in accordance with the national spontaneous reporting system, including the details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>

<For biological medicinal products, also include a reminder to report the product name and batch details>.

<Mention if product is subject to additional monitoring and the reason why>

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

Annexes (if applicable)

<Link/reference to other available relevant information, such as information on the website of a competent authority>

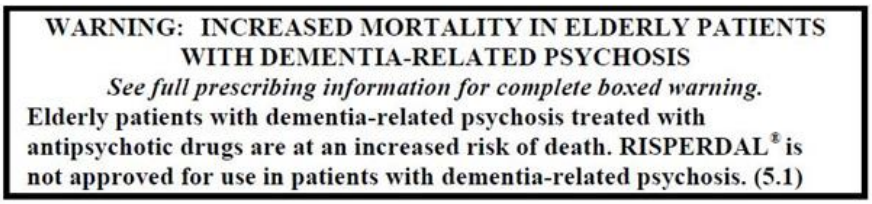
<Additional scientific information, if applicable>

<List of literature references, if applicable>

44 Zeitoun et al (2015) at pg. 716.

45 https://www.ema.europa.eu/en/documents/template-form/guideline-good-pharmacovigilance-practices-annex-ii-templates-direct-healthcare-professional_en.pdf October 2017

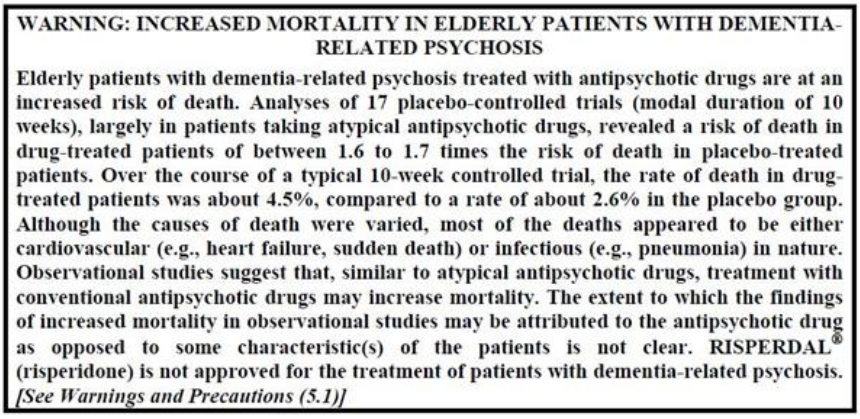
Figure 2 **Example of EMA DHCP from October 2017**



WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

See full prescribing information for complete boxed warning.

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. RISPERDAL® is not approved for use in patients with dementia-related psychosis. (5.1)



WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. RISPERDAL® (risperidone) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions (5.1)]*

Figure 3 **Example of 'BlackBox Warning' Issued by the FDA**

BBWs[46] are the PSM staple at the FDA.[47] Consistent with the tendency of the FDA to ensure that DHPCs are accessible for consumers, BBWs take a form which make them highly salient to consumers. An example is shown in

Figure 3 **Example of 'BlackBox Warning' Issued by the FDA**above.[48]

I conclude on the issue of PSMs that neither agency likes to withdraw from the market, and that the EMA in particular prefers to (and can) suspend market authorisation pending further scientific investigation. Both agencies rely heavily on warnings. At the FDA BBWs are correlated with use of expedited procedures but at the EMA/NAs PSMs have been more consistent over time and between procedures. The EMA/NAs often warn doctors through DHPCs which are inaccessible to consumers, whereas the use of BBWs at the FDA is highly salient to consumers.

46 See https://www.drugwatch.com/fda/black-box-warnings

47 Generally, the FDA prefers to make use of a black box warning than market withdrawal, Cassie et al (2014) found, *"The FDA approved 748 (new molecular entities) between 1975 and 2009. Of these… 114 (15.2 percent) received one or more black-box warnings. Thirty-two (4.3 percent) were withdrawn from the market for safety reasons. The total number of events (label changes for all black-box warnings and withdrawals) was 208"* and *"By twenty-five years after their introduction to the market, for every hundred drugs introduced to the market, there were thirty-four withdrawals or black-box warnings. Half of the new warnings appeared within twelve years of the drugs' introduction; half of the withdrawals occurred within five years. Drugs approved after the enactment of PDUFA were significantly more likely to receive a blackbox warning or withdrawal than drugs approved before PDUFA's enactment."* Cassie et al (2014) at pg. 1455

48 https://www.drugdangers.com/risperdal/black-box-warning/

2.2.2 Direct to Consumer Advertising

The legal authority for the EMA, NAs, and the FDA to regulate advertising (generally) is not so clear as it is in the case of their regulation of licensing: in fact, the EMA has no legal power to regulate advertising.[49] A detailed overview of the regulation of advertising (and DTCA) in the US has been given in Chapter One.

I add some further brief points here about the European experience. In the EU, as of 1990 all EUMS had bans in place on DTCA.[50] That ban was adopted on the EU level in Directive 92/28/EEC.[51] The period 2000 to 2002 saw the first attempt by the Commission to overturn this ban.[52] It proposed amendments to Directive 2001/83/EC to allow for the dissemination of information to patients in relation to some drugs.[53] The Commission's proposal was opposed by a range of health and consumer groups and was voted down by the EP. In 2006, a second attempt was made. The Commission, supported by the pharmaceutical industry lobby and an industry funded consumer group, *"made a legal proposal to relax the ban."* This was opposed by the European Public Health Alliance, an interest group consisting of health organisations, patients, and consumer organisations. In 2008, the Council rejected the proposal and thus DTCA remains banned under Article 88 of Directive 2001/83/EC.

2.2.3 Summary

On licensing, the FDA has taken a generally cautious approach since the 1960s. This has resulted in long TTAs at the FDA relative to the EMA/NAs, particularly in the 1960s-1970s. PDUFA led to selective use of expedited procedures for products to treat certain diseases. Now, the FDA approach to licensing is bifurcated: it licenses fast and slow. Where it uses its

49 According to Sifuentes *"Consequently, the national regulatory authorities are responsible for regulating pharmaceutical advertising, which is instead less restrictive in the United States."* Sifuentes (2015). See also https://www.fdanews.com/ext/resources/files/archives/f/FDL.pdf

50 See Geyer (2011).

51 It is now found in DIRECTIVE 2001/83/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 November 2001 on the Community code relating to medicinal products for human use. Under Article 88, *"Member States shall prohibit the advertising to the general public of medicinal products which… are available on medical prescription only , in accordance with Title VI; (b) contain substances defined as psychotropic or narcotic by international convention, such as the United Nations Conventions of 1961 and 1971. 2. Medicinal products may be advertised to the general public which, by virtue of their composition and purpose, are intended and designed for use without the intervention of a medical practitioner for diagnostic purposes or for the prescription or monitoring of treatment, with the advice of the pharmacist, if necessary. 3. Member States shall be entitled to ban, on their territory, advertising to the general public of medicinal products the cost of which may be reimbursed. 4. The prohibition contained in paragraph 1 shall not apply to vaccination campaigns carried out by the industry and approved by the competent authorities of the Member States. 5. The prohibition referred to in paragraph 1 shall apply without prejudice to Article 14 of Directive 89/552/EEC. 6. Member States shall prohibit the direct distribution of medicinal products to the public by the industry for promotional purposes."* See also Council Directive 92/28/EEC of 31 March 1992 on the advertising of medicinal products for human use.

52 Geyer (2011).

53 Ibid.

expedited procedures and licenses fast, however, it tends to license for only a shallow range of indications. Moreover, it heavily uses PSMs – particularly BBWs – where it has licensed fast under the expedited procedures. Overall, therefore, the FDA approach is still cautious. More cautious than the approach of the EMA/NAs, which have consistently had faster TTAs when considering only *active* review times and where both agencies use their standard procedures. At the EMA/NAs expedited procedures are used less often and PSMs are not correlated with review deadlines. There is a preference for non-public DHPCs over BBWs as PSMs; and, there is the possibility to suspend market authorisation and order further scientific investigation instead of ordering (or recommending) market withdrawal. On DTCA, in the US this is permitted, has never been banned, and is heavily used by industry. In the EU it has been banned in all EUMS since 1990 and at the EU level since 2001. The transatlantic divergences are summarised in their most simple form in Table 10 below. In Section 2.3 Public Interest Approach I consider the regulation of licensing and DTCA from a public interest perspective and I assess the regulatory positions taken by the US and the EU against public interest theory.

Table 10 Transatlantic Divergence in Licensing (TTAs and PSMs) and DTCA

Jurisdiction	Licensing (TTAs and PSMs)	DTCA
US	More Cautious	Permitted
EU	Less Cautious	Banned

2.3 Public Interest Approach

As set out in the introduction, the key market failure justifying regulation of the pharmaceutical sector in the case of licensing and DTCA[1] is the potential overconsumption of products which impose negative externalities upon society through adverse drug reactions (ADRs).[2] Now I consider the public interest justifications more critically and apply them to seek to justify the transatlantic divergences in licensing and DTCA.

2.3.1 Licensing

Prior approval (in the form of licensing) may be the appropriate regulatory instrument in order to avoid the risk of catastrophic harm from new pharmaceutical products.[3] Its use might achieve this by preventing consumers from gaining access to the product until the necessary information has been collected and analysed to show that the product is safe enough for use[4] and that catastrophic harm will not occur if the product is released to the market. This, combined with mandatory labelling (including instructions for use and indications) are aimed to promote optimal – neither under nor over – consumption of the product when combined with doctor matching. The purpose of licensing, therefore, is to ensure that for the class of consumers for which it is approved (in the indications and instructions for use) the benefit-risk profile of the product is positive: i.e. it is safe and effective for these consumers, when using the product correctly. If this is the case then, assuming that doctor matching is effective and that the label instructions are followed, use of the product will generate positive externalities for society and not negative externalities. If, however, the agency does not grant a license (or delays granting a license) in a case where a positive benefit-risk profile of consumption is presented, then the licensing process leads to underconsumption. Therefore, when making a licensing decision for a given indication and class of consumers and taking in to account the label instructions which can be provided, the licensing authority performs a risk versus risk trade-off between the type I and type II errors which may be made. In theory the agency, with perfect information, performs this cost-benefit analysis: weighing the expected cost to human health of permitting or denying a license, and makes the licensing decision accordingly**.** This is shown below in Table 11.

1 I note, however, that DTCA may affect the price failure too, through brand loyalty.

2 Unsafe or improperly labelled or improperly classified for sale products

3 For a basic overview of the public interest arguments in favour of prior approval see Ogus, Anthony I. Regulation: Legal form and economic theory. Bloomsbury Publishing, 2004.

4 When doctor matching is applied and when the product is correctly labelled and when the label instructions are followed by consumers

Table 11 Potential Type I and Type II Errors by the Agency

Error Type	Type I	Type II
	Safe drug unapproved	Unsafe drug approved
Costs to Human Health	Benefits foregone	ADRs

To do this the agency needs to receive information about the product – the clinical trials data found in the licensing application dossier[5] - and analyse it. The justification for this task to be undertaken by a specialised public regulatory agency is that both the information itself and the results of analysis of the information have public good qualities, being non-rival and non-excludable. The act of certification (the grant of the license) itself also has public good qualities because – alongside the mandatory labelling – it signals information about the product to consumers and to doctors.

Behavioural Complications for Public Interest Approach

What economic theorists claim to lie in the 'public interest' may, however, be very different from what the public – or consumers – actually demand from agencies. Their demands are analysed fully below in the private interest section of this Chapter; however, I believe it is useful to set out some theoretical insights here, in order to smooth the transition from public to private interest analysis later on.

The behavioural sciences have illuminated several ways in which the task set out above can be made more difficult to achieve correctly because of cognitive biases resident in various actors involved in the licensing process. Viscusi first applied behavioural insights to pharmaceuticals regulation in 1996.[6] He noted that the preference of the FDA for type I over type II errors – particularly during the 'drugs-lag' era - represents a violation of decision theory: an asymmetry between willingness to accept risk and willingness to pay to avoid a risk.[7] Cognitive biases can influence the regulation of pharmaceuticals in several different ways. These can affect bureaucratic decision makers in agencies, legislators, or ministers directly. Or, they can affect public perception of the risks posed by new pharmaceutical products. In the former case the mechanism of effect is clear, the biases lead decision makers to err on the side of caution. Alternatively, they can affect legislators and/or ministers who, in turn, put pressure on the agency through various means such as committee hearings, or the appointment and removal of senior bureaucrats.

In the case of public risk perception, this reaches policy through a more convoluted route. The legislature and executive, seeking to maximise vote share, will respond to public demand for regulation and subsequently may pressure an agency such as the FDA to take (perhaps) a cautious approach. An agency may also respond to the media or consumer pressure directly.

5 There needs to be no asymmetry of information between the firm and the agency in this respect.

6 See Viscusi, W. Kip, Wesley A. Magat, and Robert Scharff. "Asymmetric assessments in valuing pharmaceutical risks." Medical care 34, no. 12 (1996): DS34-DS47

7 He stressed that rational choice may explain this asymmetry through income or substitution effects although he considered the magnitude of the FDA's overcaution too great to be explained by these. Substitution effects may go some way towards explaining the reversal of the drugs lag for therapeutically novel drugs.

Alternatively, the legislative/executive coalition may create the agency, establishing its procedural rules or legislate to change these, and those rules and procedures may have the effect of biasing the agency towards (for example) a cautious approach. The mechanism of effect in any given case will likely be through a mixture of all these routes. Those active in the interest group may be successful only as a result of their ability to capture public attention through the media, which in turn may be attributable to cognitive biases affecting risk perception by the general public. Disease-specific interest groups, such as the 'Aids Coalition to Unleash Power' (ACT-UP) in the 1980s, have also enjoyed success due to their ability to gather wide public support.[8] Sunstein and Kuran refer to such actors as, 'availability entrepreneurs'[9] for their ability to use the media to harness the availability heuristic to further their political objectives.[10]

Those biases potentially affecting bureaucrats, legislators and government ministers are: omission effects, endowment effects, status quo bias, and regret avoidance.[11] Viscusi later added ambiguity aversion[12] which can be considered a variant on certainty effects. Omission effects indicate a preference for causing harm through inaction rather than through action, and may act upon both agency decision makers and government actors who do not wish to be politically associated with the approval of a drug which later leads to a public health disaster. Status quo bias - an exaggerated preference for the prevailing arrangement over novel proposals - is linked to omission effects. Ambiguity aversion and certainty effects may affect all relevant actors in government, the agency, and the general public. In particular: a decision maker considering an entirely new chemical entity may issue a refusal in a case where there exists uncertainty over the effects of the new drug, yet despite that uncertainty, the expected benefit would be higher for a rational decision maker than that for a drug with a fixed and known range of outcomes. Endowment effects becomes particularly prescient in the case of a regulator which has built up a reputation for protecting the public from unsafe drugs. Those biases affecting public risk perception overlap with those above. However, some biases such as system neglect and probability neglect will not likely affect those in the agencies who are assisted by a large amount of empirical data. Hence the certification function of licensing finds an additional public interest justification. Hindsight bias, on the other hand, may affect public perception of the gravity of errors previously made by the agency. The overlap it shown in the Venn diagram in Figure 4 **Relevant Cognitive Biases which may Affect Licensing (and Affected Actors)**below.

8 See Dunbar, Mary M. "Shaking up the status quo: how AIDS activists have challenged drug development and approval procedures." Food Drug Cosm. LJ 46 (1991): 673.

9 See Kuran, Timur, and Cass R. Sunstein. "Availability cascades and risk regulation." Stan. L. Rev. 51 (1998): 683.

10 These groups have generally campaigned for the relaxation of safety and efficacy standards to expedite approval, rather than advocating more stringent safety standards. I set out in more detail in the private interest section below how various groups and organisations have affected the regulation of licensing and DTCA in the US and the EU. At this stage I note how behavioural explanations may partly account for how these groups and organisations have behaved.

11 See Viscusi (1996)

12 See Viscusi, W. Kip, and Richard J. Zeckhauser. "Regulating ambiguous risks: the less than rational regulation of pharmaceuticals." The Journal of Legal Studies 44, no. S2 (2015): S387-S422

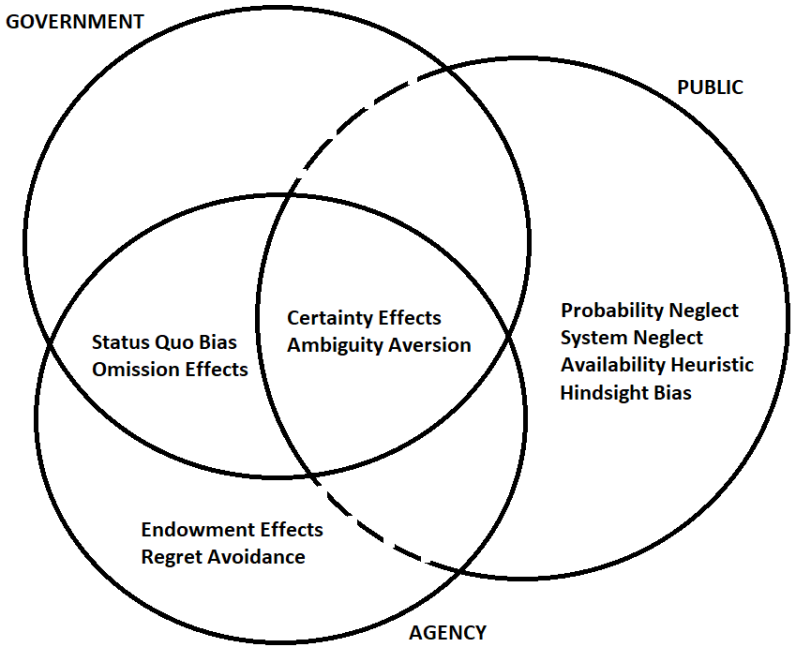


Figure 4 **Relevant Cognitive Biases which may Affect Licensing (and Affected Actors)**

System neglect and probability neglect, both reinforced by the availability heuristic,[13] are assumed to affect primarily the general public in their perception of the risk of new drugs. Cass Sunstein focuses upon these biases in, *"Laws of Fear".*[14] Probability neglect is the tendency of lay people to think about risk in 'black and white' terms, i.e. either a new drug is safe or it is not. A drug approved by the FDA which later turned out to cause an adverse reaction in a small number of people thus represents, to the public, a failure by the agency. This is despite the fact that safety is a relative concept and for all side effects to manifest, most drugs will require administration to millions. Linked to probability neglect is system neglect: the inability of the public to consider the counterfactual scenario in which the purportedly 'dangerous' drug is not approved. There are difficulties faced by the public in picturing 'statistical' lives lost because of type I errors. The role of the media in this is key. Moreover, the availability heuristic, is recognised by Sunstein,[15] to affect public perception of risk and is conditioned by the media. Both probability and system neglect may be reinforced by hindsight bias.

13 On the availability heuristic see Tversky, Amos, and Daniel Kahneman. "Availability: A heuristic for judging frequency and probability." Cognitive psychology 5, no. 2 (1973): 207-232. On system and probability neglect see Sunstein, Cass R. "The Laws of Fear, 115 Harv." L. Rev 1119 (2002): 1123. Sunstein, Cass R. "Probability neglect: Emotions, worst cases, and law." The Yale Law Journal 112, no. 1 (2002): 61-107. Sunstein, Cass R. "Terrorism and probability neglect." Journal of Risk and Uncertainty 26, no. 2-3 (2003): 121-136.

14 Sunstein (2005)

15 See Sunstein (2005). See also Sunstein, Cass R. "The availability heuristic, intuitive cost-benefit analysis, and climate change." Climatic Change 77, no. 1-2 (2006): 195-210. Sunstein, Cass R. "The law of group polarization." Journal of political philosophy 10, no. 2 (2002): 175-195. Sunstein, Cass R. "What's Available-Social Influences and Behavioral Economics." Nw. UL Rev. 97 (2002): 1295. Sunstein, Cass R. "On the divergent American reactions to terrorism and climate change." Colum. L. Rev. 107 (2007): 503.

In this subsection I have set out the basic public interest justification for a system of pharmaceutical product licensing and the reasons why it is justified in the public interest to place that/those functions in the hands of a public agency, some of which may be based upon cognitive biases which are likely to affect the public but not agency officials. I have set out what public interest theory dictates the approach should be to the licensing cost-benefit analysis, and I have set out several behavioural explanations for why the approach of a given agency may depart from that approach. Later in this Chapter, where I undertake a private interest analysis of the differences in licensing times, the behavioural complications to the public interest approach which I have set out above become crucial for understanding the demands of consumers and the responses of the agencies. That is why I have set these theoretical observations out in this section: what lies in the 'public interest' may, and often does, differ from what the general public (consumers) demands from agencies. This is a point developed throughout this Chapter and the remainder of this work. First, in the next subsection I consider a public interest approach to the regulation of DTCA.

2.3.2 Direct to Consumer Advertising

If the claims of safety and efficacy which are made in advertisements are true[16] then the ability of pharmaceutical firms to communicate information directly to consumers can help to solve the under-consumption problem. This is achieved by encouraging consumers to see a doctor, which may result in a prescription and consumption. However, if only information about benefits is provided to consumers, and information about risks is not, then this can lead to over-consumption. Surveying the literature lying in favour of DTCA: Lizuka[17] found that it has a market expanding effect, and Brekke[18] found that DTCA and detailing (advertising to doctors) are complements. Huh and Langteva[19] believe that in the long run DTCA will increase competition and lower prices for consumers. In relation to optimal information provision, Holmer[20] points out that DTCA can act as a trigger for patients to visit doctors, from which point the doctor can take over in the context of the normal patient-doctor relationship, which need not be undermined by DTCA. According to Shaw, the increase in patient visits can lead to large social benefits,[21] particularly in terms of diseases which are underdiagnosed such as high blood pressure, high cholesterol, and diabetes.

16 Something which the FDA has clear authority to ensure. In detailing and DTCA firms are only permitted to make efficacy claims in respect of indications for which the product has been licensed and thus for which efficacy has been proven. If the information communicated about the benefits of the product (efficacy claims) are untrue then this may lead to overconsumption.

17 Iizuka, Toshiaki. "What explains the use of direct-to-consumer advertising of prescription drugs?." The Journal of Industrial Economics 52, no. 3 (2004): 349-379.

18 Brekke, Kurt R., and Michael Kuhn. "Direct to consumer advertising in pharmaceutical markets." Journal of health Economics 25, no. 1 (2006): 102-130.

19 Huh, Jisu, and Rita Langteau. "Presumed influence of direct-to-consumer (DTC) prescription drug advertising on patients: The physician's perspective." Journal of Advertising 36, no. 3 (2007): 151-172.

20 Holmer, Alan F. "Direct-to-consumer prescription drug advertising builds bridges between patients and physicians." Jama 281, no. 4 (1999): 380-382.

21 Shaw A. Direct-to-consumer advertising of pharmaceuticals: DTC regulation. ProQuest. Mar, 2008.

Moreover, in the case of diseases which were thought to be incurable, DTCA can bring the attention of sufferers to the existence of a new pharmaceutical treatment. Bonaccorso and Sturchio[22] argue that DTCA increases consumer knowledge and defends the rights of individual patients to information. Jones and Garlick[23] point out that patient compliance with treatment plans may be improved in a case where the patient receives information through DTCA. Kravitz and Bell[24] believe that DTCA can improve the patient doctor relationship rather than undermining it. Rados[25] argues that DTCA normalises embarrassing conditions, making patients more likely to seek help and speak openly to their doctors, also improving the quality of discussions between doctors and patients.

Public interest arguments against DTCA focus on the quality of information provision and the asymmetry between information provided about risks and benefits, respectively. They also incorporate behavioural insights which acknowledge the bounded rationality of consumers. On information provision, firms have incentives only to advertise the benefits and not the costs associated with use of the drug.[26] Detractors claim that DTCA undermines the professional judgment of doctors and that the choice of prescription is manipulated.[27] That, it is argued, is harmful to patients and increases the cost of healthcare to society through wasted expenditure on unnecessary or ineffective drugs.[28] In relation to bounded rationality, it is said that the volume of pharmaceutical DTCA in the US leads to an information overload to consumers.[29] In light of this, when making requests to their doctors for prescriptions, consumers are likely to be guided by the availability heuristic and firms become locked in a costly race to increase brand exposure. Good[30] concludes that much of DTCA in the US makes use of the affect and availability heuristics, seeking to associate certain brands with improved social and interpersonal relationships. The importance of the availability heuristic in the context of pharmaceuticals is confirmed by Ju[31] who considers that without mandatory warnings being given in DTCA, consumer choice will be dictated by whichever firm makes the strongest statements about the positive effects of its drugs.

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22 Bonaccorso, Silvia N., and Jeffrey L. Sturchio. "Direct to consumer advertising is medicalising normal human experience." Bmj 324, no. 7342 (2002): 910.

23 Jones, T. and Garlick, W. (2003) 'Should drug companies be allowed to talk directly to patients?', British Medical Journal, 326:7402, 1302. Available online at: http://www.bmj.com/content/326/7402/ 1302.2.full.pdf (accessed 11 January 2011).

24 Kravitz, R. L., and R. A. Bell. "Direct-to-consumer advertising of prescription drugs: balancing benefits and risks, and a way forward." Clinical Pharmacology & Therapeutics 82, no. 4 (2007): 360-362.

25 Rados, Carol. "Truth in advertising: Rx drug ads come of age." FDA consumer 38, no. 4 (2004): 20-27.

26 See Ogus (2004).

27 See Auton, Frank. "The advertising of pharmaceuticals direct to consumers: a critical review of the literature and debate." International Journal of Advertising 23, no. 1 (2004). See also Auton, Frank. "Direct-to-Consumer Advertising (DTCA) of Pharmaceuticals: an updated review of the literature and debate since 2003" Economic Affairs 26, no. 3 (2006).

28 Comanor, William S. "The political economy of the pharmaceutical industry." Journal of economic literature 24, no. 3 (1986): 1178

29 Hollon, Matthew F. "Direct-to-consumer marketing of prescription drugs." CNS drugs 18, no. 2 (2004): 69-77.

30 Good, Megan C., and Bruce A. Huhmann. "Social relationships and social anxiety appeals in direct-to-consumer advertising." Journal of Marketing Communications 24, no. 4 (2018): 393-411.

31 Ju, Ilwoo, and Jin Seong Park. "Effects of risk disclosure prominence in direct-to-consumer advertising (DTCA) of prescription drugs: An integrative cognitive process model." Health marketing quarterly 35, no. 1 (2018): 32-46.

Hollon[32] is very critical of DTCA. In his view advertisements are likely to rely on emotional appeals without providing valuable educational information to help vulnerable consumers make autonomous choices. He additionally argues that most consumers place false confidence in the truth of information given in DTCA, mistakenly believing that if the statement has been cleared for broadcast or publication by the regulator, then the information contained therein must be entirely true. Those with psychological and neurological illnesses, he argues, are particularly vulnerable to misleading statements made in DTCA. He argues that public provision of information would be much more effective at satisfying the optimal information goal and could be funded by a tax on DTCA. Medawar[33] argues that DTCA is designed solely to sell products rather than provide information. Mintzes[34] says that it can medicalise non-essential health issues. Jones and Garlick[35] claims that DTCA is likely to focus on only a small number of 'lifestyle' conditions and not serious diseases. Angell[36] points out that DTCA unnecessarily increases the demand for drugs, and Law[37] states that DTCA weakens the patient-doctor model. Mintzes believes that DTCA discourages positive lifestyle changes, instead encouraging consumers to seek a pharmaceutical remedy for every complaint.[38] Frosch[39] echoes the concern that DTCA results in an unbalanced promotion of benefits and side effects. Shaw[40] is concerned about the direction of health expenditure and the diversion of resources from research and development, and Vedantam[41] considers that DTCA promotes the misconception that newer and more expensive drugs are more effective than existing or generic medications.

To put these observations in economic terms, it can be argued that there is a divergence of public and private interests. There is a public interest in the dissemination of information about products – which is a public good. However, the private interests of pharmaceutical firms (their profit motive) moves them to only disseminate that information which increases sales – i.e., information regarding the benefits of the product. Regulation can be enacted in the public interest to mandate symmetrical provision of information regarding both costs and benefits of the products however the bounded rationality of consumers may frustrate the purposes of such regulation. Unless consumers are fully able to understand all information

32 Hollon (2004)

33 Medawar, Charles. "Health, pharma and the EU: A briefing for members of the European Parliament on direct-to-consumer drug promotion." portal web Social audit (2001).

34 Mintzes, Barbara, Morris L. Barer, Richard L. Kravitz, Arminée Kazanjian, Ken Bassett, Joel Lexchin, Robert G. Evans, Richard Pan, and Stephen A. Marion. "Influence of direct-to-consumer pharmaceutical advertising and patients' requests on prescribing decisions: two site cross sectional survey." Bmj 324, no. 7332 (2002): 278-279. Mintzes, Barbara. "For and against: Direct to consumer advertising is medicalising normal human experience." BMJ: British Medical Journal 324, no. 7342 (2002): 908.

35 Jones and Garlick (2003)

36 Angell, M. (2005) The Truth about the Drug Companies: How They Deceive Us and What to Do about it (New York: Random House).

37 Law, J. (2006) Big Pharma: How the World's Biggest Drug Companies Control Illness (London: Constable).

38 Mintzes, B. (2006) 'Disease mongering in drug promotion: Do governments have a regulatory role?', PLoS Medicine, 3:4.

39 Frosch, D., Krueger, R., Hornik, R., Cronholm, P. and Barg, F. (2007) 'Creating demand for prescription drugs: A content analysis of television direct-to-consumer advertising', Annals of Family Medicine, 5:1, 6–13.

40 Shaw (2008)

41 Vedantam, S. (2006) 'Cost benefits of new schizophrenia drugs doubted', Washington Post, 1 December. Available online at: http://www.washingtonpost.com/wp-dyn/content/article/2006/11/30/AR2006113001532.html (accessed 11 May 2010).

regarding costs and benefits and are not prone to give greater weight to benefits, which may appear more salient to them than costs, then there is a risk that consumer product choices will be distorted. Then, there may be overconsumption of certain products because of DTCA being permitted, even where regulation exists to ensure symmetrical information provision. However, where there is a doctor who acts as intermediary, explaining the information to consumer, then overconsumption is less likely to result.[42] In this case, however, one might ask why there is a need to advertise directly to *consumers* in the first place.

To summarise, it seems that from a public interest perspective, DTCA of prescription pharmaceutical products will not add many benefits in terms of information provision to the doctor guidance and monitoring already in place because of the need for a prescription. The doctor is already the subject of direct information provision from pharmaceutical companies through detailing and it is doubtful whether some of the highly technical information about the product is likely to be better or equally well understood by the consumer rather than by doctors. Whilst DTCA may encourage some consumers to seek help from their doctors regarding under-diagnosed conditions, this leads to the danger of DTCA being based upon emotive appeals only, and becoming a technique to pressure the doctor in his or her prescription decision, via the demands of the consumer. This risks causing over-consumption, particularly where information about benefits is provided but not information about risks. In terms of the wider impacts on the pharmaceuticals market it may also therefore skew the research and development activities of firms towards development of products which are likely to generate the highest revenues through DTCA. As such it can lead to overinvestment in developing products aimed at those who are particularly susceptible to broadcast advertising, including the elderly and those who suffer from certain neurological and psychological conditions. These investments, by industry, would be to the detriment of those consumers suffering from other diseases but who are not so susceptible to broadcast advertising. DTCA has arguably led to the focus of the US pharmaceutical industry (USPI) on the development of 'blockbuster drugs' in the past few decades. It may also explain why research and development portfolios have become relatively narrow and are subject to diminishing returns on investment in recent years, threatening the viability of USPI.

2.3.3 Assessment of US and EU Systems from Public Interest Perspective

I now assess the positions taken on licensing and DTCA in the US and the EU against my conclusions on the public interest analysis above. Doing so reveals a mismatch between the positions which each jurisdiction (individually) takes on the two aspects of regulation.

42 I credit my supervisor, Professor Kantorowicz-Reznichenko, for her assistance in developing this part of the analysis.

Licensing

Investigating the US drug lag, in 1973 Peltzman empirically analysed the effects of the Kefauver-Harris amendments of 1962.[43] He found that the requirements had caused research and development costs to double, yet fewer new chemical entities were being approved by the FDA. He recognised that some unsafe drugs were being kept off the market but found that the lesser risk of a type II error had often been traded off against the higher risk of a type I error. Viscusi later wrote about this trade-off in relation to the period 1972 to 1978: comparing FDA approvals to those of its UK counterpart[44]. He noted nine examples of type I errors made by the FDA but only five type II errors avoided. For example, the beta blocker propranolol (specifically to treat hypertension), which was approved in the UK in April 1969 but not in the US until June 1976. A confidential report to the House of Representatives from the US General Accounting Office in May 1980[45] highlights the case of propranolol as a clear example of undue delay at the FDA.[46] Wardell, a medical doctor, later argued that this type I error had cost the lives of thousands of US patients in the US.[47] It is likely that the NAs at the time, whilst less cautious than the FDA, also preferred type I errors. Teff,[48] considering the UK Medicines Act 1968, cited concerns regarding the effect of stringent testing requirements upon innovation, and the resulting incentives to industry to focus on 'me-too' drugs. Stringent licencing requirements, in this way, may have a 'chilling effect' upon innovation. Applying established insights from the study of bureaucracy behaviour, Teff claimed that the UK regulation had caused a preference for type I over type II errors. This was noted even though the UK agency was and is considered to be one of the fastest in the EU to grant approval, suggesting that the approaches of the NAs across the EU were similarly slow, albeit not as slow as that of the FDA. In addition, the EMA has committed more type I errors over type II errors although, again, not to the extent as the FDA for the same period.[49]

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43 Peltzman, Sam. "An evaluation of consumer protection legislation: the 1962 drug amendments." Journal of political economy 81, no. 5 (1973): 1049-1091.

44 Viscusi (1996)

45 United States General Accounting Office Report to the Subcommittee on Science Research and Technology House Committee on Science and Technology. FDA Drug Approval – A Lengthy Process that Delays the Availability of Important New Drugs. HRD-80.64 May 28 1980.

46 A situation later maligned by those infuriated by the FDA's delay in approving new drugs to treat AIDS patients, see Relihan, Julie C. "Expediting FDA Approval of AIDS Drugs: An International Approach." BU Int'l LJ 13 (1995): 229.

47 See Wardell (1978)

48 Teff, Harvey. "Regulation Under the Medicines Act 1968: A Continuing Prescription for Health." The Modern Law Review 47, no. 3 (1984): 303-323.

49 An actual comparison (in hypothetical monetised values) of the costs of type I and type II errors is very difficult to undertake for obvious reasons: the quantification problems associated with hypothetical foregone benefits. The studies set out above focus on the relative risks of committing the different types of error, seeming to assume that they would be equally costly to society. Professor Kantorowicz-Reznichenko suggests to me that in the absence of empirical work demonstrating a precise cost comparison, there may be other reasons why society does (and perhaps, should) prefer type I errors. The (modern) Hippocratic Oath says 'first do no harm,' and it seems true that society generally prefers harms caused by omission and not by act. Indeed, this is reflected by the stance of criminal and tort law in the US and across Europe. I do not see a reason why – now having the insight (e.g., the behavioural sciences' insights into omission bias) we lacked in ancient Greece – we should prefer to harm through omission. Qualitatively, I cannot see why harm through omission would be preferred. That just leaves the quantitative question, which is difficult to answer, but there are good reasons for believing that quantified harm caused by type I errors would be just as great, if not greater, than that caused by type II errors.

Both the FDA and the EMA/NAs, therefore, may prefer type I over type II errors, but the FDA more so in the period 1962-1992. As set out above, the difference in TTAs has closed in the intervening decades, however the FDA's approach is more cautious than that of the NAs/EMAs overall. Arguably the effect of PDUFA and the expedited procedures at the FDA has been to skew efforts towards faster TTAs in favour of products which treat certain diseases. Whilst there are general standards in place at the FDA determining which types of product will benefit from the expedited review procedure, the literature review above indicates that it is products for certain diseases.

Carpenter[50] believes that expedited review is granted more often for arthritis products than it is for products treating asthma, even though the death rate for asthma was nine times that for arthritis in the 1990s. Subsequently. He notes that arthritis receives a lot more attention in the US media and he says, *"perhaps this is not surprising, since the early 1980s arthritis drugs have consistently been approved with much greater speed (an average of twenty months) than have drugs for asthma (an average of thirty-two months, or a full year more)."* Disease specific consumer-group activism is likely to be more successful where the disease in question is of the type which is likely to receive a lot of media attention. The EMA/NAs are less likely than the FDA to use expedited review selectively for certain types of diseases.[51] This suggests that the EMA's balance between type I and type II errors is not likely to be more efficiently struck in the case of certain 'media-friendly' diseases than for other diseases, and the lack of DTCA in the EU/EUMS assists in this. Moreover, the EMA/NAs' general approach seems to strike that balance more efficiently in the first place. I argue that the FDA's general tendency towards caution (preference for type I errors) manifests in the correlation between expedited review and PSMs: not seen at the EMA/NAs. The preference for different forms of PSMs by the FDA (BBWs) and the EMA (DHPCs) may be explained by the private interest theories set out in Section 2.4 Private Interests, Groups, Organisations, and Institutionsbelow.

On licensing, when looked at in isolation, both the US and the EU/EUMS seem to depart – historically and perhaps currently – from the approach which would be best justified by public interest theories of regulation. They depart from this approach in different ways, and therefore public interest theory alone is insufficient to fully explain the transatlantic divergence in the regulation of licensing of new pharmaceutical products. This theory does not yet explain: 1) why the FDA generally takes a more cautious approach (longer TTAs) than the EMA/NAs; 2) why the FDA now (past 25 years) prefers to use its expedited procedures more often and for certain products to treat certain conditions; and 3) what accounts for the differences in the FDA and the EMA/NAs use of PSMs (form and frequency). I suggest possible private interest explanations for these, below.

DTCA

Public interest arguments are set out above both in favour of and against permitting DTCA of prescription pharmaceutical products. On balance, I have concluded that DTCA will not bring social benefits without having implications for the doctor-patient relationship. The permission of DTCA is likely to lead to a pharmaceutical product market in which development of new products is skewed towards those which can generate 'blockbuster' revenues through use of DTCA, and in which consumers have a relatively strong influence over the prescription

50 Carpenter (2004)

51 They are less likely than the FDA to use these procedures at all.

decision. On the other hand, banning DTCA is likely to help maintain the doctor's authority over the patient and the treatment decision. It is also likely to avoid skewing the development of new drugs towards those which will generate most revenues as a result of DTCA.[52] The divergence in approaches to DTCA between the US and the EU/EUMS is not explained by public interest theory alone. To understand that divergence more fully it is necessary to understand why one jurisdiction has weighed certain arguments more strongly than the other jurisdiction.

2.3.4 The Public Interest Puzzle: Magnitude of Type II Errors

After considering public interest theory, a puzzle is presented. When considering *both* aspects of regulation at the same time, there seems to be incongruence between the approaches taken to licensing and to DTCA in both jurisdictions. The FDA takes a generally cautious approach to the licensing of new pharmaceutical products. Yet, the US has never banned DTCA. Public interest theory informs that a cautious approach to licensing seeks to minimise type II errors. Yet, by permitting DTCA – with its market-expanding effects and its weakening of the oversight of doctors – the US ensures that if a type II error occurs, then the harm that results from such a type II error would be greater than it would has the product not been the subject of DTCA. In the US, the lack of caution shown on DTCA is not mirrored by the general caution shown for licensing. On the European side, the relative lack of caution shown on licensing is not mirrored by what some might see as excessive caution when it comes to the blanket ban on DTCA.[53]

Therefore, public interest theory – further illuminated with behavioural insights – has not been able to fully explain the approaches taken to licensing and DTCA in the US and the EU, respectively. I argue below that this puzzle can be resolved by examination of the relevant organisations and interest groups which have shaped the regulation of licensing and DTCA in the US and the EU: 1) the regulatory agencies (FDA, EMA and NAs); 2) doctors; and 3) consumers.

52 In the same way as the expedited licensing procedures lead to a relative preference for type II errors in cases where the disease to be treated is 'media-friendly'.

53 A tradeoff between protections is possible – i.e., that the US allows DTCA because it has exercised such stringency in licensing, and vice versa for theEuropean regulators. This point is developed more fully below.

2.4 Private Interests, Groups, Organisations, and Institutions

In the first six subsections of this Section I consider what I have found to be the most important interest groups and organisations impacting upon the regulation of licensing and DTCA in the US and the EU: the FDA, the EMA, the NAs, doctors, and consumers. First, I adopt the characterisation of these groups and organisations, which were set out in Chapter One. Then, I consider specific aspects of extant private interest theories of regulation which may apply to these groups and organisations in their impact upon the regulation of licensing and DTCA. I conclude then that an extended version of Daniel Carpenter's reputation model of bureaucracy behaviour best fits the organisations and interest groups here. Armed with this - and considering their *specific* incentives in the cases of advertising and licensing - I set out how these groups and organisations have demanded and/or supplied these aspects of pharmaceuticals regulation in the US and the EU over the past century. My analysis of institutions is separate from my analysis of private interests. Formal legal and informal social institutions, I say, can determine the level of access to power and influence over the creation of regulation in each jurisdiction, and in doing so institutions can shape regulatory divergence via the medium of interest group lobbying. They can also constrain or expand the range of choices available to regulators when supplying regulation – for example constitutional legal institutions may not permit a regulator to regulate in a manner demanded by one interest group.

2.4.1 Relevant Interest Groups and Organisations

2.4.1.1 The FDA, EMA and the NAs

A description of the key characteristics of the FDA, the NAs, and the EMA – by reference to their histories in the US, EUMS, and EU respectively – has been given in Chapter One. These characteristics are shown below again in Table 12.

Table 12 The FDA, the EMA and the NAs Key Characteristics (2)

FDA	NAs/EMA
'Direct to Consumer Accountability'	'Double' (NAs) and then 'Treble' (EMA) 'Insulation'
Relative Resistance to Industry Influence	Capture by Default
Politicised Science	Science Excludes Politics

2.4.1.2 Doctors

Doctors, as a group, play a key role in the regulation of DTCA in the US and the EU, alongside consumers and to some extent the agencies. In this section I sketch some key differences between doctors in the US and doctors in the EU/EUMS as interest groups, respectively. I do this in order to establish the foundation for the private interest account set out below for the transatlantic divergence in DTCA.

As an interest group, doctors in the US are widely considered to be much stronger[1] than those in Europe. Wilsford argues[2] - comparing France and the US – that the autonomy of the state in matters of healthcare in France, in addition to the cohesiveness of the medical profession as an interest group in the US, explains why France is better at controlling the cost of care than the US. He extends this analysis to also cover the UK, Italy and Germany, again arguing that in all there has been a trend to *"control escalating costs' by curbing both the medical profession's clinical autonomy and physcians' incomes."* This is also the case in the US, but due to the lower autonomy of the state there in healthcare the process has proceeded much more slowly. The power of doctors as an interest group is thus linked to the question of who pays for healthcare. In the US, the payers: employers and insurers, are relatively poorly coordinated with each other, and are not so effective a bulwark against the power of the medical profession on the question of cost containment measures as is the French state. Doctors subsequently have a greater say over policymaking in the US. Thus – as argued also by Wilsford – doctors there harnessed scientific advancements to their own advantage to increase their power and position throughout the first half of the 20th Century. Wilsford points out that in the latter half of that century doctors in France began to see a decline in their power (from the 1950s) due in part to the expansion of socialised medicine and the need for successive French governments to contain healthcare costs. That story is repeated across the EUMS where there are predominantly socialised healthcare systems.

Doctors: United States

The strength of doctors as an interest group is linked to their independence and autonomy. Doctors are stronger as a group - and have better protected their independence - where they did not face a stronger adversary to negotiate with - such as the state in its provision of socialised healthcare. This is the case in the US. Doctors in the US fully self-regulate as a profession, whereas in the EU – for example in the UK – doctors have sometimes now lost

1 US doctors spend very significant sums lobbying against cost-containment measures in healthcare. It appears, in terms of expenses on Federal and State campaign contributions, this is even more than spent by the Pharmaceutical companies in the US. Wouters, states in his empirical study of lobbying expenses, *"Across all industries, only 5 organizations reported more spending than PhRMA: the US Chamber of Commerce ($1.7 billion), the National Association of Realtors ($602 million), the American Medical Association ($462 million), the American Hospital Association ($426 million), and General Electric ($423 million). Following PhRMA, the seventh and eighth ranked spenders were the Blue Cross Blue Shield Association ($391 million) and AARP (formerly American Association of Retired Persons) ($334 million)." Thus, 5 of 8 organizations with the largest lobbying expenditures were health care related."* Wouters, Olivier J. "Lobbying expenditures and campaign contributions by the pharmaceutical and health product industry in the United States, 1999-2018." *JAMA internal medicine* 180, no. 5 (2020): 688-697.)

2 Wilsford, David. *Doctors and the state: the politics of health care in France and the United States*. Duke University Press, 1991.

self-regulatory power.[3] I argue here too that doctor autonomy is closely linked to consumer autonomy. Consumers who exercise autonomy over their own healthcare decisions detract from the autonomy of the doctor.[4] This is because the interaction between doctor and consumer becomes one in which the doctor provides the consumer with the good or service the latter seeks, rather than providing expert advice and direction which the consumer follows.[5]

Here, I call the autonomy of the doctor vis a vis the consumer 'downwards-facing doctor autonomy' to distinguish this from the autonomy of doctors vis a vis the state, agencies or hospitals which might be called 'upwards-facing doctor autonomy'. There is a trade-off between consumer autonomy and downwards-facing doctor autonomy. The greater the former the lesser the latter, and vice versa. Consumers generally have greater autonomy over their healthcare in the US than they do in the EU.[6] This in turn is due to doctors in the US having greater autonomy, when compared to the EU doctors, vis a vis actors which may have captured them - such as hospitals and government agencies administering socialised healthcare systems. Doctors are paramount in the US system, and have been effective at avoiding capture.[7] However, as was hypothesised, above, in the case of the agencies (which if they are not captured by industry are likely to be captured by consumers), doctors in the US too have been left open to capture both by their own consumers of healthcare services (their patients), and by the pharmaceutical industry, precisely *because* they have not been captured by agencies and hospitals. Thus, whilst US doctors have a high level of upwards-facing autonomy from hospitals and agencies, they may have less upwards facing autonomy from the pharmaceutical industry than do EU doctors, and they may have lower levels of downwards facing autonomy to patients than do EU doctors.[8]

Starr argues that the key to understanding the success of US doctors in avoiding capture was the direct link they were able to establish with their consumers.[9] By cultivating a form of

3 Dixon-Woods, Mary, Karen Yeung, and Charles L. Bosk. "Why is UK medicine no longer a self-regulating profession? The role of scandals involving "bad apple" doctors." *Social science & medicine* 73, no. 10 (2011): 1452-1459.

4 Pellegrino, Edmund D. "Patient and physician autonomy: conflicting rights and obligations in the physician-patient relationship." J. Contemp. Health L. & Pol'y 10 (1994)

5 There are a number of different conceptions of patient autonomy, this is the one adopted here. For an overview see Zachry III, Woodie M., and Diane B. Ginsburg. "Patient autonomy and the regulation of direct-to-consumer advertising." Clinical therapeutics 23, no. 12 (2001): 2024-2037.

6 On this see, Starr, Paul The Social Transformation of American Medicine (New York: Basic Books, I983): Stavropoulou, Charitini. "18 The doctor–patient relationship: a review of the theory and policy implications." The LSE companion to health policy (2012): 314: Dent, Mike, and Majda Pahor. "Patient involvement in Europe–a comparative framework." Journal of Health Organization and Management 29, no. 5 (2015): 546-555: Van den Brink-Muinen, Atie, P. F. M. Verhaak, J. M. Bensing, Ottomar Bahrs, Myriam Deveugele, Linda Gask, Francisca Leiva et al. "Doctor–patient communication in different European health care systems:: Relevance and performance from the patients' perspective." Patient education and counseling 39, no. 1 (2000): 115-127: Roberts, Kathleen Johnston. "Patient empowerment in the United States: a critical commentary." Health Expectations 2, no. 2 (1999): 82-92: Daniels, Norman. "Understanding physician power: A review of the social transformation of American medicine." Philosophy & public affairs (1984): 347-357.

7 Starr, Paul (I983)

8 See Pellegrino, Edmund D. "Patient and physician autonomy: conflicting rights and obligations in the physician-patient relationship." J. Contemp. Health L. & Pol'y 10 (1994): 47: Benbassat, Jochanan, Dina Pilpel, and Meira Tidhar. "Patients' preferences for participation in clinical decision making: a review of published surveys." Behavioral medicine 24, no. 2 (1998): 81-88.

9 Starr, Paul (I983). Daniels, Norman (1984)

brand loyalty, doctors in the US were in a strong position versus hospitals because doctors would ultimately bring the consumers to the hospitals.[10] However, in order to cultivate that loyalty, US doctors had to compete with each other for consumers initially and, in doing so, one thing which they offered to consumers was a high degree of autonomy.[11] US doctors were happy to provide this autonomy to their patients, and to compromise their own downwards facing autonomy, precisely because the end result of providing it was to protect their upwards-facing autonomy vis a vis hospitals.[12] In this sense, upwards-facing doctor autonomy and consumer autonomy seem to mirror each other. If one is high the other will be too. The result of this system being settled upon was a state of affairs in the US whereby doctors have a relatively high level of autonomy, and consumers have a relatively high level of autonomy, but the patient-doctor relationship is one in which the doctor relatively more often provides goods and/or services demanded by the consumer than one in which the doctor advises the consumer on what goods and services the consumer should consume.[13] Doctors in the US do not have such a high degree of authority over their consumers as is found in some EUMS healthcare systems.

Upwards-Facing Autonomy: Avoidance of Capture by Hospitals and Agencies

Doctors in the US were able to avoid capture by hospitals by gaining the loyalty of their consumers. What really occurred was that the *lack* of barriers to entry to the doctor's profession in the US in the 1600s and 1700s meant that doctors *without* the loyalty of their consumers could not survive in the profession – because they would be competed out of the market but other doctors. In addition, Starr argues that doctors in the US were able to coordinate effectively as one group (of equals).[14] They strengthened their power as an interest group by raising effective barriers to entry such as high costs of training and strict professional ethical codes.[15] This led to them having a strong negotiating position against the hospitals which required their services. Combined with the loyalty of the consumer which the hospitals needed, this left doctors in a very strong position in the US by the late 19th and early 20th centuries. Then, given their strength by the early-mid 20th century, when EUMS began to introduce socialised healthcare systems, doctors in the US were able to strongly oppose similar moves in the US. Indeed, the limited socialised healthcare measures introduced in the US since the 1950s and 1960s represented little or no incursion on US doctors' independence and autonomy.

10 Ibid.

11 Daniels, Norman (1984)

12 Pellegrino, Edmund (1994)

13 I am not speaking in absolutes, patients in the US go to their doctors for advice, and treatment options. If they do not like the advice or options, they take a 'second opinion'. However, see Murray, Elizabeth, Bernard Lo, Lance Pollack, Karen Donelan, and Ken Lee. "Direct-to-consumer advertising: physicians' views of its effects on quality of care and the doctor-patient relationship." The Journal of the American Board of Family Practice 16, no. 6 (2003): 513-524. See also Murray, Elizabeth, Bernard Lo, Lance Pollack, Karen Donelan, and Ken Lee. "Direct-to-consumer advertising: public perceptions of its effects on health behaviors, health care, and the doctor-patient relationship." The Journal of the American Board of Family Practice 17, no. 1 (2004): 6-18.

14 Starr, Paul (I983)

15 Ibid. See also Daniels, Norman (1984)

Consequent Capture or Alliance/Integration with US Pharmaceutical Industry

Starr[16] – writing for readers based in the medical profession[17] – is quick to point out the lack of capture of US doctors by hospitals, but less quick to point out their alliance with (or capture by, or perhaps partial vertical integration with) the pharmaceutical industry. This became particularly significant in the middle of the 20th century, just as doctors in Europe began to be pressed by EUMS governments based on cost containment. This alliance is evidenced most clearly, I argue, by the introduction of the compulsory prescriptions system in the US around 1951, and by the practice of 'detailing' to doctors by USPI which was the form of advertising prevalent even before DTCA emerged from the 1980s onwards. I argue in Chapters Three and Four that the compulsory prescription system[18] was a means of USPI sharing the risk of a new product liability burden with doctors through the learned intermediary doctrine in US product liability law.[19] In the US in particular – compared to Europe - its introduction was a response to product liability risk, and it was able to become law through the 1951 amendments to the Food Drug and Cosmetics Act 1938 (FDCA 1938) because it was supported by US doctors allied with the pharmaceutical industry.[20]

Part of the bargain struck here involved US doctors continuing to receive (and increasing their receipt of) 'kickbacks'[21] (benefits) from pharmaceutical industry detailers. The Kefauver hearings in 1959-1963, for example, heard of collusion between US doctors and the USPI which shocked consumers. The American Medical Association (AMA) Journal made millions in product advertising and thus doctors were unlikely to challenge efficacy claims made therein.[22] Surveys undertaken by Morgan et al (2006),[23] Wazana in 2000,[24] and Campbell et al in 2007[25] indicate that US doctors receive substantial kickbacks from pharmaceutical industry detailers, and that most consider this to be proper, and that a large proportion of them believed their prescribing decisions would be affected by these kickbacks.[26] This is despite concerns over a perceived lack of doctor independence prompting a number of (self)

16 Starr, Paul (I983)

17 See Berliner, Howard S. "Starr wars." (1983): 671-675 at pg. 671.

18 Temin, Peter. "The origin of compulsory drug prescriptions." The Journal of Law and Economics 22, no. 1 (1979): 91-105. See also Marks, Harry M. "Revisiting" the origins of compulsory drug prescriptions"." American Journal of Public Health 85, no. 1 (1995): 109-115.

19 See e.g. Bordes, Ozlem A. "The Learned Intermediary Doctrine and Direct-to-Consumer Advertising: Should the Pharmaceutical Manufacturer Be Shielded from Liability." U. Det. Mercy L. Rev. 81 (2003): 267.

20 And to a lesser extent, I argue, retail pharmacists who sought clarity on labelling regulations.

21 On the nature of those kickbacks, see Blumenthal, David. "Doctors and drug companies." American Journal of Ophthalmology 139, no. 3 (2005): 583.

22 https://en.wikipedia.org/wiki/Estes_Kefauver

23 See Morgan, M. A., Jason Dana, George Loewenstein, S. Zinberg, and J. Schulkin. "Interactions of doctors with the pharmaceutical industry." Journal of Medical Ethics 32, no. 10 (2006): 559-563.

24 See Wazana, Ashley. "Physicians and the pharmaceutical industry: is a gift ever just a gift?." Jama 283, no. 3 (2000): 373-380.

25 Campbell, Eric G., Russell L. Gruen, James Mountford, Lawrence G. Miller, Paul D. Cleary, and David Blumenthal. "A national survey of physician–industry relationships." New England Journal of Medicine 356, no. 17 (2007): 1742-1750.

26 Morgan et al (2006)

regulatory responses[27] in the US.[28] By contrast, in the EUMS in the middle of the 20th century employment of doctors by socialised healthcare systems, and their consequent lack of independence, left less room for them to ally with the pharmaceutical industry there and to receive these kickbacks. In the US, the relationship between doctors and the pharmaceutical industry is symbiotic and is facilitated by the independence of doctors from the state in matters of healthcare. In the EU the relationship between doctors and the state is symbiotic and precludes cooperation or alliance to any great extent between doctors and the pharmaceutical industry.

The practice of detailing and kickbacks leads to the phenomena of 'off-label prescribing' and 'off-label promotion' in the US which is considered troubling from a regulatory perspective.[29] I consider the off-label problem before moving on. Doctors in the US have successfully defended their right as independent experts to prescribe any pharmaceutical product they know of, for any indication as they see fit.[30] However, FDA regulations and other US laws prohibit the pharmaceutical sector from *promoting* products to doctors or patients for any indication which does not appear on the product label agreed and mandated by the FDA. So, off-label promotion is prohibited but off-label prescribing is allowed. Given that the pharmaceutical industry, in its alliance with doctors, needs doctors to prescribe the products of the industry, there are clear incentives set for the pharmaceutical industry to avoid seeking (and incurring the cost of) FDA approval for broad indications. Instead, they seek only narrow indications, apply some of the money saved towards doctor kickbacks, and use these to promote to doctors for off-label uses.[31] Off-label promotion in the US is common.[32]

For example, in May 2004 Warner-Lambert paid 430m USD in settlement for off label promotion. In 2007 Bristol Myers-Squibb settled for a total 515m USD for promoting a product approved by the FDA to treat adult schizophrenia and bi-polar disorder instead for paediatric use and to treat dementia, for which it was not FDA approved.[33] In 2010 Astrazeneca faced a lawsuit valued at 520m USD for illegal promotion of Seroquel – a treatment approved by the

27 See Grande, David. "Limiting the influence of pharmaceutical industry gifts on physicians: self-regulation or government intervention?." Journal of general internal medicine 25, no. 1 (2010): 79-83.

28 Morgan et al (2006)

29 See e.g. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/label-and-investigational-use-marketed-drugs-biologics-and-medical-devices and the literature cited below.

30 Malinowski argues that *"the discretion to prescribe dimensions beyond the clinical research that puts new drugs on pharmacy shelves has been shaped by two historic influences: a legacy of physician… solidarity, autonomy, and selfdetermination that predates the contemporary commercialization of medicine by more than half a century, and regulatory necessity due to the limits of science and innate crudeness of pharmaceuticals prior to the genomics revolution (drug development and delivery based upon genetic expression)."* Off-label prescribing is thus indicative of US doctors' independence. Malinowski, Michael J. "Doctors, Patients, and Pills-A System Popping under Too Much Physician Discretion-A Law-Policy Prescription to Make Drug Approval More Meaningful in the Delivery of Health Care." *Cardozo L. Rev.* 33 (2011): 1085.

31 The sanctity of off-label prescribing leads, though, to moral hazard on the part of the US pharmaceutical industry. Firms circumvent the rigorous requirements of cautious FDA licensing but tacitly/implicity promote the new product to doctors for a use for which the firm does not have to go to the expense (and risk) of seeking approval from the FDA as an approved indication. It can be seen here how strong cautious FDA scrutiny on licensing contributes to the likelihood that off-label promotion will occur. Thus, a strong and cautious FDA, responsive to consumers, actually pushes doctors and the pharmaceutical industry closer together in the US.

32 Rodwin, Marc A. "Rooting out institutional corruption to manage inappropriate off-label drug use." *The Journal of Law, Medicine & Ethics* 41, no. 3 (2013): 654-664.

33 https://www.nytimes.com/2010/10/03/business/03psych.html

FDA for schizophrenia, bipolar disorder and bipolar depression, which Astrazeneca promoted to psychiatrists and other doctors for aggression, Alzheimer's disease, dementia, depression and other off label uses.[34] GlaxoSmithKline agreed to pay 1.043 billion USD for off-label promotion of Paxil, Wellbutrin, Advair, Lamictal and Zofran in July 2012.[35] There are many others examples. I argue that the compulsory prescriptions system and the collusion between doctors and USPI in detailing and kickbacks (as exemplified by the magnitude of the off-label promotion problem) is evidence of the strong alliance between doctors and USPI.

In more recent decades the alliance may have strengthened. Fisher[36] argues that 'medical neoliberalism' has increased the closeness of the alliance between doctors and the pharmaceutical industry in the US. Arguably, US government measures (in the 1980s onwards) to curb the income and autonomy of US doctors - in efforts towards cost containment - pushes doctors as a group further towards cooperation with the pharmaceutical industry. In addition, the increase in DTCA since the 1980s forges a closer direct link between the pharmaceutical industry and consumers, weakening the position of doctors within that alliance[37] and necessitating that they find new ways to cooperate with (and be indispensable to) the pharmaceutical industry. Fisher points out[38] that from the mid-1980s onwards, in the US, the pharmaceutical industry has contracted independent doctors to run clinical trials on new products prior to seeking FDA approval for the product. For this, US doctors are paid well by the pharmaceutical industry and uninsured US consumers are able to receive access to unlicensed products – on an investigative basis – which they would otherwise not have access to. This, Fisher believes, solves the problem for doctors of reduced real incomes in recent decades due to US government cost containment measures, and inflated liability insurance premiums due to increasing volume of litigation in the US. Consumers, doctors, and the pharmaceutical industry all benefit from this arrangement, according to Fisher.[39] Privately run clinical trials are just one example of the latest trend in cooperation between US doctors and the pharmaceutical industry.[40] USPI is known, for example, to buy prescribing data from retail pharmacies to target specific doctors for detailing.

In summary, well-co-ordinated doctors in the US historically competed for consumers and thus survived in the profession by building up a loyal consumer base. This, and their ability to coordinate well with each other as equals meant that they avoided capture by hospitals and agencies, maintaining their independence and power against the fragmented interest groups who paid for healthcare in the US, where there is only a weak state tradition in healthcare provision. The need to compete for consumer (originally), however, led to a high degree of autonomy being offered to (and demanded by) consumers in their healthcare. In addition,

34 https://www.justice.gov/opa/pr/pharmaceutical-giant-astrazeneca-pay-520-million-label-drug-marketing

35 https://www.justice.gov/opa/pr/glaxosmithkline-plead-guilty-and-pay-3-billion-resolve-fraud-allegations-and-failure-report

36 Fisher, Jill A. "Coming soon to a physician near you: Medical neoliberalism and pharmaceutical clinical trials." Harvard health policy review: a student publication of the Harvard Interfaculty Initiative in Health Policy 8, no. 1 (2007): 61.

37 Because now the pharmaceutical industry can rely on consumers to seek the products from the doctors without needing doctors to induce the demand of the consumers.

38 Fisher (2007)

39 Ibid.

40 See Grande (2010).

the lack of capture by hospitals and agencies left US doctors open for a form of capture in close alliance, or partial vertical integration, with USPI.

Doctors: EU/EUMS

Turning to Europe, Wilsford has argued that doctors are relatively weak in France due to the strong state tradition in healthcare.[41] Immergut[42] expands on this to explain that the weakness of doctors (vis a vis US doctors) in some EUMS is strongly linked to socialised healthcare systems. And, that the ability of doctors to use political and legislative institutions to access power determined the extent to which socialised healthcare systems came to dominate the medical profession in these EUMS.

Capture by Hospitals and Agencies and Loss of Doctor Autonomy

Daniels concurs in kind, arguing that in Europe, over the course of the 20th Century, doctors were less well able to protect their autonomy vis a vis hospitals and agencies than were doctors in the US.[43] In the EUMS, where healthcare is often funded through social insurance, usually the state paid the hospital which paid the doctor; or the state paid the doctor directly. Government agencies and hospitals, therefore, holding the purse-strings, had more influence over EU doctors than did EUMS consumers. Moreover, the centralised nature of healthcare provision in some EUMS did not provide much opportunity for doctors to forge a direct link with consumers**.** The structure of healthcare provision in the EUMS meant that the doctors, being subject to agency and hospital management, were liable to be moved from hospital to hospital, or clinic to clinic, over time. In addition, the accountability of doctors was generally upwards facing towards the agencies and hospitals at which they were employed. Doctors generally did not have to compete for consumers within these systems, or at least to a much lesser extent than in the US. To the extent that doctors were accountable to consumers, this was normally via the agency or hospital. These factors all tend towards low level of upwards-facing autonomy for EUMS doctors, but also towards also low levels of doctor accountability to consumers.[44]

Finally, since health insurance is subsidised (or healthcare is funded from taxes) to a much greater extent in most EUMS than it is in the US, the input of consumers into the financial elements of their individual healthcare decisions is less relevant in much of the EU than in the US. How is it that doctors in the EUMS historically (in the first half of the 20th Century) were unable to resist the advancement of socialised healthcare systems? The organisational set up of healthcare systems in Europe at the same time made it more difficult for European doctors to coordinate.[45] In particular, Daniels points to the split, in much of Europe, between 'gatekeeper' doctors (based in the community) and hospital doctors, which he describes as an *"aristocracy"* amongst European doctors[46]**.** These two groups did not collaborate with each other as equals, and thus they weakened the total strength of the profession as an interest group. Indeed, in the UK National Health Service the elite hospital doctors were for a long

41 Wilsford (1991).
42 Immergut, Ellen M. *Health politics: interests and institutions in Western Europe*. CUP Archive, 1992.
43 Daniels, Norman (1984). Dent, Mike (2015)
44 Pellegrino, Edmund (1994). Dent, Mike (2015).
45 Daniels, Norman (1984)
46 Ibid

time of paramount importance within the structure and supported its introduction, to the detriment of the community 'gatekeeper' doctors.

In addition, it is argued that the EUMS healthcare systems are institutionally structured to give greatest voice in healthcare policymaking to bureaucrats and administrators – with doctors and consumers competing for influence within these centralised structures. Thus, greater autonomy for consumers will lead to less (not more, as in the US) upwards-facing autonomy for doctors in the context of a centralised (or corporatist) socialised healthcare system. Kuhlmann and Allsop[47] claim that doctor self-regulation in the UK has been weakened more than in Germany partly since the corporatist system in Germany has not allowed the voices of (e.g.) consumers to be heard, which in turn is because doctors dominate the discourse in healthcare policy discussions. In the UK, an even more centralised structure (for the NHS) was long dominated by UK doctors, until a series of scandals led to institutional reforms permitting pluralistic stakeholder representation within the system.[48] Doctors across the EUMS have experienced a trend towards loss of self-regulation, unlike in the US where this remains in place. For example, a 2001 reform in the UK equalised the number of lay and professional members of UK doctors' self-regulatory body the General Medical Council.[49]

Lack of Competition Amongst Doctors in the EUMS/Low Consumer Autonomy

In Europe, due to the systems of socialised healthcare, doctors do not compete with each other for patients in the same way that they do in the US. Siciliani, considering managed competition in European healthcare systems, remarks that attempts to introduce competition between doctors in these systems have been *"controversial"* including in the Netherlands, Germany, France and Portugal.[50] Cabiedes chronicles how 'managed competition' in socialised healthcare systems has struggled to be achieved, particularly in some of the Southern EUMS (SEUMS).[51] In the UK, it is arguable that general practitioners are not competing on quality (of service provided) in the same way that doctors in the US do to keep their consumers. It follows that where doctors are not competing, on quality, for consumers, it is less likely they will structure their practice towards meeting specific consumer demands: consumers are presumably likely to rate a doctor as higher in quality where their specific wishes are accommodated regularly.

Santos et al[52] found, after empirical analysis in the UK, that even though *"patients are more likely to choose practices which earned more quality points under the… pay for performance scheme"* this is only after controlling for other surgery characteristics which suggests *"that patients are more likely to choose practices with female GPs [general practitioners], more clinics and longer opening hours."* Where there is a lack of competition amongst doctors, this indicates a low level of autonomy for consumers, who cannot exert so much influence over

47 Kuhlmann, Ellen, and Judith Allsop. "Professional self-regulation in a changing architecture of governance: comparing health policy in the UK and Germany." *Policy & Politics* 36, no. 2 (2008): 173-189
48 Ibid.
49 Gray, Denis Pereira. "Deprofessionalising doctors?: The independence of the British medical profession is under unprecedented attack." (2002): 627-628.
50 Siciliani, Luigi, Martin Chalkley, and Hugh Gravelle. "Policies towards hospital and GP competition in five European countries." *Health Policy* 121, no. 2 (2017): 103-110
51 Cabiedes (2001)
52 Santos, Rita, Hugh Stanley Emrys Gravelle, and Carol Propper. "Does quality affect patients' choice of doctor? Evidence from the UK." (2013).

the doctor and their decision-making (e.g. prescribing) and instead must passively accept the advice of the doctor. Low consumer autonomy in healthcare here is caused by the fact that doctors do not need to please consumers, because they do not need to keep consumers: having been captured by hospitals and agencies, their income does not depend on keeping consumers as their patients.

No Capture by Pharmaceutical Industry

Capture by hospitals and agencies has, in relative terms however, shielded doctors in the EUMS from capture by the EU pharmaceutical industry (EUPI).[53] Doctors will be less reliant on 'kickbacks' from pharmaceutical detailers where they have secure, employed positions, and do not need to compete with each other for patients. Tight control over the working conditions, locations, hours, and communications systems of doctors by their employer agencies which administer those systems make it more difficult for doctors to have regular contact with pharmaceutical industry detailers. Cost containment measures aimed at controlling the prescribing discretion of doctors (e.g. generic prescribing requirements in the UK or prescribing budgets in Germany) – found only where socialised healthcare systems exist – cut the expected (revenue) benefits to pharmaceutical firms from heavy detailing and thus cut incentives to spend money on doctor kickbacks.

In summary: European doctors originally stratified in to two classes – elite hospital doctors and community gatekeeper doctors – which weakened their (total) position as an interest group against the introduction of socialised healthcare systems. Once those systems had emerged and EUMS states developed a strong tradition in the healthcare system, the position of doctors was permanently weakened versus their independent US counterparts who had not been captured by hospitals and agencies. Being mostly employed and subject to the control of the socialised healthcare systems, EUMS doctors did not need to offer high levels of autonomy to EU consumers in order to build or maintain a consumer base for their practices. As such EU consumers remained relatively passive recipients of the advice of EUMS doctors. The capture by hospitals and agencies did, however, have the effect of leaving no room for capture of EUMS doctors by EUPI, and as such EUMS doctors are not so strongly allied with this industry than US doctors are.

The contrast between US and EU doctors is shown below in Table 13. These insights are important for understanding the private interest explanations for how the transatlantic divergence in DTCA came about.

53 Morgan, M. A., Jason Dana, George Loewenstein, S. Zinberg, and J. Schulkin. "Interactions of doctors with the pharmaceutical industry." *Journal of Medical Ethics* 32, no. 10 (2006): 559-563. Indeed, in the UK the relationships between doctors and the pharmaceutical sector seem a lot better and a lot tighter regulated than the relationship between US doctors and the pharmaceutical sector.

Table 13 Doctors in the US and EU/EUMS and Relationships/Autonomy

	US	**EU**
Autonomy v the State (hospitals/agencies)	High	Low
Autonomy v Pharmaceutical Industry	Low	High
Autonomy v Consumers	Low	High
Consumer Autonomy (see below)	High	Low

2.4.1.3 Consumers

I have used the term 'consumer' in this work so far in many contexts where it might jar. For example, I have referred to the interaction between doctors and consumers, where most would say 'patients'. 'Consumers' is a term to cover the ordinary person in the US and the EU. That term has been in vogue for some years, potentially replacing 'voters', 'patients' 'workers' and 'taxpayers' all of which equally refer to the ordinary person or 'citizen' i.e. beneficiary of basic civil and political rights in a given society. The emergence of the term 'consumer' as a catch-all for all ordinary people has occurred in academia[54] in tandem with an understanding that most ordinary people in the advanced economies of western societies now are – first and foremost – consumers. That is because both the EU and the US are consumer societies. As such, civil and political rights must be bestowed upon 'consumer citizens'[55] in a way which is relevant to their primary role in these societies as consumers. This work concerns healthcare products thus I refer to consumers as consumers of healthcare services (otherwise known as 'patients' of doctors) and consumers of healthcare products (here a more orthodox use of the term consumer).

By this stage I have already raised several points regarding US and EU/EUMS consumers, respectively, in the history given in Chapter One, in my discussion here of the FDA, NAs and EMA and then of doctors in the US and the EU. I have noted, in particular, the relatively passive attitude of EU consumers first to the creation of the European Communities, and then to the deluge of consumer protection laws enacted in their favour by the EUMS via the EU throughout the latter half of the 20th Century. I have noted how EUMS Consumers – when it comes to healthcare matters – find a focal point for expression of anger and discontent in the Health Ministries of the EUMS rather than at the EU level, and that this anger is expressed through incumbent political parties. Moreover, consumer activism in pharmaceutical product licensing matters – at the EU level – has been institutionalised by the EMA and the EU, and I have argued this to be top-down and ineffective to achieve accountability of the EMA to consumers. Overall, I have argued that EU consumers have passively accepted many things

54 See Abraham, John, and Graham Lewis. "Citizenship, medical expertise and the capitalist regulatory state in Europe." *Sociology* 36, no. 1 (2002): 67-88.

55 See Trumbull, Gunnar. Consumer capitalism: politics, product markets, and firm strategy in France and Germany. Cornell University Press, 2006.

from government, from industry and from regulatory agencies such as the EMA, and also from their doctors, whose advice they do not habitually question.

By contrast US consumers, I have already noted, have actively fought for their protections by putting direct pressure on Congress because of a series of scandals. US consumers actively monitor the FDA via the media. When it comes to their doctors, US consumer, having a relatively high level of autonomy, go to their doctors not to passively take advice but relatively more to actively seek access to those products and treatments which they want to consume.

US Consumer Society, Tradition of Consumer Activism, and the New Consumer Movement

Most scholars identify the 20th century as the beginning of the 'new consumer movement' where, in the US, consumers began to organise *as* consumers and demanded protections of an economic nature, in the market, relating to the price and quality of consumer goods. Estes Kefauver was a key figure in that movement and the Kefauver hearings of 1959-1963 were a key moment. Glickman,[56] however, argues that 'consumer activism' is a US tradition stretching back to the nation's origins in the revolutionary war of 1775-1783. At this time and in between, consumer activism was not limited to securing economic protections in the market but extended also to socio-political and moral or ethical aims. I argue, here and in Chapter Six, that the rise of the new consumer movement in the 20th Century is attributable to the longstanding tradition of consumer activism in the US, in that they are both reflective of underlying US culture. The tactics developed by the latter assisted the former. The new consumer movement has been quick to organise, lobby, raise awareness, harness the media, target the Federal as well as State governments, and organise boycotts and walkouts – to achieve its aims. As Glickman argues, these methods were developed by earlier generation of consumer activists and were at the immediate disposal of the new consumer movement from the outset of the 20th Century. The new consumer movement, like the progressive era consumer activists and other consumer activists in generations before did not, for example, allow themselves to be absorbed by political parties or labour unions, or to be institutionalised and emplaced top-down in political institutions.

Glickman[57] notes the relationship between consumer activism, the new consumer movement, and 'consumer society.' According to him, consumer activism (both the new consumer movement and the tradition of consumer activism) grows out of consumer society. In a consumer society, consumption is highly valued.[58] A great portion of the economy depends upon ordinary peoples' consumption of consumer goods. Consumption signals status to others in society, for example through the consumption of certain branded goods. One hallmark of a consumer society is the widespread presence of advertising of consumer goods. Consumer society results from and rests upon a high level of economic freedom – the

56 Glickman, Lawrence B. "" Buy for the Sake of the Slave": Abolitionism and the Origins of American Consumer Activism." American Quarterly 56, no. 4 (2004): 889-912. Glickman, Lawrence B. Buying power: A history of consumer activism in America. University of Chicago Press, 2009

57 Ibid, in both works

58 Baudrillard, Jean. *The consumer society*. Vol. 245. london: sage, 1998.

freedom to buy and sell on the private market.[59] There is little state provision. The US is the world's foremost example of a consumer society,[60] although some Western EUMS are not far behind, including former EUMS the UK: compared to the US, however, most EUMS economies rely less upon consumption, upon retail and upon consumer credit. Glickman says that once one is living as a consumer in a society (such as I have described here), then one will likely have a view of the power of one's individual consumption and non-consumption choices. That view might even be *"inflated"*.[61] To have that view is to understand that individual consumers have power because of their position in market networks. This means they were entitled to demand things (whatever that was) and where their demands were not met, they could and would sanction the rest of the market network. Consumers saw themselves as principals, and others in the network as agents. It is from this understanding that the tactics of consumer activism were developed, and those same tactics were adopted by first the progressives, and then the new consumer movement.

The US tradition of consumer activism began in the revolutionary war[62] with the tipping of tea into the Boston river. Much later, after US independence, and during and in the run up to the US civil war, consumers in the northern states who favoured abolition boycotted slave made goods and instead sold 'free goods.'[63] This resulted from the same understanding. That understanding led to direct political power for consumer activists without the need for boycotts and other tactics: the mere threat of these sufficed. And so, in the US, Congress and the President – having noted the success of these tactics through history – always had to listen to those interest groups which (regardless of the objective sought – liberal economic, or socio political) could potentially disrupt markets and the economies through boycotts, 'buycotts', and walkouts. The same tactics were used during the civil rights movement in the southern states during the 1960s. In the 21st century this form of consumer activism – done for the purposes of furthering a political or social agenda - still exists. Consumer boycotts of brands still occur over, for example, the working conditions in those factories[64] or for other political reasons.

However, around the beginning of the 20th Century – the new consumer movement had begun to emerge, mostly stripped (by the end of the 1950s) of a particular moral agenda and focused only on liberal-economic goals. Consumer activists had long recognised their power to affect the actions of other actors in the market network, and conceived of themselves as principals in that network to the agent producers. However, the new consumer movement

59 See Goodwin, Neva, Julie A. Nelson, Frank Ackerman, and Thomas Weisskopf. "Consumption and the consumer society." *Global Development and Environment Institute* (2008): 1-26. They also note that consumer societies are driven by consumer credit. See also Burton, Dawn. *Credit and consumer society*. Routledge, 2012.

60 Goodwin, Neva R. *The consumer society*. Island Press, 1996. On levels of consumer credit/debt and the history of this in the US see Marron, Donncha. *Consumer credit in the United States: A sociological perspective from the 19th century to the present*. Springer, 2009. See Montgomerie J. (2007) The Logic of Neo-Liberalism and the Political Economy of Consumer Debt-Led Growth. In: Lee S., Mcbride S. (eds) Neo-Liberalism, State Power and Global Governance. Springer, Dordrecht. https://doi.org/10.1007/978-1-4020-6220-9_10 at pg.157

61 Glickman (2009).

62 Ibid.

63 Glickman (2009). See also Glickman (2004)

64 Hollenbeck, Candice R., and George M. Zinkhan. "Consumer activism on the internet: The role of anti-brand communities." *ACR North American Advances* (2006)

(which arose in the US) saw themselves as inherently *vulnerable* rather than powerful[65] and needing to organise on a 'standing' basis to protect their interests specifically *as* consumers.

This, too, came from the rise of the consumer society in the US. The consumer society put on the market more and more consumer goods with more complex chains of supply. Instead of seeing themselves as being the powerful ones in those networks, the new consumer movement activists saw themselves as potentially victimised due to those complex chains of supply. In response, US consumers drew on the longstanding US tradition of consumer activism, its methods, and tactics. The interests of this group - organised now on a standing basis through, for example, the National Consumer League[66] - lay in specifically the safety and quality of products, rather than in some separate political or moral agenda. Glickman[67] says, *"those groups coalesced in the 1930s into something known as the "consumer movement," an organized political effort on behalf of consumers, whose chief aim was… 'protecting and promoting the consumer interest.'".*[68] He continues, *"what distinguished the "consumer movement" from previous and contemporaneous movements of consumers was precisely this emphasis on consumers themselves as the chief beneficiaries of political activism. These groups claimed to represent the "consumer interest," an interest that, for the first time, became seen as within the purview of state regulation."*

The agenda which remained no longer had a strongly moralistic basis. The moral high ground was now occupied by the civil rights movement, with which former progressives were not necessarily aligned. Former progressives instead came to form a faction which was anti-business and pro-regulation only in so far as this protected their economic rights as consumers. That is to say, their rights to quality and price combinations in consumer goods which did not pass risk and cost from producers to consumers. This was the new consumer movement. Because this faction found its roots in pre-McCarthy women's Christian organisations whose voice was not and could not be channelled through labour unions or (directly) through established political parties, the new consumer movement, too, stood independent from (but allied with certain) mainstream political parties. McCarthyism also weakened trade unions in the US – in a way not experienced by trade unionists to such an extent anywhere in Europe at the time. Trade unions had been the traditional means for 'ordinary people' – identifying then as workers rather than as consumers - to advance political and economic interests.

What was left for doing this was only the new consumer movement. I.e. it was a set of consumers (representing a much wider group of consumers) who saw themselves simply as market actors, demanding protection in markets. They were seeking guarantees of quality and safety in the products which they purchased in order to ensure that they had not been short-changed.[69] Thus, where a pharmaceutical product posed a risk of injury which was not

65 Glickman (2009).

66 Wolfe, Allis Rosenberg. "Women, consumerism, and the national consumers' league in the progressive era, 1900–1923." *Labor History* 16, no. 3 (1975): 378-392.

67 Glickman (2009). See also Glickman (2004)

68 See also Sorenson, Helen Laura. "consumer movement, what it is and what it means." (1941).

69 Much of consumer safety regulation can be framed simply as correcting failures in the signalling functions of prices. E.g. an unsafe product sold to consumers at a low price actually imposes a net cost on the consumer due to the risk of accidents. See Landes, William M., and Richard A. Posner. "A positive economic analysis of products liability." The Journal of Legal Studies 14, no. 3 (1985): 535-567.

reflected by a lower price, consumers pushed for provision of information in labelling to assist in price comparisons and, where products were so dangerous that no consumer would pay any price for them, for agencies to keep these products off the market in the first place. This was the support base for Senator Kefauver in 1959 and the major audience for his hearings of 1959-1963. Primarily concerned in 1959 with pharmaceutical product prices, but by 1962 after the revelations of the thalidomide disaster significantly more concerned with safety aspects of pharmaceutical product quality.

US Consumers and the FDA

Consumer activism at the turn of the 20th Century is what set in motion the modern system of pharmaceuticals regulation in the US.[70] It was in response to *the Jungle* that US consumers –the progressives who would later become the new consumer movement - put pressure on Congress to protect them from the food industry whose products they relied upon, but whose factories and slaughterhouses they could not inspect themselves. Consumer pressure on Congress resulted in the Federal Food and Drug Act (FFDA) 1906 which set certain standards for the food and pharmaceutical industries. The same reaction from US consumers was seen in response to the Elixir Sulfanilimide disaster in 1937, and consumer pressure on Congress led to the FDCA 1938 and pre-market safety testing for pharmaceutical products. The Kefauver hearings already had the attention of activist consumers when the thalidomide revelations provided US consumers with a basis to pressure Congress for the Kefauver-Harris Amendments of 1962 and the modern FDA pharmaceuticals licensing system as it exists today. The problem with the prevalence of consumer activism in the US was that consumers are such a large group that occasionally they had to split into smaller groups with objectives different to the larger group. Hence the wider consumer group and the disease specific consumer groups being opposed to each other.[71] In the pluralistic US society however, since the 1980s, the process of ad hoc networking and coalition building[72] has resulted in an equilibrium which leads the FDA to be generally cautious, by default, whilst occasionally expediting review in particular when faced by a strong lobbying group or coalition which may or may not include pharmaceutical companies.[73] Carpenter notes that during the 1980s in to the 1990s *"citizens' groups came to the fore…. Many unorganized disease communities, witnessing the political and economic successes of the AIDS and breast cancer advocacy coalitions, have been motivated to form their own groups and to enter the political arena."*

US Consumers and US Doctors

I turn now to the relationship between consumers and doctors. Healthcare services are consumed in the same way as pharmaceutical products. In the same way that US consumer activists have seen their ability to exert market power by boycotting consumption, they have long seen how to exercise power over their healthcare services provider by switching provider. Hence the argument of Starr given above, and developed by me, in the section on US doctors. Faced with the threat of losing their consumers to other doctors and thus having to fall out of the market (because, unlike in Europe, and particularly in the 16th, 17th and

70 See the detailed history and overview provided in Chapter One.
71 Carpenter (2004)
72 Mahoney, Christine. "Networking vs. allying: the decision of interest groups to join coalitions in the US and the EU." *Journal of European Public Policy* 14, no. 3 (2007): 366-383.
73 Carpenter (2004)

18th Centuries, few barriers to entry to the profession existed protecting doctors from competition), US doctors have always had to give their consumers what they want. I say that in the latter half of the 20th Century this market imperative came to be justified by US doctors under terms like 'patient autonomy',[74] 'patient empowerment'[75] and 'patient-centred medicine' all of which recognise the status of US doctors as primarily market actors.[76]

In many ways, patient empowerment follows from and causes patient centred medicine. In societies where the doctor is reified in his social status and his acts are unquestionable, the focus of medical care is really upon him and his expertise, and not upon the patient. The patient merely provides a data input for the doctor's diagnosis and then prescription. In such societies doctors are less likely to have to compete for patients. They will have secured social status, esteem, and therefore an entitlement to patients through high educational achievement which also act as a barrier to entry preventing competition. In many ways systems of socialised healthcare, which prevent a close link forming between subgroups of consumers and their doctors, also stands in the way of patient-centred medicine and cause doctors to be aloof and removed from their patients. Kaba and Sooriakumaran[77] point out that in ancient societies this is how the patient-doctor relationship was originally conceived, with the doctor's role in society being more related to mysticism and the gods. As societies and science developed, doctors remained set apart from patients. The act of embellishing themselves with titles, and with educational qualifications etc. meant that they saw patients impersonally, as mere objects for scientific investigation. This understanding of the doctor-patient relationship lay under the design of modern hospitals in the late 19th and early 20th century, with patients confined to beds, visited, and spoken to rarely by specialists and with most of the human contact occurring with lesser staff members (such as nurses) to whom those tasks had been delegated. Activist consumers are unlikely to accept this wholly passive status, particularly in a system of private insurance where the consumer's ex ante payment (in premiums) for her care as a patient makes her feel that she should have more control over her healthcare, and that she should receive more attention from her doctor. If this is not the case, then another doctor will offer it.

As such, 'patient' autonomy/empowerment/centred medicine has developed in US medicine to assist doctors in keeping their patients. The need for doctors to keep their patients arises from the threat of consumer activism – i.e. boycotts. That in turn arises from consumer society, in which consumption – including of healthcare services – is seen as a solution to many problems. The same goes, more narrowly, for consumption of pharmaceutical products. I argue in Chapter Four and Chapter Six that in a consumer society consumers will want to be

74 Fox, Nicholas J., Katie J. Ward, and Alan J. O'Rourke. "The 'expert patient': empowerment or medical dominance? The case of weight loss, pharmaceutical drugs and the Internet." *Social science & medicine* 60, no. 6 (2005): 1299-1309.

75 Roberts, Kathleen Johnston. "Patient empowerment in the United States: a critical commentary." Health Expectations 2, no. 2 (1999) See also Nafradi, Lilla, Kent Nakamoto, and Peter J. Schulz. "Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence." *PloS one* 12, no. 10 (2017): e0186458."

76 Kaba and Sooriakumaran describe patient-centred medicine as focusing on the 'real reason' why the patient has visited the doctor. It facilitates patient autonomy by building cooperation between patient and doctor such that the doctor can trust the patient to treat themselves using dangerous substances and the patient trusts the doctor sufficiently to follow her advice. Kaba, Riyaz, and Prasanna Sooriakumaran. "The evolution of the doctor-patient relationship." *International Journal of Surgery* 5, no. 1 (2007): 57-65.

77 Ibid

able to choose between branded originators and generic products and thus do not wish for restrictions upon their ability to choose nor their doctor's ability to prescribe these – for example through the mandatory (and implied consent) generic substitution found in parts of Europe. And, moreover, in a consumer society any perceived problem the empowered, autonomous, and activist consumer has with their own life or body is – in her view – solved by the purchase and consumption of products on the free market. It is easier to see now, therefore, why US consumer society has brought forth DTCA. The availability of information, to consumers, enables their autonomy and their activism. Hence the rise of the internet as a source of information has contributed to consumer activism in the US and worldwide.[78] Although, it is perhaps difficult to see yet why the FDA has not exercised stricter control over DTCA given the FDA's imperative to protect consumers from unsafe products.[79] How else is consumer activism linked to empowerment and autonomy, and how has this affected the interaction of consumers and doctors in the US? The relaxation of restrictions in the US upon DTCA which occurred around 1997, took place in the broad political context of consumer activism described above, and which specifically in the medical context favoured greater 'patient' autonomy over their healthcare decisions. The wider context and the narrower medical movement occurred from the 1960s onward. It was marked, for example, by milestone legal developments. The case of *Roe v Wade*[80] declaring state bans on abortion unconstitutional, was one driver of patient-consumers' heightened demands for greater say over their healthcare choices.[81]

EU/EUMS Consumers Post-war Passive Acceptance of the EEC, Welfare States and Consumer Protections

I first note that many EUMS and therefore the EU as a whole are not such clear examples of consumer societies. As measured in 2006[82] 75% of US householders were in debt with 48% having consumer loans. In Europe, the UK was highest with 55% households in debt and 34% consumer loans. The Netherlands was next with 59% and 26% respectively. France 48% and 33%. Sweden 46% and 30%. Germany 34% and 23%. Spain 32% and 19%. Italy 17% and 18% and Greece 14% and 9%. There are higher levels of household debt in the EUMS since the financial crisis of 2008,[83] however the 2006 picture is more representative of the frequency of EUMS household consumer debt at a time when (many would say) consumer society was at its height.[84] In addition, as a percentage of GDP final consumption in 2019 is 81.83% in the US[85] but only 72.81% in Germany, 76.82% in France, 78.5% in Italy, 76.22% in Spain, 68.39% in the Netherlands, 74.43% in Belgium, 69.97% in Denmark, 71.21% in Sweden, 75.38% in Finland, and 71.14% in Austria. In the UK it is higher than the US level at 83.65%. The consumption figures show only small, but very consistent transatlantic differences however the frequency of households with debt is telling, and the contrast between the US and the

78 Hollenbeck and Zinkhan (2006).

79 Which is also driven by the threat of consumer activism, seeking to force fair price/quality combinations.

80 Roe v. Wade, 410 U.S. 113

81 Van de Pol, Pepijn KC, and Frank GA De Bakker. "Direct-to-consumer advertising of pharmaceuticals as a matter of corporate social responsibility?." Journal of Business Ethics 94, no. 2 (2010): 211-224.

82 Crook, Jonathan. "Household debt demand and supply: A cross-country comparison." *The economics of consumer credit* (2006): 63-92. At pg. 63

83 See Chmelar, Ales. "Household debt and the European crisis." (2013).

84 OECD (2021), Household debt (indicator). doi: 10.1787/f03b6469-en (Accessed on 06 May 2021)

85 https://data.worldbank.org/indicator/

biggest EUMS. Together these figures indicate that consumer credit is (at least historically) more widespread in the US than it is in the major EUMS suggesting a culture in which consumer credit is the norm. That, I say, is because they are less clear examples of consumer societies albeit that – compared to much of the rest of the world – they are certainly consumer societies.

How does this link to consumer *activism* v consumer *passivism*? I cannot and do not argue that ordinary people in the EUMS are not 'activist', that they do not have political aims and objectives. My question is *how* they are activist. My answer is that ordinary people in the EUMS – relative to those in the US – are passive *as consumers*, even if in the 20th Century and further back in history they have been activist as: (violent) revolutionaries, trade unionists on strike, protestant reformers etc. What is typical of US culture and history and not so much the case in the EUMS is the expression of political will through *consumer* activism.

In the 20th Century, I say, they have been more likely to express themselves politically not as consumer but through those (relatively few) institutions which existed within the EUMS corporatist structures of government (which themselves were devolved after the defeat of fascism from highly centralised, monolithic state structures). Those institutions included: trade unions, churches, political parties (which themselves were often linked to the first two) and industry sectors amongst others. The state and its democratic institutions would provide a neutral ground within which these corporatist factions would bargain and negotiate with each other. As the 20th Century drew on, in Europe, corporatism became neo corporatism[86] as that bargaining process moved out of central government ministries to, for example, agencies. Pluralism – which exists in the US to a greater extent than in the EUMS – permits any individual or group a say through political institutions or outside of them (e.g. through the media), without requiring them to formalise that expression through the established channels. Thus, the Christian women of the 1890s to 1920s could not be heard within trade unions or state or federal legislatures but they were free to organise in the National Consumer League and express their concerns to the public at large via the media, through demonstration, and through their consumer activist activities. My argument is that corporatism (later neo corporatism) in some EUMS –Germany[87] is a good example – made it more difficult for ordinary people to organise as consumers, to employ the tactics of consumer activist which were being used in the US and to obtain the results seen there, until much later in the 20th Century, bordering on the 21st Century. Thus, consumer society, consumer activism and pluralism are linked enabling the successes of US consumers as consumers in relation to 20th Century pharmaceuticals regulation. On the other hand, a more muted consumer society, passive consumers and corporatist/neo-corporatist structures are linked to explain why EUMS consumers choose to express themselves via established political parties to centralised Ministries and why they largely neglect the EU, preferring the national level.

These links make sense because, within the political structures seen in the EUMS, the established fora and the established corporatist institutions enabled EU consumers to obtain many benefits that US Consumers were not even asking for at the time, and by obtaining those benefits, EU consumers drastically reduced their need for those things that US

86 See Abraham and Lewis (2002)

87 See Kuhlmann, Ellen, and Judith Allsop. "Professional self-regulation in a changing architecture of governance: comparing health policy in the UK and Germany." *Policy & Politics* 36, no. 2 (2008): 173-189.

consumers did ask for. Thus, what EU 'ordinary people' sought after the second world war was a welfare state and social security. They did this (in western Europe) through the established channels – i.e. electing established socialist parties into government, Clement Attlee's labour party for example unseated Winston Churchill's conservative led wartime government in 1945 despite Churchill being credited for much of the UK's success in the war. Whilst in the US the postwar period saw a suspicion amongst some regarding private enterprise and its scientific advancement and the effects of this on society, the US took a very different path in response. There was no wholesale change in the structure of society similar to the broad nationalisations undertaken by new socialist governments in some Western EUMS (only very limited socialised healthcare was introduced) – the US fully rejected both communism and socialism. But the US failure to do so left something for US consumers to focus on (e.g. the excesses of the pharmaceutical industry) and the pluralistic structure of US politics enabled consumer activists to express it. In the EUMS the wants and needs of the ordinary people were satisfied after the war. That was the result of years of effort on the part of trade unions and established political parties which remained strong in these EUMS long after McCarthyism in the US. Consumers in the EUMS, having succeeded as 'workers' instead of 'consumers' at that point, built post-war states in Europe which would hand them everything they sought, on a plate for much of the next 50 years whilst these consumers could passively accept it.

These newly constructed states in the EUMS often provided healthcare services and pharmaceutical products free at the point of need to consumers. Thus, the type of further consumer protections handed down to EUMS/EU consumers over those fifty years were somewhat different and often went further than what US consumers were seeking and receiving – such as limited market-focused rights to accurate quality/price combinations in products. The measures being enacted in Europe (particularly by France and Germany and often by them via the EU itself), and passively accepted by EU/EUMS consumers in the 1960s through to the 2010s included: compensation from airlines for cancelled flights, rights for the consumer in e-commerce, rights for consumers in distance selling, and rights for consumers in receipt of credit. These all go beyond what the consumer would be entitled to demand as a market actor. They are more socialist in nature, essentially forcing the sharing of corporate profits from the sale of goods and services, with the whole body of consumers.[88] These were given on top of an already burgeoning welfare state which provided universal access to healthcare, unemployment benefits etc.

Arnull and Wincott[89] describe mid twentieth century European consumers as still mired in the 'wartime' deference to authority, thus passively accepting the creation of the European Communities. I think it is true to say that the war left many craving peace and strong political institutions to achieve that. But by 1957 they had – peacefully and through existing political channels – ensured that those holding power in the EUMS governments represented the interests of the ordinary working people who had suffered so much between 1939 and 1945.

88 Neither did consumers particularly fight for these in Europe. They were given by government as part of coordinated European initiatives coming out of the EU and many of them and an unsolicited (by consumers) attempt to make ordinary Europeans pay attention to the EU, to favour the EU, to start engaging with the EU, and therefore to overcome the democratic deficit problem.

89 Arnull, Anthony, and Daniel Wincott, eds. Accountability and legitimacy in the European Union. Oxford University Press on Demand

Trumbull[90] has noted the plethora of consumer protection legislation passed in France and Germany – it was elsewhere in the EUMS too of course – in the following decades. France, Germany and others faced an imperative to cooperate with each other in the context of the new postwar Europe. Hence, they seized upon elements of their domestic legal systems which favoured 'the buyer', 'the victim', 'the worker' or any other alternative name for the 'consumer' and repackaged these as 'consumer protection law' at the European level. They did this to give a set of legal measures which they could implement domestically, in tandem, drawing them closer together as nations, and also providing a direct link between (what later became) the EU and the people of Europe in order to overcome the growing problem of the perceived democratic deficit in Europe. Thus, these French and German governments were obviating two risks at once. They were avoiding political revolution domestically and avoiding conflict with each other by using established political structures to provide real reform for ordinary people, and by creating a new bureaucratic superstructure through which some of these forms would be delivered, also ensuring peace and cooperation between those nations.

This process was top-down. It represented centralised (European) law-making in a corporatist, later neo-corporatist institutional context, not a response to pluralistic stakeholder involvement and consumer activism as was the case in the US. Whilst consumer groups (wide or narrow) in Europe have come to look more and more like US consumer groups over the course of the latter half of the 20th Century and first 20 years of the 21st Century, they are still well behind their American counterparts. They are still more likely to express themselves through political parties and through labour unions, than to create an entirely new group and organise a boycott. And, they are still more likely to vent their concerns at their domestic ministers and governments than at the EU level, than are their American counterparts at the Federal level and through the major political parties there.

In summary, consumers in the EUMS have remained relatively passive in the 20th century because EUMS governments provided them, as soon as possible after the war, all they could ask for. The alternative to this was a risk of war or revolution. Over the century, the EUMS political structure devolved from highly centralised to corporatist to neo corporatist. Having already been given everything, EU/EUMS consumer had little need to demand more, and were content to express themselves through the corporatist and neo corporatist system rather than pushing for pluralistic reform.

EU/EUMS Consumers and the NAs/EMA

The Thalidomide disaster in the Europe led to the systems of licensing pharmaceutical products – in 1967 (the UK) and 1976 (Germany) through health ministries. Later, neoliberal ideals in the 1980s led to creation of the NAs, separate from Ministries. Kraphol argues that it was the creation of the NAs which ensured that the EMA, once established to harmonise the market, would work smoothly.[91] However, in all of this, as they were at the creation of the Communities in 1957, EU/EUMS consumers are described as "passive" by Abraham and Lewis.[92] After thalidomide, they say, the UK and German governments saw the risk that trust between citizens and a state which enveloped medical expertise (in the eyes of consumers)

90 See Trumbull (2018)

91 Krapohl, Sebastian. "Thalidomide, BSE and the single market: An historical-institutionalist approach to regulatory regimes in the European Union." *European Journal of Political Research* 46, no. 1 (2007): 25-46.

92 Abraham and Lewis (2002)

may break down fully were such a disaster to occur again.[93] Once again, therefore, EUMS governments act proactively – through existing institutions – to protect the status quo by giving consumers what they want and what they would - were it not automatically delivered – actively seek. Thus, according to Abraham and Lewis these two EUMS governments unilaterally expanded the boundaries of their welfare states to also take responsibility for the licensing of new medicines. The UK in the Medicines Act 1967 and Germany in its Medicines Act 1976. I have already set out in Chapter One in the discussion of the EMA and the NAs the relationship which is seen between the EU/EUMS consumers and these agencies. There is a tendency at the EUMS level for consumers to target Ministries and Ministers, and a tendency at the EU level for consumer groups to be mere fronts for industry, hence the top-down institutionalisation of consumer participation at the EMA.

EU/EUMS Consumers and EU/EUMS Doctors

In relation to EU/EUMS consumers and EU/EUMS doctors, I have already indicated that socialised healthcare systems in the EUMS lower patient/consumer autonomy by removing the need for doctors to compete to secure patients and by removing opportunities for doctors to form close ties with patients. EU consumer/patients therefore, I argue – relative to US consumer/patients – passively accept the advice of their doctors more often. I add to this the observation that when one has paid for one's healthcare through taxes and it is free at the point of need, the cost one has incurred is less salient than when one receives a bill (even if insured). The diminished salience of cost leads to lower incentives to monitor quality. EU/EUMS consumer patients should likely therefore be more willing to accept whatever treatment is available, rather than demanding the latest, the best, and/or a choice. In what I believe is a separate point, but related through underlying culture, the relative aloofness of doctors vis a vis consumer patients within EUMS socialised healthcare systems, is likely to result from and cause a prevalent social norm whereby doctors cannot be questioned and are held in high social esteem. Arguably, in a system such as that in the US where there are lower barriers to entry (historically) to the medical profession and where doctors must accommodate and please patients in order to keep them as consumers, then patient-centred medicine emerges more easily, and the advice or actions of doctors can be questioned more easily.

Summary and Conclusions

In the US, a rich tradition of consumer activism throughout the nation's history, spanning the progressive era, meant that after the US had decisively rejected socialism in the 1950s, any opposition to pharmaceutical industry excesses was expressed in market-oriented liberal terms as a demand for accurate price-quality combinations in pharmaceutical products.

93 According to Abraham and Lewis, true consumer activism in the case of pharmaceuticals – which had been seen in the US from the 1938 onwards and from 1906 onwards if one includes food quality standards - has only emerged in Europe in the very last decades of the 20th century and first of the 21st *"Consequently, the last two decades of the 20th century have seen an almost continuous flow of campaigns and court cases by consumer organizations and patient groups aimed at improving citizens' rights to security in health via greater public access to the medical science of the regulatory state and opposition to medical experts linked to the pharmaceutical industry. Such active citizenship supports the thesis of 'disorganized capitalism' insofar as it implies a greater critical reflexivity on the part of consumers. It also represents a challenge to medical autonomy and dominance by questioning the social viability of medical expertise in industry and the regulatory state."* Abraham and Lewis (2002).

Moreover, the rejection of comprehensive socialised medicine and a comprehensive welfare state meant that consumers had to be particularly vigilant when it came to the safety of pharmaceutical products. The Kefauver hearings and the thalidomide disaster made the FDA the focal point for that vigilance. The tradition of consumer activism within the context of the (more and earlier) pluralist US political system meant that consumer interest groups could organise and did so without being incorporated into existing institutions such as political parties, the pharmaceutical industry or trade unions; indeed, the progressive era activist which the later new consumer movement stood on the shoulders of, and mimicked the tactics of, organised originally because they had no place within those established institutions. This meant, in the pluralist system, then and now, they used the media to exert pressure, and this is expressed in the second half of the 20th Century both by the Kefauver hearings and the pressure exerted by disease specific consumer groups such as the AIDS activists in the 1980s. The rejection of comprehensive socialised medicine also entrenched consumer activism in the provision of healthcare services, whereby consumers – holding power as the income source of US doctors – sought patient-centred medicine, information, empowerment and autonomy, things which individual US doctors had long been compelled to offer them in order to stay competitive in the market. The key characterisation of the groups and the characterisation of the groups which they relate to are shown below in Table 14, which also draws on the insights set out in Chapter One about the relationship between consumers and the EMA and NAs.

Table 14 Consumers in the US and the EU/EUMS Relative to Each Other: Characterisation/Relationships

	US (activist)	**EU (passive)**
Relationship with Government	Vigilance/activism	Passive acceptance of benefits
Relationship with Agencies	Activism: use of media	Focal point is Ministers instead
Relationship with Doctors	Market power/autonomy	Social esteem/accept advice

In the post-war EUMS, governments were impelled by the need to avoid revolution or another war, first to provide for their citizens by way of a comprehensive welfare state and second to cooperate with each other through economic integration. The first was achieved and became so institutionalised in the EUMS that consumers had little need or reason to actively seek more. They passively accepted the welfare state and the creation of the EC and passively accepted protections and gifts from both over the remainder of the 20th Century. Because the welfare state and the EC were created within the context of the post-war political institutions, moulded in some countries to devolve the formerly centralised, hierarchical modes of governance (associated with fascism) into a corporatist political structure; the political pressure – if any – exercised by ordinary EUMS citizens – was directed through these corporatist (and later neo-corporatist) channels such as via existing political parties and trade unions, and directed at central government ministries and ministers.

There was thus less occurrence in the EUMS of consumer activism as consumers, relatively little independent organisation of consumers in consumer groups outside of the existing corporatist institutions, and relatively few examples of consumers using the media to gain widespread support for causes. Instead, where represented in healthcare decision making

their involvement was institutionalised from the top-down by agencies such as the EMA. Moreover, given the comprehensive nature of the socialised healthcare systems, consumers in the EU were not incentivised so much to be vigilant regarding the price and quality of pharmaceutical products. Socialised healthcare systems also affected how EUMS consumers interacted with their doctors, passively accepting advice and services, and holding doctors in the unquestioning high esteem which those doctors demanded in part compensation for the lower incomes they received as a result of their capture by hospitals and agencies. In the next section I describe how the actions of the FDA, the EMA, the NAs, and doctors and consumers, in both jurisdictions (in relation to the formation of the regulation of licensing and DTCA), was affected by the characteristics of these groups as I have described them here.

2.4.2 Private Interest Theories and Extended Reputation Model

I set aside, for a moment, this characterisation of the groups and organisations. Now I discuss private interest theories, and later I apply these private interest theories to the groups and organisations to seek an explanation for the regulatory divergences. I begin by discussing bureaucracy behaviour. Then, I set out the extended reputation model before turning to apply that in the subsections below.

Bureaucracy Behaviour

The original analysis of Niskanen[94] was that agency bureaucrats seek positive feedback from the legislature and the executive and seek to maximise their budgets and the extent of their regulatory remit. On the contrary, Peltzman[95] and Stigler[96] claimed that agencies responded primarily to the industries which capture them and seek to maximise positive feedback from those industries. Our discussion above has already diminished the role of capture in relation to the FDA, whilst recognising that capture may be more of an issue at the European agencies. Offering a more detailed account of what agencies respond to, Joskow in 1971[97] and Noll in 1985[98] proposed external signalling theories. The agency, it is argued, responds to signals from several different external sources including the legislature, executive, industry, and consumer groups. Olson suggested that the FDA responds primarily to signals from industry, albeit that these signals act as a proxy for drug quality and the ultimate aim is likely to be the protection of consumer safety.[99] She accepted that the FDA also responds to signals from the legislature, executive and public. On the subject of what bureaucratic agencies maximise, she argued - as did Joskow and Noll - that they maximise positive feedback from those whose signals they are receptive to and seek to minimise negative feedback or *"hassles"* from those

94 Niskanen, William A. "Bureaucrats and politicians." The Journal of Law and Economics 18, no. 3 (1975): 617643.
95 Peltzman, Sam. "Toward a more general theory of regulation." The Journal of Law and Economics 19, no. 2 (1976): 211-240.
96 See Stigler, George J. "The theory of economic regulation." *The Bell journal of economics and management science* (1971): 3-21.
97 Joskow, Paul L. "Publicly-Owned Electric Utility Profits and Resource Allocation: A Comment." Land Economics 47, no. 3 (1971): 316-317.
98 Noll, R. G. "Government administrative behavior: a multidisciplinary survey and synthesis." Regulatory Policy and the Social Sciences (1985).
99 Olson, Mary. "Substitution in regulatory agencies: FDA enforcement alternatives." The Journal of Law, Economics, and Organization 12, no. 2 (1996): 376-407.

actors. The reason is that the agency wishes to protect its autonomy and is best positioned to do so by pleasing its audience, not giving cause for interference.

Extended Reputation Model

Whilst this theory fits (particularly) the case of the FDA very well, it is not complete, in that it gives no way of ranking the importance of those audience members to the agency. The key to this, argues Carpenter, is reputation.[100] He agrees with Olson that the agency seeks positive feedback from multiple actors but believes that consumer groups, the legislature and the executive are important alongside industry actors.[101] He also agrees with Olson that bureaucracies do this ultimately in order to protect their autonomy.[102] The desire of an agency to protect its reputation will determine the order in which it prioritises feedback from those actors and that order depends, in turn, upon what constitutes the agency's reputation. Reputation is defined by Carpenter as *"a set of shared beliefs about an organisation, its capacities, intentions, history and missions that are embedded in a network of multiple audiences including the legislature, industry and consumers."*[103]

In the case of the FDA, the early reputation was for public protection. Originally, this meant protection from type II errors and unsafe drugs. The historical story explains this: it was the 'heroic' role of FDA officials in averting a Thalidomide crisis in the US which cemented the FDA's reputation for protecting consumers. In the 1980s, the FDA's reputation for consumer protection was challenged by disease specific consumer groups who drew attention to the existence of type I errors. In the view of: 1) the branches of government (as evidenced by PDUFA 1992), 2) consumers (led by disease specific consumer groups), and 3) industry (which saw an opportunity to become allied with consumers regarding TTAs): the reputation was challenged on the basis that the FDA's failure to promptly license life-saving products was harming consumers rather than protecting them. The agency then sought to protect its reputation, lobbying Congress itself for the introduction of PDUFA,[104] which ultimately led to the bifurcated licensing approach seen today.

The FDA therefore, as has been set out above, clearly does respond to multiple audiences. In terms of which of these the FDA responds to as a matter of priority, and how it responds, according to Carpenter the FDA seeks foremost (now) to respond to signals transmitted by the media and disease specific consumer groups. That is because these actors cause mistakes made by the FDA to become highly visible to consumers generally, thereby maximising reputational damage. On the basis of this, Carpenter models the licensing approval decision of the FDA as a stopping problem.[105] To explain: in the view of the agency, ideally it would never issue an approval as this would remove all risk of type II errors being committed. It would not do so save for the existence of 'waiting costs.' These are imposed by politicians, firms, disease specific interest groups and the media in all the ways which have been outlined above. Where those actors raise waiting costs (in terms of reputational damage) the FDA will expedite the process. Carpenter's empirical work supported this by showing that waiting

100 Carpenter (2012)
101 See Carpenter (2004)
102 See Carpenter (2012)
103 See Carpenter (2004)
104 See Olson Mary K. "Regulatory reform and bureaucratic responsiveness to firms: The impact of user fees in the FDA." Journal of Economics & Management Strategy 9, no. 3 (2000): 363-395.
105 See Carpenter (2002)

times were inversely correlated with the wealth of disease specific interest groups, the extent of media coverage and the number of such groups which existed.[106] Carpenter's model explains the turnaround in the drugs lag that occurred after PDUFA, and shows that this was ultimately the result of pressure from those disease specific interest groups, harnessing use of the media to raise the visibility of type I errors and maximise damage to the reputation of the FDA caused by its long TTAs.

The reputation of the EMA/NAs is different. For the reasons set out above, its primary audience is the EUMS government ministers and industry. The original mission statement of the NAs when they still resided within government departments was for consumer protection (in the wake of Thalidomide) but the mission statements of the NAs as established separate from those Ministries was additionally to assist industry. The EMA, in turn, was established pursuant to the mission of harmonising the EU pharmaceutical product market. Due to the lack of direct-to-consumer accountability, EU consumers are not key audience members for the EMA/NAs, however, because EUMS government ministers are directly accountable to those consumers for matters which the EMA/NAs contribute to regulating, those Ministers are a key audience for the EMA/NAs. Because of the mission statement at agencification and at the creation of the EMA, industry is also a key audience. Industry expects the EMA/NAs to keep the process of pharmaceutical product licensing apolitical by not allowing consumers serious influence over the process. The EUMS health ministers expect that the EMA/NAs will not favour the partisan political interests of any one of the EUMS. Both audiences are satisfied so long as a 'neutral' and robust scientific approach is taken by the EMA/NAs to the licensing of new products. This is therefore the reputation of the EMA/NAs, which they seek to protect in the many ways set out above and in Chapter One.

The remarks made in the preceding two paragraphs apply the reputation model of Carpenter to the agencies. I extend that model by incorporating the insights relating to industry, doctors, and consumers, which are set out above. The explanation for transatlantic divergence in licensing approval times can thus be summarised as in Table 15 below. This is my extended version of Carpenter's reputation model which also includes Table 8, Table 13, and Table 14, related to the agencies, to consumers and to doctors in the US and the EU. Here, therefore, I synthesise my characterisation of the groups and organisations, with the private interest theories set out above.

106 Ibid

Table 15 Extended Reputation Model Applied to FDA and EMA/NAs

	FDA	EMA/NAs
Reputation	*Consumer Protection/Quick Product Access* *Scientific Expertise (but politicised)*	*Science Based Assessment* *Apolitical*
Main Audience	*Primarily Consumers*	*Primarily Industry and EUMS Ministers*
Industry	*Relative Resistance to Industry Influence*	*Industry Capture by Default*
Doctors	*Safety gatekeeping* *(US doctors accommodate consumers)*	*Reliance on doctor matching* *(EU/EUMS doctors advise consumers)*
Consumers	*Highly responsive/directly accountable* *(activist US Consumers)*	*Less responsive/lack of accountability* *(passive, institutionalised EU consumers)*

To summarise: the FDA, being the subject of consumer scrutiny in the tradition of the Kefauver hearings has – since the 1962 Amendments – taken a generally cautious approach to the licensing of new drugs, because caution was what was demanded in the wake of the Thalidomide tragedy. From the 1960s to date, however, activist US consumers have been the FDA's primary audience. This means the FDA cannot avoid politicisation of product approval because the process must be accessible to consumers and therefore cannot be overly technical-scientific. Because the process is politicised, the FDA is subject to pressures directly from consumer activists via the media, and through Congress and the executive. In addition, other interest groups including doctors and industry seek to exert pressure through various channels but the FDA, being directly accountable to consumers can neither adopt a wholly scientific approach nor can it abandon its generally cautious approach. Together, disease-specific consumer groups and industry (mostly consumers, though) have achieved reforms at the FDA (via legislation passed in Congress such as PDUFA) to expedite procedures to make products available quicker, and this now forms a part of the reputation which the FDA seeks to protect. These products are skewed, however, towards those diseases which are most media-friendly, and the expedited procedure represent a genuine exception to the generally cautious approach. Because of direct-to-consumer accountability, and because the generally cautious approach cannot be abandoned, relative to the EMA the FDA is resistant to industry influence as direct-to-consumer-accountability acts as a counterbalance to the influence from industry.[107]

When it comes to US doctors – who accommodate US consumers relatively more often than EU doctors – the FDA must act as a 'safety gatekeeper'. This means that the FDA can rely less on doctor matching to provide an additional safety measure against adverse drug reactions. Knowing that newly licensed products will be subject to heavy DTCA, and knowing that this weakens the authority of US doctors over US patients (already, I argue, weaker than in the EU/EUMS); the FDA is even more stringently subject to consumer demands for caution in

107 That results from user fees and the fact that industry actors collect the scientific data for license applications

licensing. That is because consumers demand that any product advertised to them, and which may be prescribed by their doctor, must be safe for use.

The centralised procedure overseen by the EMA/NAs has a strong reputation for science-based assessment of products on licensing. The fact that the EMA and the NAs originally grew out of an effort to depoliticise product licensing in the EUMS (the NAs) and to harmonise the market in Europe (the EMA) has necessitated the scientific-technical and apolitical approach. The scientific approach both causes and is facilitated by a lack of direct-to-consumer accountability in the EU/EUMS where consumers are either passively institutionalised in the process, or direct their demands at the health Ministries in the EUMS and, as such, the primary audience of the EMA is industry and the EUMS Ministers. Industry capture by default occurs because the rigorously scientific approach is based upon clinical trials data submitted by industry following the provision of scientific advice by the EMA to industry actors. When it comes to doctors, the relationship between relatively passive EU/EUMS consumers and EU/EUMS doctors who do not need to compete for patients means that the EMA/NAs can rely, to a greater extent than the FDA, upon doctors to impose an extra layer of safety between doctor and consumer in the prescribing decision. This further diminishes the pressure that would be on the NAs/EMA from consumers and facilitates its approach to licensing which accommodates industry.

Below, I will draw upon the extended reputation model set out above to explain the approaches taken to licensing and DTCA, first in the US and then in the EU.

2.4.3 United States

I begin with the US, and with licensing, and I am seeking to explain the aspects of the divergences set out at the end of the public interest section above, namely: 1) why the FDA generally takes a more cautious approach (longer TTAs) than the EMA/NAs; 2) why the FDA now (past 25 years) prefers to use its expedited procedures more often and for certain products to treat certain conditions; and 3) what accounts for the differences in the FDA and the EMA/NAs use of PSMs (form and frequency). In discussing the US approach to licensing, I consider first the private interests of the FDA, then US doctors, then US consumers, before turning to repeat the process with the US regulation of DTCA.

2.4.3.1 Licensing

The FDA

The generally cautious approach of the FDA to licensing is seen most clearly during the drugs lag period of the 1960s and 1970s. Carpenter argues that the changes that occurred in the 1980s and 1990s in the introduction of PDUFA and the expedited procedures occurred in reponse to direct consumer pressure via the media (e.g. AIDS activists) as well as through Congress (which passed the reforming legislation). Hence the FDA approach to licensing today is bifurcated when it comes to TTAs. Where a product is not media-friendly and activist

consumers are unable to capture the wider public attention via the media to pressure for expedited approval, then the product must go through the standard procedure and the TTA will still be slightly longer than that at the EMA/NAs.

The FDA takes this cautious approach where politically feasible for it to do so, to protect its reputation for consumer protection. However, to protect its other reputation for quick consumer access to products, wherever media attention can be marshalled by activist US consumers, the FDA will use its many expedited procedure (which it does often). This has resulted in the situation where for certain products, TTAs at the FDA are significantly quicker than those for the EMA/NAs using its standard procedures. This bifurcation reflects the fact that the FDA is responsive most of all to its primary audience of activist US consumers, and that it seeks to protect its twin reputations for consumer protection and quick consumer access. In addition, due to DTCA and the relatively weak market power of US doctors vis a vis US consumers, the FDA must act as a safety 'gatekeeper' – i.e. it must keep products which are unsafe[108] off the market because once these products reach the market, relatively few safety measures are in place to protect consumers from the product. This analysis is borne out by the evidence provided above regarding TTAs at the FDA since the 1960s as well as the heavy politicisation of its processes during that period.

Table 16 Bifurcation TTAs/PSMs at the FDA and Overall Cautious Approach

Procedure	Types of Product	TTAs	PSMs
Expedited	Products to treat 'media-friendly' diseases such as certain cancers and arthritis	Relatively fast compared to NAs/EMA	More frequent
Standard	All other products	Relatively slow compared to NAs/EMA	Less frequent

This bifurcation – displayed above in Table 16 - presents the FDA with a dilemma because of the risk that a product which is subject to expedited review and faster TTAs has a latent defect, or a defect which was not caught at the licensing stage perhaps because of the political pressures on the FDA to approve the product quickly. The FDA partly accounts for this problem by investing heavily in pharmacovigilance (see Chapters Three and Six). However, as set out above, the FDA prefers not to issue full market withdrawal decisions relative to the international community. This makes sense because market withdrawal would be a very public admission by the FDA that it had made a mistake in licensing – something which would harm its reputation for consumer protection. Maor[109] argues that agencies with a reputation for scientific expertise in licensing[110] are incentivised to avoid issuing market withdrawals because it will harm that reputation. The EMA and the FDA both have a reputation for

108 Pose a negative risk-benefit profile for *all* consumers

109 Maor, Moshe. "Organizational reputations and the observability of public warnings in 10 pharmaceutical markets." *Governance* 24, no. 3 (2011): 557-582.

110 I.e., agencies that conduct actual review of scientific evidence on licensing rather than 'shadowing' the analysis undertaken by other agencies

scientific expertise in licensing,[111] and this is arguably the primary reputation of the EMA. For the FDA this also forms a part of its reputation, but the FDA's primary reputation is for consumer protection/quick product access, and so the scientific assessment process at the FDA become politicised. The FDA – I argue here – has found a way to handle the twin consumer demands for quick access and protection in a way which protects its reputation for both, and its reputation for scientific expertise.[112]

To do so, it makes extensive use of BBWs. This is a measure which is very salient to consumers, highlighting *how* the FDA is protecting them. The FDA's use of BBWs interacts with its tendency – observed by Barber and Benjamin[113] - to restrict indications when licensing fast. Where the FDA expedites review, it licenses for a relatively narrow range of indications knowing that some US doctors are likely to prescribe for a wider range of indications (whether this is the result of illicit off-label promotion or not). Use of the product for off-label indications may pose large benefits to certain consumers (in the absence of alternative treatments for example) but not yet be supported by clinical trials data.

This approach by the FDA ensures that the product is on the market, and therefore consumers – through their doctors – have access to it for the broader indications. However, in this case it is US doctors, not the FDA, who take the risk of reputational damage in the eyes of US consumers if ADRs occur. Where these do occur, the FDA can mandate a BBW making it clear the product is not, and never was, approved for those indications. In this case US consumers will likely blame their doctors, or – if it promoted off-label and the same is proven during litigation - the pharmaceutical industry. Through its approach, the FDA maintains its reputations for: 1) scientific expertise in licensing; 2) quick access to products; and 3) consumer protection. In addition, consumers will maintain their confidence and trust in the FDA. Moreover, off-label prescribing itself is a form of real-world clinical trial which can show efficacy and safety – i.e., provide the data which was lacking when the FDA (in haste, responding to consumer demand for access to the product) licensed for narrow indications. After a period on the market, and off-label prescribing/use, where there are no or only few reported safety issues, the FDA will quickly approve additional indications. These phenomena may explain the difference between the EMA and FDA in the range of indications initially approved for new products.[114] It may also explain why the FDA focuses more closely on symptoms (and therefore indications) most salient to consumers compared to the EMA/NAs[115] and why the FDA can often expedite regulatory approval for new indications for certain products without formal clinical trials evidence.[116]

111 Hence as set out above both the FDA and the EMA issue fewer market withdrawals than does, for example, Health Canada.

112 Particularly since the increase in use of expedited procedures which has occurred since PDUFA.

113 See Barber IV, Benjamin, and Luis Diestre. "Pushing for speed or scope? Pharmaceutical lobbying and Food and Drug Administration drug review." *Strategic Management Journal* 40, no. 8 (2019): 1194-1218.

114 See Kashoki, Mwango, Zahra Hanaizi, Stella Yordanova, Richard Veselý, Christelle Bouygues, Jordi Llinares, and Sandra L. Kweder. "A comparison of EMA and FDA decisions for new drug marketing applications 2014–2016: concordance, discordance, and why." *Clinical Pharmacology & Therapeutics* 107, no. 1 (2020): 195-202 at 195

115 See Howie LJ, Hirsch BR, Abernethy AP. A comparison of FDA and EMA drug approval: implications for drug development and cost of care. Oncology (Williston Park). 2013 Dec;27(12):1195, 1198-1200, 1202 passim. PMID: 24624536.

116 See Hatswell et al (2016)

US Consumers

The activist US consumers of the new consumer movement (focused on the market-oriented objective of accurate price-quality combinations) exert pressure on the FDA to ensure that pharmaceutical products on the market do not contain defects not reflected in the product price. This group exerts pressure demanding general caution by the FDA when it comes to both TTAs and PSMs. That group sits on one shoulder of the FDA. On the other shoulder sit disease-specific consumer groups demanding quick product access, who have a relatively high willingness to pay for these products once on the market. The need to satisfy both sets of consumer interest groups at once accounts for the bifurcated FDA approach to licensing. It also explains why the FDA prefers to invite consumers groups to participate in the licensing process – more than the EMA does.[117] Public participation in decision-making leads to shared responsibility if a mistake is made (type I or type II error) and so the FDA minimises negative media coverage (and visibility) of mistakes by ensuring public participation. At the EMA/NAs, by contrast, EU/EUMS consumers were likely to blame ministers instead of agencies anyway, and their involvement in the licensing process could only weaken rather than strengthen the scientific reputation of the EMA. The FDA shares responsibility for decision making with US consumers by involving them ex-ante, and tries to shift blame for mistakes ex-post: not to the consumers which hold it in high esteem but to doctors (see above) and/or the pharmaceutical industry.

US consumers hold relatively high market power over US doctors and thus have a relatively high say over the prescribing decision. Studies show that resulting US consumer demands for certain products are one major reason why the AMA opposes DTCA, and responses from a Pharmaceutical Research and Manufacturers of America (PhRMA) survey[118] show that one major concern with DTCA is the tendency for US consumers to pressure their doctors in to prescribing certain products. As a result, US consumers demand even more from the FDA. They don't want to be limited in their choice of product to consumer, but they want a guarantee from the FDA that every product on the market is safe[119]

US Doctors

US doctors must accommodate their consumers to keep them. However, they also want to avoid liability from prescribing a product that might harm a patient. They may take calculated risks, for example, in prescribing off-label. And, in choosing to do so, they may receive kickbacks from pharmaceutical industry detailers. The market will sort those US doctors whose professional expertise moves them to accurately estimate prescribing risks from those who lack that expertise. The latter will either never prescribe off label or will prescribe recklessly off label. In the first case these doctors will lose patients by failing to accommodate them (granting access to products in cases where the FDA has not yet approved them for the relevant indication) and in the second case they will lose patients because of having contributed to harming them. The doctors with the greatest expertise will end up with the most patients and with the most pharmaceutical industry kickbacks. They may even become 'celebrity' doctors, or 'opinion-leaders' whose views may persuade consumers to pressure

117 See Chapter One

118 https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/0-9/2017-Direct-to-Consumer_071817-FINAL.pdf

119 I.e. that it has a positive benefit-risk profile when used in accordance with instructions.

the FDA to approve products/new indications. US doctors support this system of licensing, in which the best (most expert) doctors will end up as the wealthiest doctors.

In conclusion, the approach of the FDA to licensing is supported by US consumers and by US doctors, and both the approach of the FDA and the support of doctors and consumers is attributable to the characteristics of each of the groups and the organisation set out in the extended reputation model shown in Table 15 above.

2.4.3.2 Direct to Consumer Advertising

Industry is in favour of permitting DTCA[120] in the US. I argue in this section that US consumers are also generally in favour of DTCA, but only on the condition that (they believe) all DTC advertised products are perfectly safe to use for all to whom they are advertised. US doctors are opposed to DTCA but have not succeeded in obtaining a ban. Caught in the middle is the FDA, which could feasibly have strengthened its reputation for consumer protection (whilst still giving consumers the DTCA which they want) by maintaining the 1969 regulations and their applicability to print and broadcast DTCA. These limited the practicability of both types of DTCA by requiring full and symmetrical information (both risks and benefits) to be provided to consumers in the DTCA.[121] Yet it did not. Instead, it rolled back these requirements and paved the way for a significant expansion of DTCA since the 2000s. The effect of this has been to push the FDA further towards its safety gatekeeping role - and thus a cautious approach to licensing. This is because DTCA combined with the high market power of consumers relative to doctors, means that much of the safety oversight which would result from doctor matching is lost.[122] It is perplexing at this stage in the analysis why the FDA took this approach, when to have maintained the requirements of the 1969 regulations would have suited its objectives according to the extended reputation model set out above.[123]

120 See Geyer, Robert. "The politics of EU health policy and the case of direct-to-consumer advertising for prescription drugs." The British Journal of Politics and International Relations 13, no. 4 (2011): 586-602, Iizuka (2004), Brekke (2006).

121 Regulations promulgated in 1969 by the FDA stipulated that in the case of prescription drugs these adverts must: 1) not be false or misleading; 2) present a *"fair balance"* of information describing both risks and benefits of the product; 3) include facts *"material"* to the uses for which the product is being advertised and; 4) include, *"a brief summary"* that mentions every risk which is described in the product label.

122 Yet, when latent defects appear in products, DTCA has the effect of raising the salience of the role of pharmaceutical companies in the harm that was caused to consumers, thereby diminishing the role of doctors and of the FDA in this, in the eyes of consumers. Coupled with punitive damages awards and product liability claims, the FDA may therefore be happy to permit DTCA as a way of focusing blame elsewhere. This argument is supported by the fact that the learned intermediary doctrine in US product liability law, which protected the pharmaceutical firm in cases where a doctor acted as prescribing intermediary, has been relaxed in recent years in cases specifically where the injuring product was advertised direct to consumers.

123 Still, it is perplexing why the FDA would not want to exercise very salient and visible control over DTCA when the product is advertised – given the characteristics of the FDA set out above. It is therefore confusing at this stage why the FDA has gone the route of rolling back restrictions on DTCA instead of maintaining or increasing them. I argue below that the legal institution of free speech protection in the US is what has made the major difference over the past decades.

US Consumers

US consumers are in favour of DTCA. DTCA reduces their need to rely upon information provision from their doctors and thus increases their market power over their doctors. Indeed, Joseph et al[124] found through survey evidence in the US that consumer opinions of DTCA was "*generally positive."* A survey undertaken by PhRMA[125] indicates that many US consumers welcome the information they receive through DTCA.[126][127] They also found that *"fewer than 10 percent of consumers believe that their physicians should be their sole source of pharmaceutical information"* supporting the argument that empowered US consumers seek information to emancipate themselves from US doctors. In addition, Wilkes et al[128] note that DTCA is likely to change the doctor-consumer relationship, and Spake and Joseph[129] note that DTCA can cause US consumers to go to doctors seeking a specific prescription for a particular advertised product. US consumers' affection for DTCA is, however, premised upon an assumption that because the product is licensed and is being advertised, it is 'perfectly' safe. This places further pressure on the FDA, where DTCA occurs, to act in its gatekeeping role and to ensure the universal safety of products.

US Doctors

US doctors are clearly opposed to DTCA. This is for two reasons. The first is that DTCA changes the doctor-consumer relationship so that the consumer has relatively more market power over the doctor (due to information asymmetries being reduced). The second is that DTCA diminishes the importance of US doctors to USPI in the distribution of pharmaceutical products. With DTCA, US doctors become less important to the pharmaceutical industry for selling products. The marketing of pharmaceutical products for on-label use is now also done direct to consumers, and US doctors lose some of the kickbacks which they once received from detailers. Hence, the opposition of the AMA to DTCA as early as 2007[130] and renewed calls in 2015 to ban DTCA.[131] Why strong US doctors – calling for greater control or a ban on DTCA – are out-lobbied at the FDA by USPI requires further explanation, particularly where a compromise along the lines of the 1969 regulations would have satisfied US consumers whilst also allowing the FDA to maintain its reptation for consumer protection. The relaxation of the requirements of the 1969 regulations was done in tandem with requiring firms to tell consumers to ask their doctors for further information (instead of providing full, symmetrical

124 Joseph, Mathew, Deborah F. Spake, and Zachary Finney. "Consumer attitudes toward pharmaceutical direct-to-consumer advertising: an empirical study and the role of income." International Journal of Pharmaceutical and Healthcare Marketing (2008).

125 The pharmaceutical lobby in the US which should thus be treated with some caution.

126 https://www.phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/0-9/2017-Direct-to-Consumer_071817-FINAL.pdf

127 DTCA seems to be more popular with US consumers than it is with consumers in New Zealand the only other country on earth apart from the US which permits DTCA of prescription pharmaceutical products. https://www.health.govt.nz/system/files/documents/publications/dtca-summary-submissions.pdf

128 Wilkes, M.S., Bell, R.A. and Kravitz, R.L. (2000), "*Direct-to-consumer prescription drug advertising: trends, impact, and implications*", *Health Affairs*, Vol. 19 No. 2, pp. 110-26.

129 Spake, D.F. and Joseph, M. (2007), "*Consumer opinion and effectiveness of direct-to-consumer advertising*", *Journal of Consumer Marketing*, Vol. 24 No. 5, pp. 283-92.

130 https://ama.com.au/position-statement/direct-consumer-advertising

131 https://www.ama-assn.org/press-center/press-releases/ama-calls-ban-dtc-ads-prescription-drugs-and-medical-devices

information in the broadcast/print DTCA), which helps in understanding why doctors may have been placated for a while on this issue.

The FDA

An FDA which sought to please consumers by permitting them access to information through DTCA would still: a) exercise oversight regarding the truthfulness of claims made in advertising; and b) seek to ensure that there was symmetry of information regarding risks and benefits. The former has been done by the FDA since the FFDA 1906. The latter was being done until 1999 when the 1969 regulations were replaced with a requirement only that the DTC advertisement point consumers towards further sources of information (such as a doctor) for the full detailed information on product risks. As a result, now DTCA – taken alone – gives consumers asymmetrical information loaded towards product benefits. The FDA's approach to DTCA is particularly confusing given that I have identified it to be an agency which protects its reputation for protecting consumers and one which seeks positive media coverage and avoids negative media coverage. DTCA both increases the magnitude of the costs of type II errors (the 'public interest' puzzle: see Section 2.3.4 above) and the visibility of type II errors (the 'private interest' puzzle – see Section 2.4.6 below). In the second case, this is because heavy industry investment in DTCA makes the brand very familiar to consumers and thus increases the volume of media coverage if a product defect emerges. Both are things that the FDA should seek to avoid according to the extended reputation model.[132] By permitting DTCA – and by facilitating it by removing the restrictions in the 1969 regulations – the FDA puts itself under further pressure (as a safety gatekeeper) to keep all unsafe products off the market. There is therefore a mismatch between my characterisation of the FDA above in Table 15 **Extended Reputation Model Applied to FDA and EMA/NAs**(the extended reputation model - which fits the FDA's behaviour on licensing), and its behaviour in relation to DTCA.

2.4.4 European Union/EUMS

2.4.4.1 Licensing

The EMA/NAs

The reputation which the EMA/NAs have is for science-based assessments of new products. This is protected by the EMA/NAs by ensuring that the centralised procedure is perceived to be apolitical. The main audience of the EMA/NAs is industry and the EUMS ministers rather than consumers – the latter for whom the process is not accessible due to being highly technical-scientific.[133] Industry watches and holds the EMA/NAs to its reputation for scientific rigour because where the process is based upon science (and is not politicised) it favours

132 See Carpenter (2004)

133 And for whom the focal point for blame in the case of safety disasters is the domestic EUMS ministries/ministers

industry.[134] The EUMS governments also watch the EMA and holds it to this reputation because– as Gehring and Kraphol argue[135] – EUMS governments collectively do not wish for the EMA to favour the partisan interests of any one EUMS. And, so long as the approach of the EMA is rigorously technical-scientific it will not do so. The effect of industry and EUMS governments monitoring the EMA for adherence to its reputation, is that there is consistency in TTAs over time. It would be difficult for the EMA/NAs to claim that the centralised procedure was based on science alone if products to treat certain diseases were approved very quickly and products to treat other diseases were approved relatively slowly, as at the FDA. Thus, the EMA does not extensively use its expedited procedures – because the decision as to whether a product fits the criteria stipulated to enable use of the expedited procedures is an inherently political one.

Ironically, where the EMA/NAs underperform the FDA now in TTAs, this is also due to the need for the EMA/NAs to appear completely apolitical. The clock is stopped on the licensing process for the EMA to correspond (at arms-length) with industry so that the EMA/NAs can claim that these discussions did not take place during active review of the product.[136] Once clock stopping and formal approval time is taken out of consideration, the TTAs for the EMA/NAs on the centralised procedure are quick relative to the FDA where that agency does not use its expedited procedures. This is due to what I have called 'capture by default.' As set out above, the process is inherently favourable to industry. The only possible impediment would be politicisation through direct-to-consumer accountability. EU/EUMS consumers - relative to their US cousins - do not actively intervene in the EMA's work but are passively institutionalised, unable to contribute meaningfully to the scientific-technical process.[137] The result is relatively fast and relatively consistent TTAs at the EMA (active review times), and relatively little use of expedited procedures.

Turning to PSMs: like the FDA and for the same reasons, the EMA does not like to issue or recommend full market withdrawals. On the lesser measure of warnings: for the EMA/NAs to protect their reputation for an apolitical, scientific approach, there must be no observable correlation between use of expedited procedures and issue of warnings. Hence, the EMA avoids using expedited procedures relative to frequency with which these are used at the FDA. In other (non-expedited) cases, the EMA finds it easier than the FDA to raise a safety issue with a product because of the different reputations and primary audiences. The EMA then *suspends* market authorisation for further scientific investigation. The measure

134 That is because industry actors will have prepared their application to the Commission based upon advice given by the CMPH and the data is gathered by industry. Thus, the only thing that could stand in the way of a prompt and positive licensing decision is politicisation through the direct involvement of consumers (or EUMS governments) and so industry watches the EMA/NAs and hold it/them to their reputation for keeping the process apolitical and based only on science.

135 See Gehring, Thomas, and Sebastian Krapohl. "Supranational regulatory agencies between independence and control: the EMEA and the authorization of pharmaceuticals in the European Single Market." Journal of European Public Policy 14, no. 2 (2007): 208-226.

136 Appearances are everything, here. Similarly, the time added to the end of the EMA/NAs review process for the Commission to formally approve the product is done in order to reinforce the EMA/NAs reputation for keeping science and politics separate.

137 Moreover, as their focal point for any anger at any scandal would be the domestic EUMS ministers and EUMS ministries which orchestrate the national socialised healthcare systems (which employ the doctors who prescribe the products and also pay directly for the products) EU/EUMS consumers are not likely to hassle the EMA/NAs to any great extent in their work.

implemented here by the EMA reinforces its reputation. Relatively fast TTAs combined with a reluctance to recommend market withdrawal may suggest EU/EUMS consumers are placed at greater risk of ADRs from type II errors because the EMA/NAs seem to act less strongly as safety gatekeepers than the FDA. I suggest, however, that EU/EUMS consumers are equally well protected because EU/EUMS doctors take on this role. Their adoption of that role is facilitated by the relatively passive stance of EU/EUMS consumers towards those doctors.[138] The reliance of the EMA/NAs upon the safety gatekeeping role of doctors – as well as the relative lack of direct accountability between the EMA/NAs and consumers – is evidenced by the European preference for the DHPC over the BBW. The DHPC - addressed to doctors and expressed in technical language, inaccessible to consumers and not made publicly available across the EU save for in four of the EUMS - is reflective of the EU/EUMS approach in general. The EMA/NAs allow products market access relatively quickly. Consumes then rely on doctors to ensure safety (before consumption) through matching.[139]

EU/EUMS Doctors

As stated above, doctors in the EU/EUMS are relied upon relatively more to act as safety gatekeepers. Doctors in the EU/EUMS are happy to do this because, having relatively low income compared to their US counterparts - due to being employed by agencies and hospitals in socialised healthcare systems – they maximise their payment for their role in social status and esteem. The latter result foremost from their status in society as experts, whose advice is to be accepted not negotiated.

EUMS/EU Consumers

Relatively passive EU/EUMS consumers are reassured in the knowledge that ADRs – if they occur – will be treated at low or no cost by the socialised healthcare system which prescribed the offending product. If this occurs, EU/EUMS consumers are unlikely to blame either the doctor (whom they hold in high social esteem) or the agency. Instead, because s/he administers the entire system of healthcare from central government, they blame the health minister. The EMA/NAs thus avoid hassles from consumers, and the licensing process can remain apolitical. Where EU/EUMS consumers are involved in decision-making at the EMA/NAs, this is done for appearances sake mostly.

2.4.4.2 Direct to Consumer Advertising

As was the case with US regulation of DTCA, EU regulation of DTCA is puzzling. Doctors in the EU are a weak interest group relative to doctors in the US. I have also said that the EMA/NAs accommodate industry by default due to the lack of direct-to-consumer accountability. As such, one might expect the EU to permit DTCA to accommodate industry and that the objections of doctors would be overruled. A partial answer comes from the observation that EU/EUMS consumers are less empowered in general and seek information less in relation to their healthcare than US consumers. A more compelling answer is provided when considering

138 This is assisted by the absence of DTCA in the EU/EUMS.

139 Hence the provision of information direct to doctors. The lack of direct-to-consumer accountability enables the speed of products getting through the gate and similarly the relative lack of consumer empowerment in the EU means that DHPCs direct to doctors suffices.

the fact of the existence of socialised healthcare systems in the EU. The imperative of cost control leads EUMS governments and ministers to oppose DTCA which would likely itself empower consumers and move them to seek the DTC advertised products from their doctors.

The EMA/NAs

The EMA does not have the authority to regulate advertising to the same extent that the NAs (under the domestic EUMS health ministries) do. Thus, whilst I have identified that the EMA is likely to accommodate industry by default, this accommodation extends to the licensing process but not to advertising. It seems the Commission would welcome a relaxation of the ban on DTCA – hence its attempts in 2000-2002, and again in 2006, to relax this ban: on both occasions allied with industry.[140] It was the EUMS governments acting in the Council which rejected the proposal in 2008, with representations made by EU doctors and consumers.[141] At the EUMS domestic level, the NAs which may have the power to relax restrictions on DTCA, are under the authority of the domestic EUMS health Ministries and are thus unlikely to allow DTCA for the reason set out above – cost containment.

EU/EUMS Doctors

EU/EUMS doctors are opposed to DTCA. This is evidence by their opposition to the Commission proposal to relax the ban in 2006 – as a part of the lobbying group the 'European Patient Healthcare Alliance'. However, in the EU/EUMS, the effect of socialised healthcare is that doctors are less subject to market forces anyway, which means they have less need to compete to retain patients and are less accessible to the pharmaceutical industry for kickbacks. A loss of market power and/or kickbacks is likely to be less important as a reason to EU/EUMS doctors to oppose DTCA as it is in the US. However, EU/EUMS doctors enjoy high social esteem and this forms part of their compensation for their work, which is less well paid in monetary terms than in the US. I say that the social status of doctors in the EU/EUMS would be threatened by DTCA, and this is – to a greater extent than in the US – likely to be a substantial reason for their opposition to DTCA.[142]

EU/EUMS Consumers

Ordinary EU/EUMS consumers have no particular reason to seek the information which would be provided by DTCA. Whereas in the US a doctor's consultation – at which information would be provided - will cost the US consumer money directly (or as an insurance deductible), in Spain, in the UK and in many other EUMS it is free[143] to obtain this information from the doctor. EU/EUMS consumers, traditionally holding doctors in high social esteem, and feeling no entitlement to challenge the information provided by doctors, are happy to passively accept the advice of doctors instead of seeking secondary sources of information.

140 Which also established a consumer interest group – the 'Pharmaceuticals Forum' to front the campaign.
141 This supports the argument that the Commission and the EMA would support a relaxation of the ban on DTCA, thus accommodating industry, but it is the EUMS governments who oppose it, and that opposition is supported by doctors and some EU/EUMS consumers (e.g., the European Public Health Alliance).
142 This opposition is intensified as a result of the fact that EU doctors – being less subject to market conditions, and captured by socialised healthcare agencies and/or hospitals – end up with lower average incomes than their US counterparts. A more significant part of their renumeration for their work, therefore, is not the monetary payment they receive but the social status and esteem that goes with being a doctor.
143 At the moment of provision.

2.4.5 Public Interest Puzzle Resolved

At the end of the public interest section, I set out the public interest puzzle, which is that if the FDA (and the US system) wished to minimise type II errors, it would both license cautiously and ban DTCA. The positions on licensing and DTCA in both jurisdictions individually may offset each other. I.e., a permissive approach to DTCA in the US may be compensated for by a cautious approach to licensing[144] and, in the EU/EUMS a fast approach to licensing which could result in type II errors is mitigated by a ban on DTCA. The private interest theories discussed, and the private interest model arrived at to explain agency behaviour, has assisted in developing an understanding of how licensing and DTCA are regulated in the US and the EU. The resultant regulatory outcomes do diverge from what public interest theory might suggest when considered in isolation. If one agrees[145] with the insights of Viscusi on licensing, one can see that FDA direct-to-consumer accountability (and thus its objective of protecting its twin reputations) leads to a preference for type I errors in the US. The US system of regulation also has a weaker safety gatekeeping role for doctors, and more empowered, demanding consumers, in addition to DTCA. Therefore, the FDA approach is easier to justify in public interest terms due to the commensurately greater potential for catastrophic harm that might be caused by type II errors were the FDA to be less cautious. On the EU side, the relatively less cautious approach to licensing is easier to justify in public interest terms when one takes in to account the lack of DTCA, and the relatively strong safety gatekeeping potential of EU/EUMS doctors. It is arguable, therefore, that both systems are justifiable in public interest terms when licensing and DTCA are considered at the same time.

2.4.6 The Private Interest Puzzle: Visibility of Type II Errors

At the end of the private interest section, however, I am left with another puzzle. The private interest methodology adopted was to first look at the groups and organisations and characterize them in their behaviours; then, I considered how they interact together and set out the extended reputation model. I then applied that to the regulation of licensing and DTCA in both jurisdictions and I identified that the extended reputation model aptly explains the approaches to licensing. It does not, however, seem to explain so well the approach to DTCA. What would be expected for DTCA based on the extended reputation model is the opposite

144 See Ventola C. L. (2011). Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic?. P & T: a peer-reviewed journal for formulary management, 36(10), 669–684.

145 Professor Franzoni has suggested to me that some would not believe Viscusi in his accusation that the FDA is too cautious. Indeed, in his paper (Viscusi, Magat and Scharff, 1996) he does not undertake a quantitative comparison of the costs and benefits of Type I v Type II errors (which is very difficult to do), instead framing the problem in abstract terms*: "Ie, if a product increases the mortality risk by P and decreases the mortality risk by Q, where Q exceeds P, then on balance the product will increase longevity. Overall, from a decision- theoretic point of view we should look at the net risk associated with the product and not treat the component parts differently"* It seems to me that Viscusi's argument, albeit not demonstrated empirically, is compelling. However, I recognise the two important limitations: 1) we do not know for sure which have been/would be more costly: Type I or Type II errors; and, 2) society may prefer (and who are we to question the legitimacy of its preference?) errors of omission over errors of commission: see the footnote in Section 2.3.3 above.

to what is found for the regulation of DTCA. I set out this private interest puzzle regarding the concurrent regulation of licensing and DTCA in the US and the EU in Table 17 **The Transatlantic Pharmaceutical Puzzle (Private Interest)**below.

Table 17 The Transatlantic Pharmaceutical Puzzle (Private Interest)

	Agency Reputation/Audience	Result Licensing	Expected DTCA	Reality DTCA
US	FDA Consumer protection and product access: Consumers	Relatively cautious	Banned	Permitted
EU/EUMS	EMA/NAs science based assessment: Industry/EUMS governments	Relatively fast	Permitted	Banned

By way of example, the FDA approved the drug Vioxx in 1999 and between 1999 and 2004 its licence-holder Merck spent $160.8 million on DTCA. The drug was withdrawn in 2004 and it was found that it may have caused between 88,000 and 140,000 cases of serious heart disease.[146] The type II error of the FDA in approving Vioxx (based on bad clinical data) was made highly visible by the media following withdrawal precisely because the product had been so heavily advertised prior to being withdrawn. The media reports news stories according to consumer demand for those stories. Consumer demand for news is correlated with consumer awareness of the issues reported. DTCA raises public awareness of certain products and thus DTCA makes type II errors very visible to consumers. This example illustrates the intuitive logic that an agency seeking to protect a reputation (in part) for consumer protection would not allow DTCA. Far less would that agency continue to permit DTCA after a scandal such as Vioxx, yet that is what the FDA did.[147] This is why in Table 17 above I say that the US system would be expected to ban DTCA. I turn below to consider relevant institutions to find a solution for this private interest puzzle.

2.4.7 Relevant Institutions: Socialised Healthcare and Free Speech

Socialised Healthcare in the EU

I have already explained the effects of this institution on the regulation of DTCA and licensing in the EU. Crucially, socialised healthcare leads to a need for cost containment by EUMS ministers which leads EUMS governments to oppose DTCA. It also leads to strong downwards facing doctor autonomy in the EUMS/EU and a desire on the part of doctors to protect their social status, hence the opposition of doctors to DTCA. On the part of consumers, socialised healthcare makes them less desiring of free sources of information, and more trusting of (and dependent upon) doctors, hence they do not strongly call for DTCA.

Free Speech

146 See Horton, R., 2004. Vioxx, the implosion of Merck, and aftershocks at the FDA. The Lancet, 364(9450), pp.1995-1996.
147 See Auton (2004) and Auton (2006).

I argue that the decisive difference in the case of DTCA is the legal institution of free speech protections. This takes a different form in the US than it does in the EU/EUMS and it is the form which it takes in the US – as protected by the US courts – which proves decisive in the US not banning DTCA. That legal institution does not constrain regulators, agencies, and governments in the EU in the same way as it does in the US.

There are some similarities between the US and the EU in their legal protections of free speech. To start with, in both jurisdictions freedom of speech is formally legally protected. In the US, that is primarily through the protection found in the first amendment to the US Constitution.[1] In the EU, it is protected in Article 10 of the European Convention on Human Rights ('ECHR'),[2] which applies to all member of the Council of Europe.[3] It is also protected by Article 11 of the EU Charter of Fundamental Rights (Freedom of expression and information) which applies to all EUMS. It would be too simplistic to say that in the US to restrict DTCA would be unconstitutional,[4] and that this is the only reason why there is a disjunct between the DTCA and licensing pictures on either side of the Atlantic. A blanket ban in the US would likely be held unconstitutional, under the first amendment, by the Supreme Court of the US (SCOTUS). But restriction of some kind, or a selectively enforced ban, would likely survive a first amendment challenge when assessed using the *Central Hudson* test

1 First amendment to the Constitution of the United States: *"Congress shall make no law respecting an establishment of religion, or prohibiting the free exercise thereof; or abridging the freedom of speech, or of the press; or the right of the people peaceably to assemble, and to petition the Government for a redress of grievances"*

2 Article 10 ECHR: *"Article 10 – Freedom of expression: 1. Everyone has the right to freedom of expression. This right shall include freedom to hold opinions and to receive and impart information and ideas without interference by public authority and regardless of frontiers. This article shall not prevent States from requiring the licensing of broadcasting, television or cinema enterprises: 2. The exercise of these freedoms, since it carries with it duties and responsibilities, may be subject to such formalities, conditions, restrictions or penalties as are prescribed by law and are necessary in a democratic society, in the interests of national security, territorial integrity or public safety, for the prevention of disorder or crime, for the protection of health or morals, for the protection of the reputation or rights of others, for preventing the disclosure of information received in confidence, or for maintaining the authority and impartiality of the judiciary."*

3 As a side note, all are also members of the Council of Europe. Whilst disputes arising under the ECHR are adjudicated by the European Court of Human Rights in Strasbourg, the principal court of the EU has held that both the ECHR and the jurisprudence of the ECtHR are highly relevant to assessing fundamental individual rights protections provided by member states of the EU for the purpose of the CJEU's own jurisprudence. See also Article 11 of the EU Charter of Fundamental Rights (Freedom of expression and information) *"(1) Everyone has the right to freedom of expression. This right shall include freedom to hold opinions and to receive and impart information and ideas without interference by public authority and regardless of frontiers. (2) The freedom and pluralism of the media shall be respected."* The separate protection given to press freedom supports the argument made below that the checking-value and self-governance theories underpin European human rights jurisprudence. Any review by the CJEU, of the legality of the EU DTCA ban would be reviewed against this right (Article 11) but in doing so, reference would be made to the European Court of Human Rights' interpretation of Article 10 ECHR. The nature of the test applied by the CJEU would be somewhat different to that in the European Court of Human Rights. In Luxembourg, the focus would be on proportionality, whilst in the ECtHR the margin of appreciation doctrine is applied. In the author's view, this does not negate the argument made below that the EU DTCA ban would be very difficult to overturn and neither the argument that legal path dependency is manifest.

4 See *Thompson v. Western States Medical Center*, 535 U.S. 357 (2002)

currently in force.[5] Moreover, it could be argued that the EU-wide ban would merit a challenge before the Court of Justice of the European Union (CJEU)[6] based on Article 10 ECHR.

A challenge would likely be unsuccessful, but that is not necessarily because the free speech protection of Article 10 ECHR are less in general than those provided by the first amendment, but rather due to a form of legal path dependency which is closely linked to the doctrine of the 'margin of appreciation' employed by the European Court of Human Rights ('ECtHR'). To explain: the margin of appreciation doctrine was (originally, at least) premised upon a view of the ECHR and ECtHR as providing a supervisory jurisdiction for the protection of fundamental rights in the Council of Europe. As such, the Strasbourg Court sought to divine a minimum acceptable standard only for protection of the relevant rights and ensure that this was being complied with by the contracting parties. I have already noted above that all EUMS have bans in place on DTCA. As such, a challenge is likely to fail before the CJEU. It is not merely the case that there is little free speech protection in the EU and a lot of it in the US. Despite some textual differences between the US and EU provisions, ultimately the argument I make here is that differences in the theories of free speech drawn upon in the jurisprudence of SCOTUS and the ECtHR, respectively, have led to substantive differences in the application of the free speech protections to advertising or, 'commercial speech'.[7]

In the EU it is clear that there is a separate line of jurisprudence dealing with freedom of the press, specifically[8], rather than free speech generally, and this is part of a wider conclusion to be drawn from the Strasbourg caselaw that Article 10 ECHR is more concerned with preserving liberal democracy as a political system, rather than with protecting individual rights to speech. Much is made in the caselaw of the 'checking value' of a free press against a national government potentially predisposed towards violations of other rights.[9] This view of Article 10 mirrors the text itself, which allows a national regulator (supervised by the Strasbourg court) to interfere with Article 10 rights where other social needs must be met in protection of democracy.[10] The ECtHR caselaw comes close to, but certainly does not go further than, what US scholars call the, 'self-governance theory'[11] of free speech protection. Meiklejohn, in his theory, draws a sharp distinction between private and public speech. The latter is useful to others in society for their self-governance and, he argues,[12] the law should ensure that public speech is able to be disseminated throughout society so that all members

5 See below for the full test: *Central Hudson Gas & Electric Corp. v. Public Service Commission*, 447 U.S. 557 (1980).
6 https://www.jurist.org/commentary/2013/09/elena-butti-lisbon-treaty/ *"Art. 52(3) of the CFR states that, wherever the charter contains rights that correspond to the ECHR, "the meaning and scope of those rights shall be the same" as that granted by the convention. However, in what has been defined as an "unsolved paradox," Art. 52(3) also enables the ECJ to provide "more extensive protection" than that granted by the ECHR. Art. 53 of the CFR further includes a non-regression clause by which the charter must not to be interpreted as "restricting or adversely affecting" the human rights recognized in the convention."*
7 See Johnson, Bruce EH, and Kyu Ho Youm. "Commercial speech and free expression: The United States and Europe compared." J. Int'l Media & Ent. L. 2 (2008): 159.
8 See e.g. NOVAYA GAZETA AND MILASHINA v. RUSSIA: Application no. 45083/06
9 See MORICE v. FRANCE 29369/10 at Para 125
10 See Blanks Hindman, Elizabeth. "The chickens have come home to roost: Individualism, collectivism and conflict in commercial speech doctrine." Communication Law and Policy 9, no. 2 (2004): 237-271.
11 See Meiklejohn, Alexander, Political Freedom: The Constitutional Powers of the People 26 (1965). See Post, Robert, Reconciling Theory and Doctrine in First Amendment Jurisprudence, 88 Calif. L. Rev. 2353 (2000).
12 See Meiklejohn (1965)

can benefit from it.[13] An example of private speech would be commercial speech,[14] such as advertising, which has a profit seeking basis and which is relevant only to the speaker and the customers who buy the product.[15] As such, under the Meikeljohnian self-governance view, commercial speech would benefit from fewer legal protections than would public speech. These reasons taken together may suggest why the ECtHR lacks a specific doctrine covering commercial speech per se and has dealt with fewer challenges to bans on commercial speech. A leading case is *Coca v Spain*[16] which concerned lawyer advertising. The ECtHR remarked, *"in some contexts, the publication of even objective, truthful advertisements might be restricted in order to ensure respect for the rights of others or owing to the special circumstances of particular business activities and profession."*[17] This was different to the approach taken by SCOTUS to lawyer advertising in *Re R.M.J*[18] where it was held that the State had no substantial interest in restricting lawyer advertising and thus the *Central Hudson* test was not satisfied.

By contrast, in the US, SCOTUS has heard many challenges[19] to restrictions of commercial speech under the first amendment. At first, it followed the Meiklejohn theory, leaving commercial speech outside the umbrella of first amendment protection. Later, in *Bigelow v Commonwealth of Virginia*[20] SCOTUS brought advertising under that umbrella, without departing in theoretical terms from the self-governance theory.[21] That was followed, in 1976, by *Virginia State Board of Pharmacy v Virginia Citizens Consumer Council*[22] which related specifically to a prohibition on pharmacist advertisement of pharmaceutical prices. SCOTUS held that this violated the first amendment rights of the advertiser. The current approach in the US is found in the test set out in *Central Hudson Gas & Electric Corporation v Public Service Commission of New York*[23] which has four prongs. To be protected by the first amendment, first 1) the commercial speech must concern lawful activity and not be misleading. Then, once it is protected by the first amendment then if the government wishes to restrict it 2) the government must have a substantial interest in regulating it; 3) the regulation must directly and materially advance the government's substantial interest; and, 4) the regulation must be

13 See Meiklejohn (1965) See Post (2000)

14 See Johnson (2008)

15 Most theories of free speech focus on the autonomy of the listener. Privacy rights focus more upon the autonomy of the individual to express themselves. The individual autonomy theory of free speech, however, focuses on the speaker. This theory is not dominant in either SCOTUS or the ECtHR, but it is sometimes referred to in both.

16 COURT (CHAMBER) CASE OF CASADO COCA v. SPAIN (Application no. 15450/89) JUDGMENT STRASBOURG 24 Feb 1994

17 Ibid at Para 51.

18 Re R.M.J., 455 U.S. 191 (1982). The point is not raised in this paragraph to emphasise a substantive difference in the approach to lawyer advertising but more to illustrate that commercial speech challenges are more common before SCOTUS than before the ECtHR

19 Valentine v. Chrestensen (1942): Rowan v. U.S. Post Office Dept. (1970): Pittsburgh Press Co. v. Pittsburgh Commission on Human Relations (1973): Lehman v. Shaker Heights (1974): Bates v. State Bar of Arizona (1977): Linmark Associates, Inc. v. Willingboro (1977): Ohralik v. Ohio State Bar Assn. (1978): Friedman v. Rogers (1979): Consol. Edison Co. v. Public Serv. Comm'n (1980): Hoffman Estates v. The Flipside, Hoffman Estates, Inc. (1982): Expressions Hair Design v. Schneiderman (2017)

20 Bigelow v. Commonwealth of Virginia, 421 U.S. 809 (1975)

21 See Blanks Hindman (2004)

22 Virginia State Pharmacy Board v. Virginia Citizens Consumer Council, 425 U.S. 748 (1976)

23 Central Hudson Gas & Electric Corp. v. Public Service Commission, 447 U.S. 557 (1980)

narrowly tailored. It is the fourth prong of the *Central Hudson* test which would likely cause any blanket ban on DTCA to be struck down by the courts as unconstitutional.[24]

It has been argued that the theoretical approach of SCOTUS has not been consistent over time.[25] It appears to have taken in to account several different theoretical bases for free speech but has so far failed to choose between them. The self-governance theory is one of these.[26] Others are: the 'marketplace of ideas' theory of Oliver Wendell Holmes;[27] and the individual autonomy theory, based upon strict liberal ideals.[28] That marketplace of ideas theory is found a lot less strongly in the ECtHR caselaw concerning free speech, than it is in SCOTUS jurisprudence.[29] This theory can have either a consequentialist (weak) or non-consequentialist (strong) form.[30] Generally, the theory suggests that society's search for truth is best facilitated by few or no restrictions on speech due to a marketplace for ideas existing in which better (more truthful) ideas survive and weaker (less truthful ideas) fall out.[31] In its strong form, this would suggest that whatever the marketplace produces is truth;[32] i.e. if people believe that eating high-sugar food all the time is a good way to live, then this is a good way to live.[33] The weak, consequentialist, view is sceptical of human rationality. Individuals may tend to prefer the idea that sugary food is good, but the opposite is the truth and thus, really, they should be eating low-sugar food. This is a consequentialist version of the theory because it asserts that free speech is good only in so far as few restrictions on speech facilitate the emergence of truth. Thus, it has been argued in the US - In relation to advertising of junk food – that regulation should be introduced despite commercial speech protections. Parmet points out that the jurisprudence of SCOTUS on first amendment rights is largely consequentialist in nature, and thus such regulation is legally permissible.[34]

SCOTUS seems to have treaded a line in between the weak version of the marketplace of ideas theory, and the self-governance theory of Meiklejohn.[35] This has resulted in an approach which gives less protection to commercial speech than is given to political (or public) speech, but with the rider that true commercial speech cannot be banned solely on paternalistic principles.[36] This approach can be seen in the most recent landmark case concerning pharmaceuticals advertising: *Thompson v. Western States Medical Center* where the focus of the court was upon the availability of lesser measures, the fourth prong of the *Central Hudson* test, rather than the merits or demerits of consumer choices regarding

24 See Thompson v. Western States Medical Center, 535 U.S. 357 (2002) which is the last major decision of SCOTUS on the matter. Here, the restriction on advertising of compound drugs was found to violate the first amendment, but only because it failed the fourth 'prong' of the Central Hudson test, namely that lesser measures were available to the government to meet its objective. This leaves open the possibility that a more tightly circumscribed ban would be acceptable. A blanket ban, on the other hand, would almost certainly fail the test.

25 See Blanks Hindman (2004)

26 See Meiklejohn (1965)

27 See his dissent in Abrams v. United States 250 U.S. 616 (more) 40 S. Ct. 17.

28 Greenawalt, Kent. "Free speech justifications." Columbia Law Review 89, no. 1 (1989): 119-155.

29 Ibid. See also Johnson (2008)

30 See Greenawalt (1989)

31 See Post (2000)

32 See Greenawalt (1989).

33 See Parmet, Wendy E., and Jason A. Smith. "Free speech and public health: A population-based approach to the First Amendment." Loy. LAL Rev. 39 (2006): 363.

34 Ibid.

35 See Blanks Hindman (2004)

36 See Virginia State Pharmacy Board v. Virginia Citizens Consumer Council, 425 U.S. 748 (1976) at 490.

pharmaceuticals**.** This approach is like the ECtHR approach to Article 10, which certainly protects commercial speech to a lesser degree than political speech. However, as outlined above, the preoccupation of the ECtHR concerning Article 10 is the preservation of liberal democracy and so, necessarily, the jurisprudence in Europe has given protection less often to commercial speech than has SCOTUS.

As such, my conclusion is that the institution of legal protection of free speech in the US, due to its theoretical approach, takes a relatively stronger approach to the protection of *commercial* speech than is the case in the EU. This, I argue, is the reason why the US system has not banned DTCA and why the FDA has removed the restrictions on broadcast and print DTCA which were previously found in the 1969 regulations. To maintain these restrictions or increase them would have led to a – likely successful – first amendment challenge. Coupled with US consumer desire for access to information in the form of DTCA, and industry opposition to a ban, these factors taken together persuaded the FDA to retreat from regulating DTCA and instead to focus on its role as safety gatekeeper and caution in licensing. These functions were made even more vital to the FDA's protection of its reputation as a result of DTCA being permitted. By contrast, in the EU, EUMS governments do not want to permit DTCA for fear of spiralling healthcare costs for the socialised healthcare systems there. Any potential legal challenge to the ban (based on the EU legal protections) is not so likely to succeed as it would in the US, due to the less ready application of those protections to commercial speech which, in turn, result from differences between the US and EU courts in the theoretical bases which underpin their free speech protections. The private interest puzzle is thus resolved by understanding how the institution of legal protection of free speech constrains the regulatory options of the FDA in the US and how the institution of socialised healthcare in the EU leads to opposition from EUMS governments to DTCA.

2.5 Conclusions

I began by setting out the divergent transatlantic regulation of licensing and DTCA. Then I drew upon public interest theories of regulation to consider which regulatory position – that of the US, or the EU – was most easily justified in public interest terms. I noted an initial puzzle (the public interest puzzle): that across both aspects of regulation the jurisdictions were inconsistent in their approach. The cautious approach to licensing in the US was not matched by caution in the form of a ban on DTCA, and vice versa in the EU. Public interest theory also could not explain why the FDA preferred type I over type II errors (generally slow TTAs), why it uses its expedited procedures more often and only for certain products, nor why there were differences in uses of PSMs. I turned to private interest theories to seek further explanation for the divergences. Here I developed the extended reputation model, and this helped to explain all aspects of the differences between the US and the EU on licensing. It also resolved for me the public interest puzzle, by clarifying the interaction between doctors, consumers, and agencies. The US and EU systems are both justifiable in public interest terms because the regulatory positions in each case offset each other: cautious licensing enables permissive DTCA regulation in the case of the US and the other way around in the EU. The missing piece of the puzzle here was the role of doctors, and the identity of the 'safety gatekeeper' in each case. Consumers in the EU are protected relatively strongly by doctors whereas in the US they are protected relatively strongly by the FDA. Taken together, therefore, DTCA and licensing form a system of regulation which can be configured in two different ways. The US has chosen one way (more caution-permission) and the EU the other (less caution-ban), and where consumers are left exposed to type II errors by the EMA/NAs quick TTAs, EU/EUMS doctors can be relied upon to provide an extra layer of safety oversight.

But why do the jurisdictions settle upon the configuration which they do? It is particularly confusing given that the extended reputation model would suggest the US is likely to at least restrict DTCA rather than to progressively retreat from regulating it at all. This is the private interest puzzle. In order to resolve that puzzle it was necessary to widen the screen even further, from considering first just the regulation itself, then also the groups and organisations which impact upon the development of the regulation, to the jurisdictional institutions which may constrain or expand the regulatory options of all groups and organisations within the jurisdiction. In this case I identified the presence of the social institution of socialised healthcare in the EU/EUMS (versus largely private healthcare in the US) and the legal institution which relatively strongly protects commercial speech in the US (versus one which protects it relatively weakly in the EU). The choice of system in the US is constrained by this latter institution because it makes it difficult for the FDA to legally restrict DTCA. The FDA is therefore pushed further to its exercise of caution in licensing as gatekeeper, whilst US doctors retreat from that role as the presence of DTCA makes their consumers more stridently demanding. In the EU the former institution constrains a Commission which would otherwise permit DTCA because EUMS governments in Council fear the cost implications which are attendant upon their socialised healthcare systems.

Chapter Three: Pharmacovigilance and Products Liability

3.1 Introduction

> *"My Lords, the facts of this case are simple. On August 26, 1928, the appellant drank a bottle of ginger-beer, manufactured by the respondent, which a friend had bought from a retailer and given to her. The bottle contained the decomposed remains of a snail which were not, and could not be, detected until the greater part of the contents of the bottle had been consumed. As a result… she suffered from shock and severe gastro-enteritis…"*
>
> *Lord Buckmaster in M'Alister (or Donoghue) v Stevenson*[1]

Mrs Donoghue - a consumer - had suffered personal injury due to a latent manufacturing defect in her ginger-beer. Thus, Scotland's most famous snail gave the House of Lords the perfect opportunity to lay the foundations of modern product liability law.[2]

Uncertainty over the safety of products can be addressed through incentives to take care at the development and manufacturing stage, or by monitoring of products once they reach the market, or both. In the case of pharmaceuticals: product liability and pharmacovigilance are two regulatory 'techniques' each used in the United States (US) and the European Union (EU) to reduce externalities caused by unsafe products, and thus minimize the total social cost of product accidents. They are, however, applied in different ways in both jurisdictions and neither approach seems completely justified by the public interest theory of regulation. In fact, both seem to depart substantially from what public interest theory would suggest. I argue that differences between the institutional structures of the legal systems - and the objectives of key interest groups - help explain the divergence in approaches, though not fully.

Pharmacovigilance and product liability are closely linked, and together form a 'system' which directly addresses the same underlying market failure, and the same causative information problem. Therefore, here I do not only consider the US-EU divergence, but I also consider how their regulatory 'systems' (comprising both pharmacovigilance *and* product liability) diverge from a suggested system based upon insights taken from public interest theory ('SPI' system).

Table 18 Definitions in this Chapter: Techniques and Systems

Regulatory 'Techniques'	**Regulatory 'Systems'**
Pharmacovigilance	EU Pharmacovigilance + Product Liability
Product Liability	US Pharmacovigilance + Product Liability
	SPI Pharmacovigilance + Product Liability

1 House of Lords [1932] AC 562

2 By this I mean tort liability for defective pharmaceutical products.

This means that here I discuss two sets of divergence: 1) transatlantic divergence; and 2) system divergence. The transatlantic divergence relates to differences between the US and the EU use of the techniques of pharmacovigilance and product liability. The system divergences relate to difference between the EU, the US, and the SPI systems in the way these seek to address the underlying market failure.

Commencing, below, I first set out the transatlantic divergence: horizontal differences between the US and the EU in their use of the two techniques. In the US, pharmacovigilance is Food and Drug Administration (FDA) -led and funded, with little separation of executive authority between the licensing committee and the pharmacovigilance committee at the agency: the licensing committee takes all decisions. In the EU, the European Medicines Agency (EMA) relies relatively more on collaboration with and funding from industry for pharmacovigilance. The licensing and pharmacovigilance committees at the EMA have a greater degree of separation of executive authority. In the US industry compliance with FDA mandated pharmacovigilance studies is poor relative to industry compliance with EMA mandated studies in the EU.

On product liability, in the US it is relatively difficult for a claimant to establish the liability of a pharmaceutical firm in a claim. In particular, US common law will not impose liability on a firm where the defect in the product which caused the harm was a design defect which was unknown and unknowable by the firm at the time the product was placed on the market. However, due to procedural aspects of US common law - including the availability of class action suits, and jury determined punitive damages – as well as an overall higher volume of litigation in the US relative to the EU, any given pharmaceutical firm in the US can expect relatively high overall damages awards against it where it has placed a defective product on the market. In the EU, under the Product Liability Directive 1985[3] (the 'PLD') it is relatively easy for a claimant to establish liability, and it is possible for EU Member States (EUMS) to derogate from the PLD so as to provide for liability in the case of design defects where the defect in the pharmaceutical product was unknown and unknowable at the time the product was placed on the market. However, due to the possibility of an overall damages cap in the PLD, a lack of availability of punitive damages awards in the domestic laws of the EUMS, restrictions[4] upon class action suits and an overall lower volume of litigation in the EU relative to the US; expected damages awards against any given pharmaceutical firm for any given defective product are low relative to the US.

Next, I introduce the SPI system, and I contrast this with the US and EU systems. I identify the most important divergences between the three systems. The SPI system would not fully apply product liability. It would only allow product liability claims in cases where the defendant firm had intentionally concealed information from the regulatory agency. In this case punitive damages would be made available against the firm. Otherwise, the SPI system would rely entirely upon pharmacovigilance to solve the underlying market failure. Pharmacovigilance in this case would incorporate licensing and would thus start before the product reached the market. I call this 'broad pharmacovigilance' which is contrasted with 'narrow

3 Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products.

4 Until recently there was no EU level harmonisations of class action suits, and there remains none, although 'representative actions' are now provided for under EU law.

pharmacovigilance' where licensing and pharmacovigilance remain separate and where the former ends at the time the product enters the market, and the latter takes over from that point forward. Both the US system and the EU system adopt only narrow pharmacovigilance, and product liability has full application.

As was the case for licensing and direct to consumer advertising (DTCA) in Chapter Two, one would expect – based on public interest theory – that both jurisdictions would take the same approach to the techniques and would adopt the same systems, and that the system adopted would be the SPI system. That is not the case. In Section 3.2 I identify that there is transatlantic divergence in the use of the techniques, and in Section 3.3 I find that there is also divergence on the system level, which is a uniform divergence for both the US and the EU from the SPI system. Therefore, having concluded that public interest theory cannot fully explain the transatlantic nor the system divergence, in the Section 3.4 I adopt a private interest perspective. Here I turn to lawyers, the pharmaceutical industry and other relevant groups, organisations, and institutions to seek further explanation. There, I find that analysis of the role of the pharmaceutical industries and regulatory agencies in each jurisdiction assists in explaining the transatlantic divergence in pharmacovigilance, and that analysis of the role of the US pharmaceutical industry (USPI) in the US, and the EU pharmaceutical industry (EUPI) in the EU assists in explaining the transatlantic divergence in product liability. Furthermore, analysis of the FDA in the US, and both EUPI and lawyers in the EU, assists in explaining the system divergence.

3.2 Pharmacovigilance and Product Liability

In this Section I begin by giving an overview of the essential characteristics of pharmacovigilance and product liability, and I describe the relationship of both with licensing. I then turn to describe the approaches taken to both in the US and the EU, thereby setting out the transatlantic divergences.[1]

Introducing Pharmacovigilance

Pharmacovigilance is *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine related problems."*[2] This is the definition provided by the World Health Organisation in 2002, which has been adopted by both the FDA and the EMA. Pharmacovigilance first emerged following the Thalidomide disaster of 1961[3] and the World Health Organisation established its Programme for International Drug Monitoring in 1968 after issuing a resolution calling for: *"systematic collection of information on serious adverse drug reactions during development and particularly after medicines have been made available for public use."*[4] Since then, advances in technology[5] have made it possible to monitor new pharmaceutical products on an ongoing basis, and to manage and communicate risks about those products. In the US pharmacovigilance is currently overseen by the Centre for Drug Evaluation and Research (CDER) at the FDA. Specifically, within the committee of the Office of Surveillance and Epidemiology ('OSuE') at the Division of Pharmacovigilance. The OsuE is aligned with the FDA department responsible for licensing – the Office of New Drugs, where the committee with executive power is called the New Drugs Committee (NDC). In the EU, pharmacovigilance takes place both at the EUMS and the EU level and is coordinated at the EU level by the EMA. The EMA incorporates the Pharmacovigilance Risk Assessment Committee ('PRAC') which is aligned with the Committee on Medicinal Products for Human Use (CMPH).

1 Pharmacovigilance and product liability are both referred to here as forms of regulation. This is giving a broad definition to the term 'regulation', given that regulation and liability are often discussed as separate creatures, and regulation usually refers to specific rules governing an activity. In the case of product liability, I am referring to the rules which set the standard of liability and govern awards of damages etc. In the case of pharmacovigilance - which some would describe as a practice rather than a form of regulation - I am talking about legal rules directly regulating the practice (for example, legal instruments such as the FDA Amendments Act 2007 (the 'FDAAA') and the EU Pharmacovigilance Directive and Regulation of 2010, both of which are included in the analysis below) as well as informal rules governing how it is carried out: for example the tendency of the FDA to commission its own pharmacovigilance studies instead of requiring industry to carry these out. When I refer to both pharmacovigilance and product liability, I am referring primarily to their application to 'prescription only' (PO) pharmaceutical products.

2 The Importance of Pharmacovigilance, World Health Organization 2002.

3 See Meyboom, Ronald HB, Antoine CG Egberts, Frank WJ Gribnau, and Yechiel A. Hekster. "Pharmacovigilance in perspective." Drug safety 21, no. 6 (1999): 429-447.

4 World Health Organization. (1973). Handbook of resolutions and decisions of the World Health Assembly and the Executive Board, v. 1: cumulative definitive ed.; v. 2: cumulative definitive ed.; v. 3: 3rd ed.

5 Shea, Lance L., Andre Hanson, Tiffany M. Guglielmetti, and Kimberly Levy. "Cause and Effect-Assessing Postmarketing Safety Studies as Evidence of Causation in Products Liability Cases." Food & Drug LJ 62 (2007): 445.

Table 19 Licensing and Pharmacovigilance Committees at the FDA and EMA

Agency	Licensing Committee	Pharmacovigilance Committee
FDA (US)	New Drugs Committee **(NDC)**	Office for Surveillance and Epidemiology **(OsuE)**
EMA (EU)	Committee on Medicinal Products for Human Use **(CMPH)**	Pharmacovigilance Risk Assessment Committee **(PRAC)**

As of 2018,[6] the tasks of the US OsuE are to: evaluate the safety of drugs and therapeutic biologic products; monitor and undertake surveillance of adverse drug reactions (ADRs); analyse safety signals; recommend regulatory actions and communicate relevant safety information. The OsuE coordinates the FDA Adverse Event Reporting System, a fully computerised database with 14 million ADRs reported since 1969. At the EMA, the PRAC is said to be responsible for assessing and monitoring the safety of new medicines.[7] The EMA operates 'EudraVigilance' which is a database for managing and analysing information on suspected ADRs for medicines in the European Economic Area. The PRAC evaluates safety signals from Eudravigilance and may recommend regulatory action to the EMA and NAs as a result.[8]

Relationship between Pharmacovigilance and Licensing

Both pharmacovigilance and licensing are overseen by a regulatory agency and, depending upon how one conceptualizes pharmacovigilance, the two may overlap. Licensing takes effect by preventing unsafe products from market access after they have been developed by a pharmaceutical firm. Narrow pharmacovigilance is merely a system of monitoring and recording ADRs from products after their release to the market, to see if they are safe. What I call here 'broad pharmacovigilance'[9] applies to pharmaceutical products from their early development until the end of their product life cycles. Broad pharmacovigilance integrates licensing. It further incorporates elements of product risk planning, risk management and risk communication which are absent from narrow pharmacovigilance, and which are sometimes considered functions of licensing. This relationship is shown below in Figure 5.

6 www.fda.gov/files/about%20fda/published/Drug-Safety-Surveillance-and-the-FDA-Adverse-Event-Reporting-System-%28PDF---1.31MB%29.pdf

7 https://www.ema.europa.eu/en/documents/other/european-medicines-agency-pharmacovigilance-system-manual_en.pdf

8 https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview

9 This is based in part on a framework set out in Edwards, I. Ralph. "The future of pharmacovigilance: a personal view." European journal of clinical pharmacology 64, no. 2 (2008): 173-181. See also Edwards, I. Ralph. "Good pharmacovigilance practice and the curate's egg." (2012): 429-435.

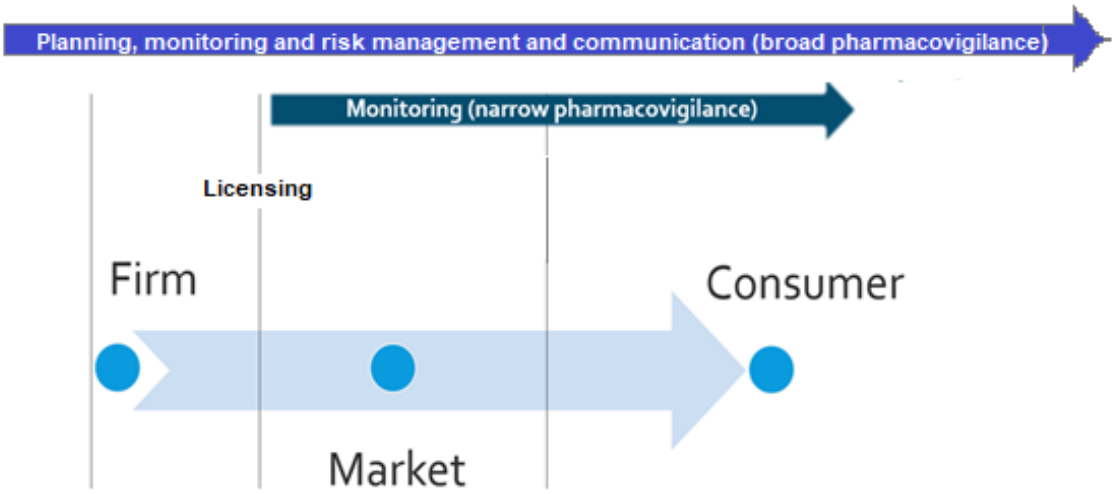

Figure 5 **Narrow Pharmacovigilance, Broad Pharmacovigilance, and Licensing**

Introducing Product Liability

Product liability seeks to compensate individuals ex-post for harm which they have suffered caused (here) by pharmaceutical product. Liability has incentive effects – it deters pharmaceutical firms from marketing unsafe products, as shown below in

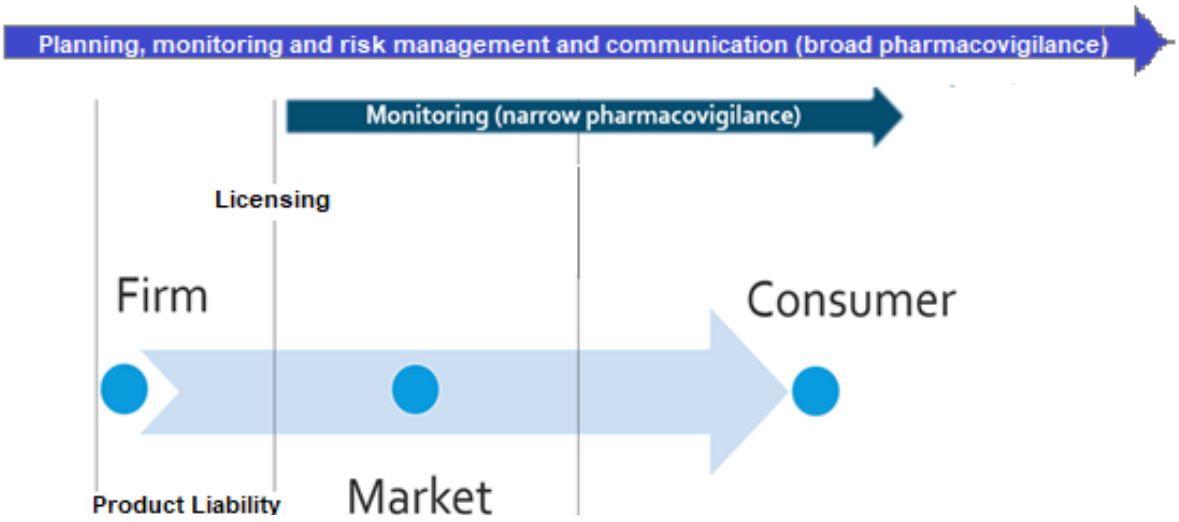

Figure 6 **Narrow Pharmacovigilance, Broad Pharmacovigilance, Licensing, Product Liability**

Figure **6**.

The process of product liability involves the bringing, by individual claimants, of claims against pharmaceutical firms in courts. In both the US and the EU, to succeed in the claim, the individual claimant must establish that the pharmaceutical product was 'defective', and that it caused the harm which the claimant seeks to be compensated. The basis of liability may be 'negligence' – where the claimant must show that the defendant pharmaceutical firm failed to exercise a level of care in their design, manufacture, or marketing of the product – and that

level of care is set by a court. Or, it may be strict liability where the defendant pharmaceutical firm will be liable for any harm without proof of failure to meet a requisite level of care, providing that the product is established to be defective and causation is made out. Where a product or class of products is exempted from strict liability, it will normally still be possible for the claimant to claim under the negligence standard, although this will be more difficult because breach must be proved.

Table 20 Standards of Product Liability

Standard	Explanation	Burden/Standard of Proof
Negligence	Claimant must prove 'breach' that defendant firm failed to exercise a standard of care set by courts.[10]	Claimant must prove on balance of probabilities for 1) breach and 2) that breach caused the harm alleged.
Strict Liability	Claimant need only prove that product was defective.[11]	Claimant must prove on balance of probabilities for 1) defectiveness and 2) that defect caused the harm alleged.

Either a judge (in most of the EU) or a jury (usually, in the US) will decide whether the claimant has succeeded in establishing these elements, according to a certain standard of proof which, in both jurisdictions for civil is the balance of probabilities: more than 50% likely that the allegations made by the claimant are true.

Table 21 Types of Defect in Product Liability

Type of Defect	Explanation
Design	The product was inherently unreasonably unsafe and neither safer manufacturing processes nor more adequate warnings would have made the product reasonably safe.
Manufacturing	The product would have been reasonably safe if it had been manufactured properly but unsafe manufacturing processes made it unreasonably unsafe (warnings do not apply in this case).
Warning	The product was inherently safe if used correctly but unsafe if used incorrectly and the defendant firm did not provide a warning against circumstances in which use would be unsafe.

10 Note that the task, upon the Claimant, of proving breach requires her to establish that the defendant firm fell short of a standard of care when producing the product. E.g. where the product is defective 'by manufacture' that might involve showing that the glass drinks bottle was fragile *because* the firm negligently failed to exercise a quality control process within its factory, and thus fell short of a standard of care owed under a duty of care to her, in failing to do so. This will be difficult for the Claimant to prove without knowledge of the processes taking place within the factory.

11 In this case, the Claimant need not prove breach (that the firm fell short of any standard of care when producing the bottle), she need only show that the bottle was defective when it reached her. She must, though, prove that the defectiveness of the bottle caused the injuries for which she seeks compensation.

For the strict liability standard, taking the US and the EU together, there are three potential ways in which product liability will consider a product to be defective. The three types of defect are set out in Table 21 above. Finally, defences may be available to the defendant firm even under strict liability. I focus on two of these here: a development risk defence, and a 'learned intermediary' defence (or, rather, doctrine). In Table 22 **Defences in Product Liability**I describe them in general terms rather than their specific legal form in the US/EU. The effect of successfully pleading a development risk defence is that the consumer cannot succeed in her claim. Because of the nature of the situation which it applies to, this means the consumer will also not succeed in any negligence claim because she will not be able to prove breach. The effect of successfully pleading the learned intermediary doctrine in either a negligence or strict liability claim is that the consumer will fail in her (strict or negligence) liability claim against the defendant firm but may still be able to succeed in a negligence claim against the professional intermediary if she can prove breach.

Table 22 Defences in Product Liability

Defence	Application	Defendant Burden of Proof
Development Risk Defence	To strict liability claims for design defects.[12]	… that the defect was truly latent: i.e. it could not be discovered by the defendant firm at the time the product was put on the market.
Learned Intermediary	To strict liability claims for warning defects and negligence claims for failure to warn.	… that the information which would have made the product reasonably safe was provided by the defendant firm to a professional (e.g. a doctor) who interacted with the consumer in their use of the product.

Having decided that the claimant has succeeded in her claim, the judge (in the EU) or the jury (in the US) must then decide how to quantify the claimant's harm and the sum which she will receive in compensation. In the US, but not in most of the EUMS, a jury may also make an

12 Confusingly, references can be found in both caselaw and academic literature to a 'development risk defence' in the case of negligence claims. Economists who analyse law might struggle to understand why I define 'development risk defence' here, as applicable only to strict liability claims. My use of 'development risk defence' here has a specified *legal* meaning. It can *only* apply to strict liability claims. For the defendant firm to plead, in a *negligence* claim, that to avoid the harm would have been too costly because it would have required research into the then-unknown or the then-unknowable is simply to plead, in legal terms, that they were not negligent. However, in a strict liability claim one cannot plead that one was not negligent because liability is strict (there is no need to establish a duty of care or breach of that duty in an act or omission falling short of a requisite standard of care) thus, here, a development risk defence is required if one wishes to absolve a firm of liability in circumstances where the defect was truly unknowable. To complicate matters further, the development risk defence in the PLD was later interpreted to apply not only where the defect was truly unknowable, but also where it was knowable but unknown. That, some have argued, turned the strict liability imposed by the PLD into mere negligence liability. See Howells, Geraint G., and Mark Mildred. "Is European products liability more protective than the restatement (third) of torts: products liability." Tenn. L. Rev. 65 (1997): 985.

additional award of punitive damages. In the US but also not in the EU[13] class-action suits are permitted. This is where an agent such as a law firm is permitted to bring a claim on behalf of multiple claimants against the same defendant/s in relation to the same product, and/or to negotiate a settlement between all claimants and the defendant/s. This procedure is commonly used in product liability suits against pharmaceutical firms in the US.

3.2.1 Pharmacovigilance

In the US, pharmacovigilance[14] is relatively tightly controlled by the FDA which commissions and pays for most post-licensing studies. Where it requires pharmaceutical firms to undertake their own studies post-licensing (so called 'Phase IV Trials') these are not well complied with by industry.[15] In the EU post-licensing studies are most often devolved to (and paid for by) industry. Where they are mandated by the EMA through Risk Management Plans ('RMPs') and Post Authorisation Safety Studies ('PASS') these are relatively well complied with compared to in the US. Within the FDA, there is overlap between the pharmacovigilance function and the licensing function of the agency. In particular, the NDC is responsible for making decisions regarding both pharmacovigilance and licensing, and the OSuE is merely a consultant to it. I call this here a 'unitary' system. At the EMA, there is a 'plural' system, where the CMPH and the PRAC both have executive authority and are required to consult each other. Below I consider the two jurisdictions' approach to pharmacovigilance in more detail.

Pharmacovigilance: United States[16]

In the US, pharmacovigilance[17] activities are primarily mandated by the FDA and/or undertaken by other public bodies. Wiktorowicz and others (2012) analysed[18] the prevalence of 'active' pharmacovigilance surveillance activities in the UK, France, the EU, the US, and

13 Although representative actions are now provided for under EU law, these are not the same as class actions.

14 I restrict my analysis of licensing and pharmacovigilance to the activities undertaken by the FDA and EMA respectively, with only passing reference to the national agencies (NAs) in the EUMS. For product liability there are bigger divergences between the two jurisdictions as a whole and a greater degree of intra EU and intra US heterogeneity than is the case for pharmacovigilance. The rules in the US are in place at the State, not the Federal, level although 'restatements' of those rules written by the American Law Institute (the 'ALI') which do not have prescriptive force in US common law (they are descriptive only) represent a good indication of the general position taken across all of the US States. Similarly, in the EU the rules governing evidence, causation and the quantification of damages awards are found at the EUMS level. Significant harmonization has taken place, however, in the PLD. Therefore, despite this intra-jurisdiction heterogeneity in product liability in both cases, I believe it is possible to make some statements about the two jurisdictions, based on the approaches taken in *most* US States/EUMS. Below, I refer to the State and EUMS level but make conclusions regarding the jurisdictions as a whole and describe the divergences at the between-jurisdiction level.

15 See e.g., Prayle, Andrew P., Matthew N. Hurley, and Alan R. Smyth. "Compliance with mandatory reporting of clinical trial results on ClinicalTrials. gov: cross sectional study." Bmj 344 (2012): d7373. See also below in detail

16 Pharmacovigilance cannot be considered in isolation without also considering the licensing system. The licensing system and the transatlantic divergences there are set out at length in Chapter Two.

17 Strong similarities exist between the US and the EU systems of pharmacovigilance because they share best practice and the two jurisdictions trade extensively with each other. See Dal Pan, Gerald J., and Peter R. Arlett. "The US Food and Drug Administration-European Medicines Agency collaboration in pharmacovigilance: common objectives and common challenges." Drug Safety 38, no. 1 (2015): 13-15.

18 Wiktorowicz, Mary, Joel Lexchin, and Kathy Moscou. "Pharmacovigilance in Europe and North America: divergent approaches." Social Science & Medicine 75, no. 1 (2012): 165-170.

Canada using information gathered from informant interviews and document review. They found *"greater reliance on industry funding and oversight of post-market research in Europe compared to an emphasis on publicly funded programs in North America"*. In their conceptual framework, the US adopted a 'managerial discretion' governance model. For example, the Food and Drug Administration Amendments Act 2007 ('FDAAA 2007')[19] permits the FDA to investigate safety issues independently. It is well resourced to do so, having wide access to databases and a wealth of research expertise within the agency. It works with a network of research centres which are entirely independent of industry.[20] With these resources it analyses pharmacovigilance data thoroughly (and on its own) in contrast to the EMA's approach in the EU, the Medicines and Healthcare Products Regulatory Agency (MHRA) approach in the UK and the Agence Nationale de Securité du Médicament et des Produits de Santé (ANSM) approach in France which – being less well resourced – *"focus on a smaller number of critical variables"* and require only summaries of randomized controlled trials from industry before making decisions. Overall, in the US post-licensing active surveillance is more common than in the EU and the EUMS surveyed by Wiktorowicz et al.[21] The authors describe the FDA's approach to post-market research as a 'regulator-directed' approach. FDA commissioned studies address specific questions set by the FDA whilst (for example) the MHRA in the UK *"supports researchers in tailoring their questions to the General Research Practice Database"* only.[22] The FDA also has a broader approach to post-licensing trials,[23] adopting more interventional trial designs rather than epidemiological approaches.[24]

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19 H.R.3580 - Food and Drug Administration Amendments Act of 2007 Public Law No: 110-85 (09/27/2007)

20 Wiktorowicz, Mary, Kathy Moscou, and Joel Lexchin. "Transnational pharmacogovernance: emergent patterns in the jazz of pharmaceutical policy convergence." *Globalization and health* 14, no. 1 (2018): 1-20.

21 The Affordable Care Act of 2010 funded up to 150 million USD per year for epidemiological safety and comparative effectiveness research up to 2019. By contrast the EMA funds urgent research for safety issues up to a maximum of 125,000 EUR per study and the EC Framework Programme funding for non-urgent studies up to 3-5 million EUR over five years. Wiktorowicz, Lexchin, and Moscou (2012).

22 In France, drug sponsors fund and oversee post-market studies. In the UK, industry similarly monitors its own products through patient registries and *"physicians, academics and professional organisations operate disease registries which include treatment and control groups that support epidemiological studies"* Wiktorowicz, Lexchin, and Moscou (2012).

23 In April 2011 FDA Guidance for Industry on Post-marketing Studies and Clinical Trials was issued giving the FDA authority also to "*require post-marketing studies or clinical trials at the time of approval or after approval if the FDA becomes aware of new safety information."* See https://www.fda.gov/media/131980/download

24 Higher levels of transparency and public participation are found in the US pharmacovigilance system than in the EU/EUMS systems. Wiktorowicz, Lexchin, and Moscou (2012). On transparency and public participation: as one might expect based upon what was learned in Chapters One and Two regarding licensing, the US has higher overall levels of both. Great efforts have been made in recent decades to ensure the independence of pharmacovigilance activities at the FDA from industry. The FDAAA 2007 imposed restrictions on 'advisory committee members' (expert advisory committees support pharmacovigilance by recommending the type of post-market study) to limit conflict of interests by ensuring no connections with the product sponsor. Whilst in the EU, the EMA negotiates post market studies with industry actors (product sponsors) and whilst these are now (since the 2010 Regulation) made public, the published summaries exclude study design details whereas the FDA's decision-making process is a lot more transparent. For example, the data made available to committees is public and the trial data of sponsors is subject to freedom of information legislation. The US system seeks to ensure important groups are represented in the pharmacovigilance process. The FDA's "Federal Partners Working Group" works with agencies such as Medicare and Medicaid. In the EMA's decision-making concerning post-market studies, national drug plans are not represented. See also Frau, Serena, Maria Font Pous, Maria Rosa Luppino, and Anita Conforti. "Risk Management Plans: are they a tool for improving drug safety?." European journal of clinical pharmacology 66, no. 8 (2010): 785-790.

Prior to the FDAAA 2007 there was widespread criticism of the FDA's *"lax oversight"*[25] of post-licensing studies.[26] Woloshin and others (2017) evaluated 614 post-licensing requirements and commitments imposed in 2009 and 2010 and found that after 5-6 years 20% of these studies had not been started, 25% were delayed or ongoing and only 54% had been completed.[27] A similar study by Prayle and others in 2012[28] examined mandatory reporting (by industry) of post-licensing trial results, and found that most trials subject to mandatory reporting did not report results within a year of completion. Goldman notes (in 2007)[29] *"compliance issues… have been conspicuously absent in the Congressional inquiries into drug safety"* supporting the argument made here that industry in the US does not cooperate well with the FDA in pharmacovigilance.[30]

In relation to the unitary nature of the system: the FDA incorporates both the NDC and the OSuE; however, the OSuE is a *"weak"*[31] adviser only to the NDC, which takes the final decisions relating to both licensing and pharmacovigilance. This effectively means that the same committee (the NDC) which makes the licensing decision is the only committee which can later reverse that decision. Unsurprisingly, therefore, the NDC has often been reluctant to take a decision to fully withdraw a license (withdraw a product from the market), and often opts instead to alter the label on the product after ADRs emerge. Carpenter notes, in 2010:[32] *"the very office of the FDA that approves new drugs—and which therefore has the least reputational incentives to revisit its past approval decisions—is also the office with legal authority over post-marketing…".* He goes on to point out that after a drug has been approved by the NDC, incentives for the sponsoring firm to comply with the FDA's wishes regarding post market studies are lost. He attributes this reality to the phenomenon of 'gatekeeping' which results from the FDA focusing closely on the market-access license decision to the detriment of pharmacovigilance, and he points to the lack of compliance with Phase IV trial requirements/commitments as evidence of this.

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25 Woloshin, Steven, Lisa M. Schwartz, Brian White, and Thomas J. Moore. "The fate of FDA postapproval studies." The New England journal of medicine 377, no. 12 (2017): 1114.

26 There was no legal power for the FDA to order post approval studies and it relied upon a system of 'commitments' with sponsoring firms (industry actors). The FDAAA gave the FDA additional power to require firms to complete these studies. It can *"establish both requirements and commitments"* to undertake post-licensing studies which are known as 'Phase IV Trials' - when it licenses, and empowers it to specify when certain milestones must be reached and to issue fines or rescind marketing approval for noncompliance.

27 Woloshin et al. (2017): 1114.

28 Prayle, Andrew P., Matthew N. Hurley, and Alan R. Smyth. "Compliance with mandatory reporting of clinical trial results on ClinicalTrials. gov: cross sectional study." Bmj 344 (2012): d7373.

29 Goldman, Stephen A. "US postmarketing pharmacovigilance compliance in the midst of regulatory uncertainty." Food & Drug LJ 62 (2007): 513.

30 Schanz, in 2007, notes the possibility of voluntary post-licensing studies undertaken by industry actors (distinct from those negotiated and required by the FDA) but he indicates that *"…though there is ample legal authority for postmarketing surveillance by the FDA, practical, budgetary, and legal barriers arguably prevent postmarketing efforts from fulfilling their optimal role…. If viewed as a business model, once a drug has been approved, pharmaceutical companies risk subsequent market withdrawal should postmarket studies uncover adverse data. Hence, their lack of enthusiastic completion of postmarket evaluations is understandable."* Schanz, Stephen J. "Pharmaceutical Postmarket Review: Fact or Fiction." Food & Drug LJ 62 (2007): 493.

31 Carpenter, Daniel. "Reputation, gatekeeping, and the politics of post-marketing drug regulation." *AMA Journal of Ethics* 8, no. 6 (2006): 403-406.

32 Ibid.

Pharmacovigilance: European Union[33]

Wiktorowicz[34] describes the EMA's approach to pharmacovigilance as 'corporatist'. She gives the example of the EMA's negotiations with industry actors in adopting RMP[35] and PASS and notes, *"while the EMA sets timetables for commitments to be met and can take action for non-compliance, in practice when delays arise the issue is raised with the company and the timetable can be changed".*[36] She further points out that pharmacovigilance activities in the EU have largely been ceded to industry over the past decade. Whilst it was once the case that the EMA could withhold market reauthorization where pharmacovigilance activities were not complied with, renewal has now become a *"routine administrative process"* and the EMA *"must now demonstrate a drug's harm to halt renewal".* In 2010 the EU passed a new Directive[37] and Regulation[38] which led to greater reliance upon industry to do the work of,[39] and to fund, pharmacovigilance. This ended requirements for public funding of ADR reporting and increased the use of RMPs.[40] Pharmacovigilance research capacity in the EU is largely provided by the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance, which receives no public funding. Pharmaceutical firms may commission this network to conduct required RMP studies. Direct public funding of post-market studies in the EU is limited relative to the US. Despite, or perhaps because of this (whilst far from

33 In the EU, the EMA operates in the centre of a decentralized system between the EMA and the NAs in the EUMS. For pharmacovigilance I look at the arrangements only on the EU level. Space precludes a full discussion at both the EU and the EUMS level for all of the divergences considered in this work, however, in Chapter Four: 'Sale Classification and Generic Substitution', I do go beyond the EU level and look at the EUMS level.

34 Wiktorowicz, Lexchin, and Moscou (2012).

35 RMP submission is not mandatory.

36 Here, too, compliance is not perfect. Giezen et al undertook a study in 2009 indicating that of 18 RMPs which identified 169 safety concerns, no full study protocols were submitted for the 47 PASS proposed to examine them. Giezen, Thijs J., Aukje K. Mantel-Teeuwisse, and Hubert GM Leufkens. "Pharmacovigilance of biopharmaceuticals." *Drug safety* 32, no. 10 (2009): 811-817.

37 Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use Text with EEA relevance.

38 REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products.

39 According to Borg, the 2010 Regulation and Directive had the aim (amongst other aims) of *"strengthening companies' pharmacovigilance systems, allowing companies to improve their systems constantly while reducing administrative burden."* In addition, it made pharmaceutical firms legally liable to carry out PASS studies. It also set up the PRAC at the EMA as well as making attempts to increase transparency by setting up an 'EU safety portal' aimed at better informing the public on all safety issues being discussed at the EU level. Borg, John-Joseph, George Aislaitner, Michal Pirozynski, and Stephen Mifsud. "Strengthening and rationalizing pharmacovigilance in the EU: where is Europe heading to?." Drug safety 34, no. 3 (2011): 187-197. The 2010 Directive and Regulation followed a 2006 Report which recommended adopting many of the features of the US system including the possibility to mandate post-market studies and to increase transparency. Bührlen, Bernhard, T. Reiß, C. Beckmann, U. M. Gassner, and C. H. Gleiter. Assessment of the European community system of pharmacovigilance. Fraunhofer-IRB-Verlag, 2006.

40 See Montanari-Vergallo, Gianluca. "Recent developments in EU and US pharmacovigilance legislation." Journal of Pharmacovigilance (2013).

perfect),[41] the PASS studies seem[42] to have been better complied with by industry in the EU than Phase IV trials in the US.[43]

They 2010 Regulation and Directive also require[44] that the CMPH will *have* to rely on the pharmacovigilance assessments made by the PRAC both pre, and post, licensing, whereas prior to the Regulation and Directive the CMPH did not have to rely on assessments made by the Pharmacovigilance Working Party (as it was then known). This is what I call a 'plural' approach to licensing and pharmacovigilance, in that executive authority at the CMPH is effectively shared with the PRAC in matters informed by pharmacovigilance studies.

3.2.2 Product Liability

In neither the US nor the EU does licensing of a pharmaceutical product insulate the firm from tort liability for the product. There are differences between the jurisdictions in the difficulty threshold for the claimant (from now on referred to as the 'consumer') to succeed in a claim, which in turn result from differences in the definition of defectiveness and the available defences. There are also differences in the procedural aspects of claims, the substantive aspects of damages awards and overall volumes of claims brought in both jurisdictions. These differences combine to mean that in the US there is a relatively high (i.e., difficult to achieve) threshold for the consumer to establish liability, but also relatively high expected damages for pharmaceutical firms. And, in the EU, there is a relatively low threshold for a consumer to succeed in a claim but also relatively low expected damages.

License Grant Does Not Insulate Firm in US or EU

There is no Federal pre-emption of State product liability law to be found in FDA regulatory approval of a pharmaceutical product. In *Wyeth v Levine*[45] the question was whether Federal law pre-empted State law in a personal injury action against a drug manufacturer for failing to include an appropriate warning label where the drug in question met the labelling requirements of the FDA. The US Supreme Court (SCOTUS) held that the FDA requirements

41 Goldacre, Ben, Nicholas J. DeVito, Carl Heneghan, Francis Irving, Seb Bacon, Jessica Fleminger, and Helen Curtis. "Compliance with requirement to report results on the EU Clinical Trials Register: cohort study and web resource." *bmj* 362 (2018): k3218

42 https://www.ema.europa.eu/en/news/over-1000-studies-now-recorded-eu-register-post-authorisation-studies

43 Almas, Mariana Ferreira Baltazar de Matos. "Lessons learned on the design and the conduct of European Post Authorisation Safety Studies (PASS): review of 3 years of PRAC oversight." PhD diss., 2017. Vora, Pareen, Esther Artime, Montse Soriano-Gabarró, Nawab Qizilbash, Vineet Singh, and Alex Asiimwe. "A review of studies evaluating the effectiveness of risk minimisation measures in Europe using the European Union electronic Register of Post-Authorization Studies." *Pharmacoepidemiology and drug safety* 27, no. 7 (2018): 695-706. See also Goldacre et al (2018)

44 Lis, Yvonne, Melissa H. Roberts, Shital Kamble, Jeff J. Guo, and Dennis W. Raisch. "Comparisons of Food and Drug Administration and European Medicines Agency risk management implementation for recent pharmaceutical approvals: report of the International Society for Pharmacoeconomics and outcomes research risk benefit management working group." *Value in Health* 15, no. 8 (2012): 1108-1118.

45 *Wyeth v Levine* 555 US 555 (2009).

established a floor, and not a ceiling, for State regulation and therefore States are free to create more strict requirements through regulation. What was not pre-empted here was liability for breach of the state regulations related to common law 'failure to warn' liability.[46] This leads to the situation where a pharmaceutical firm in the US is always subject to oversight by the FDA up to the licensing (market access) decision, but thereafter is subject to both product liability through the US State courts and pharmacovigilance oversight via the FDA.[47] Similarly, in the EU, approval of the product by the EMA or the EUMS national agencies (NAs) does not exclude liability for the product in tort either at the EUMS level or under the PLD.[48] The lack of pre-emption in both cases is noted here during the discussion of the transatlantic divergences, but it become most significant in Section 3.3.6 below, where the system divergences are set out.

Product Liability: United States

The US common law introduced strict liability for defective products (generally) in the 1950s and 1960s. At its introduction – as reflected in the American Law Institute ('ALI') Second Restatement of Torts - strict liability did not apply to pharmaceutical products[49] which were understood to be 'unavoidably unsafe'.[50] However, in the years following the Second Restatement of Torts some courts began to challenge this understanding.[51] Subsection c) of section 6 of the *Third* Restatement of Torts made clear[52] in 1998 that a pharmaceutical product (prescription drug or medical device) was not reasonably safe due to defective design only if the *"foreseeable"* benefit-risk profile of the product was such that a "*reasonable health-care provider.."* who was aware of the benefit-risk profile *"would not prescribe the drug or medical device for any class of patients"*.[53] This provides near immunity to pharmaceutical firms from strict liability claims for design defects generally, even before the

46 *Merck Sharp and Dohme Corp. v Albrecht,* decided in 2019, upheld Wyeth v Levine which contains an exception for where the FDA is shown to have considered and then rejected a more stringent warning

47 See Sharkey, Catherine M. "Federalism in Action: FDA Regulation Preemption in Pharmaceutical Cases in State versus Federal Courts." JL & Pol'y 15 (2007): 1013.

48 There is, however, a regulatory compliance defence contained within the PLD: Article 7 *"The producer shall not be liable as a result of this Directive if he proves:… (d) that the defect is due to compliance of the product with mandatory regulations issued by the public authorities…"*

49 See Lindenfeld, Eric, and Jasper L. Tran. "Prescription drugs and design defect liability: Blanket immunity approach to the increased costs and unavailability of prescription medication." Drake L. Rev. 64 (2016): 111.

50 Comment K of the Second Restatement of Torts. See Davis, Mary J. "Time for a Fresh Look at Strict Liability for Pharmaceuticals." Cornell JL & Pub. Pol'y 28 (2018): 399. *See also* RESTATEMENT (SECOND) OF TORTS § 402A (1965). Section 402A provides: *"(1) One who sells any product in a defective condition unreasonably dangerous to the user or consumer or to his property is subject to liability for physical harm thereby caused to the ultimate user or consumer, or to his property, if (a) the seller is engaged in the business of selling such a product, and (b) it is expected to and does reach the user or consumer without substantial change in the condition in which it is sold. (2) The rule stated in Subsection (1) applies although (a) the seller has exercised all possible care in the preparation and sale of his product, and (b) the user or consumer has not bought the product from or entered into any contractual relation with the seller."* See Schwartz, Victor E. "Unavoidably Unsafe Products: Clarifying the Meaning and Policy Behind Comment K." *Wash. & Lee L. Rev.* 42 (1985): 1139. Comment K exempts manufacturers of *"unavoidably unsafe products"* from strict liability for defective design. Further, Comment K has been interpreted to preclude strict liability for failure to warn if the danger was not known or was not scientifically knowable at the time the product was distributed.

51 Lindenfeld and Tran (2016).

52 Bernstein, Anita. "(Almost) No Bad Drugs: Near-Total Products Liability Immunity for Pharmaceuticals Explained." *Wash. & Lee L. Rev.* 77 (2020): 3.

53 Note that this applies only to 'prescription only' products.

latency of the defect is considered. This is because if such a defect were known at the time of licensing, the product would certainly never be granted a license. If it were unknown (latent), but knowable, then the use of the word *"foreseeable"* also implies a development risk defence. This only leaves the case where the design defect was foreseeable (knowable) but not foreseen (known), in which case the court – according to Howells and Mildred - will inevitably ask itself whether reasonable steps were taken to discover the design defect.[54] In that case the strict liability test becomes a negligence test which is a higher threshold for the consumer to establish liability. Where the defect was unforeseen (unknown) and unforeseeable (unknowable) there cannot be strict liability upon the firm for the product. It is true to say therefore, that according to the Third Restatement, US common law provides blanket immunity to pharmaceutical products from *strict* liability for all design defects, and certainly for defects which were unknown and unknowable at the time the product was placed on the market.

For warning defects, subsection d) of section 6 of the Third Restatement reflects the learned intermediary defence to strict liability claims based upon warning defects: "*(d) A prescription drug or medical device is not reasonably safe due to inadequate instructions or warnings if reasonable instructions or warnings regarding foreseeable risks of harm are not provided to: (1) prescribing and other health-care providers who are in a position to reduce the risks of harm in accordance with the instructions or warnings; or (2) the patient when the manufacturer knows or has reason to know that health-care providers will not be in a position to reduce the risks of harm in accordance with the instructions or warnings."* In recent decades, the learned intermediary defence (doctrine) has been placed in some doubt, particularly where a prescription product has been the subject of DTCA.[55] In 1999 the Supreme Court of New Jersey in *Perez v Wyeth*[56] created an exception for these products. Then, in 2007 in *State ex rel. Johnson & Johnson Corp. v. Karl*[57] the Supreme Court of West Virginia completely abandoned the learned intermediary doctrine for the common law of West Virginia. After *Karl* came *Rimbert v Eli Lilly and Company*[58] in 2008 in the US (Federal) District Court of New Mexico[59] which rejected the whole of the learned intermediary doctrine.[60]

54 See Howells, Geraint G., and Mark Mildred. "Is European products liability more protective than the restatement (third) of torts: products liability." Tenn. L. Rev. 65 (1997): 985.

55 See Green, Ronald M. "Direct-to-consumer advertising and pharmaceutical ethics: The case of Vioxx." Hofstra L. Rev. 35 (2006): 749. Mello, Michelle M., Meredith Rosenthal, and Peter J. Neumann. "Direct-to-consumer advertising and shared liability for pharmaceutical manufacturers." Jama 289, no. 4 (2003): 477-481.

56 *Perez v. Wyeth Labs., Inc. - 313 N.J. Super. 646, 713 A. 2d 588 (Super. Ct. 1997)*

57 *State ex rel. Johnson & Johnson Corp. v. Karl - 220 W. Va. 463, 647 S.E.2d 899 (2007)*

58 *RIMBERT v. ELI LILLY COMPANY*, No. CIV 06-0874 JB/LFG (D.N.M. Aug. 18, 2008)

59 Applying New Mexico Law, for the first time a Federal court rejecting the learned intermediary doctrine.

60 The effect of *Rimbert* and *Karl* has been an increase in litigation against pharmaceutical companies in the US based on negligent failure to warn and strict liability for warning defects, particularly where the product in question was a prescription product advertised direct to consumers. However, as to the learned intermediary doctrine in the case of DTCA prescription products, the picture is more mixed. The ALI already stated that it expected caselaw developments on the issue following the Third Restatement. According to the court in *Karl* (in 2007) only 21 states out of 50 had expressly adopted the learned intermediary doctrine anyway, plus North Carolina which has enshrined it in statute. Six states have adopted it in the case of non-pharmaceutical products or have looked on the doctrine favourably, and the remaining 22 states have not adopted it.

I turn now from liability to expected damages, which requires consideration of aspects of procedural law, and overall volume of litigation. Punitive damages[61] – in addition to compensatory damages – are awarded regularly in US personal injury litigation.[62] According to LexMachina[63] the number of cases filed in US Federal District Courts has been rising since 2015. There were 56,041 cases filed in 2019 and over the previous 5 years over 1.2bn USD was paid out in punitive damages. There was significant growth in punitive damages awards made between 1985 and 1990 which was driven partly by product liability cases. Generally, it is entirely up to the jury what kind of award they can make, although this may be overturned by a judge on appeal if considered to be unjust. According to Lott and Karpoff, between 1985 and 1996 there were 374 products liability cases in which punitive damages awards were sought: the highest out of any category which they surveyed.[64] Mean punitive damages in these cases was 6,184,000 USD which is almost twice the mean amount in compensatory damages of 3,734,000. The maximum punitive damages award was 101,000,000 USD. Interestingly, the median punitive damages award for these product liability cases was only 694,000 USD indicating a very wide range for punitive damages awards by juries, which underscores the unpredictability of these awards. For class action suits, which are permitted much more widely in the US than in the EU/EUMS - and which are heavily skewed towards medical and pharmaceutical company defendants - these normally result in settlement, so there are no punitive damages awards. However, the amount paid out by the settling firms is very considerable due to the number of claimants involved. This was circa 744,000,000 USD between 2015 and 2019. Taken together, jury determination of punitive damages plus the possibility of class action suits and the overall high volume of product liability litigation in the US, result in high expected damages for pharmaceutical firms.

Product Liability: European Union

In each of the EUMS there is a system of liability which operates through the courts, and this has been the case for many years. It is important to note that *"the* [PLD] *does not cover or harmonise all aspects of product liability. There is room for different national approaches, for example on systems to settle claims for damages, or on how to bring proof of damage. These are left to Member States to decide. Member State may also introduce or maintain other national instruments for the liability of producers based on fault."* 65 The PLD was introduced

61 Kuhlik, Bruce N., and Richard F. Kingham. "The Adverse Effects of Standardless Punitive Damage Awards on Pharmaceutical Development and Availability." *Food, Drug, Cosmetic Law Journal* 45, no. 6 (1990): 693-708. Accessed March 9, 2021. http://www.jstor.org/stable/26659094.

62 Lott, John, and Jonathan M. Karpoff. "Punitive Damages: Their Determinants, Effects on Firm Value, and the Impact of Supreme Court and Congressional Attempts to Limit Awards." (1998). Note that the grant of a license by the FDA does not pre-empt awards of punitive damages. See https://fedsoc.org/commentary/publications/preemption-of-punitive-damages-in-prescription-drug-litigation. See also Levy, Elissa. "The Health Act's FDA Defense to Punitive Damages: A Gift to Drug Makers or to the Public." *Fordham L. Rev.* 74 (2005): 2425.

63 https://www.globallegalpost.com/big-stories/product-liability-case-filings-in-us-federal-courts-reach-eight-year-high-49884800/

64 The House of Representatives in the US has repeatedly sought to introduce legislation which would pre-empt punitive damages awards in State courts in cases where the product in question was granted a license by the FDA. This legislation has, however, regularly stalled in the Senate, and is not yet introduced.

65 REPORT FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL AND THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE on the Application of the Council Directive on the approximation of the laws, regulations, and administrative provisions of the Member States concerning liability for defective products (85/374/EEC) COM/2018/246

for the twin (stated) reasons of consumer protection[66] and product market regulatory harmonisation amongst the EUMS.[67] It did not have direct effect, and thus required transposition into the national laws of the EUMS. This happened (for example) in 1991 in Belgium,[68] 1989 in Denmark,[69] 1998 in France,[70] 1989 in Germany,[71] 1991 in Ireland,[72] 1990 in the Netherlands[73] and 1987 in the UK.[74]

Under EU law the PLD has to be implemented correctly by the EUMS and the Commission can bring an EUMS before the Court of Justice of the European Union (CJEU) in cases where the Directive has been implemented incorrectly.[75] The PLD was lauded at the time of its introduction for placing strict liability on producers. This is achieved through Article 6 of the PLD: "*A product is defective when it does not provide the safety which a person is entitled to expect, taking all circumstances into account, including: (a) the presentation of the product; (b) the use to which it could reasonably be expected that the product would be put;* [and] *(c) the time when the product was put into circulation."* Design defects are covered in the general part of the test. The EU equivalent of strict liability for defects of warning are included in Article 6 (1) a) and b). As to the meaning of 'consumer expectations' in the case of design defects, courts and commentators have held that this is a risk-utility (risk-benefit) test: the same as is applied by the US common law courts to determine strict liability for design defects in products generally. Not, though, for *pharmaceutical* products: where the specific and much higher threshold test is set out in the Third Restatement).[76]

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66 In 1975 the European Council adopted a resolution for a preliminary programme on consumer protection and information technology. See also the Council of Europe's Strasbourg Convention (European Convention on Products Liability in regard to Personal Injury and Death) in 1977 which had a consumer protection impetus https://www.coe.int/en/web/conventions/full-list/-/conventions/treaty/091 *"The aim of this Convention is to assist the development of case law in the majority of member States, which are extending liability of producers prompted by a desire to protect consumers taking into account the new production techniques and marketing and sales methods, by giving priority to compensation for personal injury and death in introducing special rules on the liability of producers at European level.".*

67 In the years running up to 1985 the European Council decided that it was desirable to approximate the laws of the EUMS concerning the liability of the producer for damage caused by the defectiveness of products, and that this was *"necessary because the existing divergences may distort competition and affect the movement of goods within the common market and entail a differing degree of protection of the consumer against the damage caused by a defective product to his health or property".* Recitals to Council Directive 85/374/EEC of 25 July 1985 on the approximation of the laws, regulations and administrative provisions of the Member States concerning liability for defective products

68 Loi du 25/02/1991 relative à la responsabilité du fait des produits défectueux - Wet van 25/02/1991 betreffende de aansprakelijkheid voor produkten met gebreken.

69 Lov nr. 371 af 07/06/1989 om produktansvar. Justitsmin.L.A. 1988-46002-11.

70 Act 98-389, Arts 1386-1 to 1386-18 of the Civil Code

71*Produkthaftungsgesetz*

72 Liability for Defective Products Act 1991

73 Wet van 13 September 1990 houdende aanpassing van het Burgerlijk Wetboek aan de richtlijn van de Raad van de Europese Gemeenschappen inzake de aansprakelijkheid voor produkten met gebreken

74 Consumer Protection Act 1987

75 This happened for example in the case of the UK's implementation of the Directive's Article 7(e) development risk defence (see below) in S.4(1)(e) of the Consumer Protection Act 1987 in Commission v UK EU:C:1997:255; [1997] ECR I-2649.

76 Howells and Mildred (1997). The question asked is whether the product was so unsafe that it led to a reduction in overall social welfare by being placed on the market. It should be noted that there is a 'regulatory compliance' defence in the PLD under Article 7 (d): Article 7 *"The producer shall not be liable as a result of this Directive if he*

There is and was the possibility of a development risk defence being included by the EUMS when transposing the Directive into national law. That possibility is found in Article 7 e) of the PLD: "*The producer shall not be liable as a result of this Directive if he proves:… (e) that the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of the defect to be discovered…"* EUMS were permitted to exclude this defence by way of derogation from the PLD under Article 15.[77] As of 2018[78] Finland, Luxembourg and France have applied it in the case of pharmaceutical products, meaning they enable liability to be established where the design defect in a product was unknown and unknowable.[79] These EUMS comprise circa 73.5m people out of a total EU population of 448m[80] and the remaining EUMS retain the possibility to implement the development risk defence in their product liability regimes for pharmaceutical products. The PLD does not permit anything like the learned intermediary doctrine, i.e., the producer cannot absolve itself from liability based on an omission or act by a doctor under Article 8 1).[81]

On expected damages, under Article 16[82] of the PLD EUMS may provide that the total liability of a producer for any given product with any given defect is capped at 70m European Currency Units,[83] which many EUMS have adopted. Jury trials and thus jury determination of damage awards in the EU are very uncommon. In addition, class action suits are not widely permitted in the EU/EUMS.[84] Overall, the volume of litigation undertaken by European consumers under

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proves… (d) that the defect is due to compliance of the product with mandatory regulations issued by the public authorities" This applies in cases where the product is defective because of regulatory compliance. See Schebesta, Hanna. "Risk Regulation Through Liability Allocation: Transnational Product Liability and the Role of Certification." Air and Space Law 42, no. 2 (2017): 107-136.

77 Article 15: *"1. Each Member State may:…(b) by way of derogation from Article 7 (e), maintain or, subject to the procedure set out in paragraph 2 of this Article, provide in this legislation that the producer shall be liable even if he proves that the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of a defect to be discovered."*

78 (85/374/EEC) COM/2018/246 final *"Five Member States adopted the 'development risk derogation' set out in Article 15(1)(b) of the Directive, whereby a producer is also liable if the state of scientific and technical knowledge when the product entered circulation was not such that the defect could be discovered. Two Member States apply this to all sectors, while two notably exclude pharmaceutical products… The Hungarian Civil Code states that the producer of any pharmaceutical product is liable even if the state of scientific and technical knowledge at the time when the product was put into circulation was not such as to enable detection of the existence of the defect. Along the same line, the Spanish Royal Legislative Decree 1/2007 of 16 November 2007 states that producers of medicinal products, foods or foodstuffs intended for human consumption cannot invoke the exemption provided under Article 7(e) of the Directive."*

79 Spain and Hungary have both adopted the derogation, but have exempted pharmaceuticals from it, such that pharmaceutical firms can avail themselves of the Article 7 (e) defence. These and all other EUMS apart from Finland, France, and Luxembourg – in their domestic law – allow pharmaceutical firms to avoid liability if the latent defect was truly undiscoverable at the time the product was put into circulation.

80 Following the UK's departure

81 Article 8: *"1. Without prejudice to the provisions of national law concerning the right of contribution or recourse, the liability of the producer shall not be reduced when the damage is caused both by a defect in product and by the act or omission of a third party."*

82 Article 16 *"1. Any Member State may provide that a producer's total liability for damage resulting from a death or personal injury and caused by identical items with the same defect shall be limited to an amount which may not be less than 70 million ECU."*

83 A standardised unit encompassing all EU currencies.

84 For more on the Representative Actions Directive see: Visscher, L., and M. Faure. "A Law and Economics Perspective on the EU Directive on Representative Actions." Journal of Consumer Policy (2021): 1-28

the PLD is significantly lower than the volume of litigation undertaken in US State Courts for product liability claims. The fifth report on the application of the PLD[85] states that *"most product liability claims between 2000 and 2016 were actually settled out of Court. 46 % of cases were settled in direct negotiation, 32 % in Court, 15 % through alternative dispute settlement mechanisms, and 7 % were resolved through other means such as through the insurer of the responsible party. The external study commissioned for the evaluation identified 798 claims based on product liability rules from 2000 to 2016… the products most concerned are raw materials (21.2 % of cases), pharmaceuticals (16.1 %), vehicles (15.2 %) and machinery (12.4 %)."* In the words of Cavliere (2004), in the EU, *"the implementation of this Directive has not led to an expansion of product liability cases"* and *"neither the product nor the insurance market has been dislocated as in the United States"*. He attributes this to the compensatory mechanism of the welfare state, and the reluctance of public authorities to bring claims against private entities under the PLD.[86] These factors all combine to lead to low expected damages for pharmaceutical firms.

3.2.3 Summary

To summarise, the transatlantic divergence across both aspects of regulation are set out again in Table 23 below.

Table 23 Transatlantic Divergence Pharmacovigilance and Product Liability

	TRANSATLANTIC DIVERGENCE	
	Pharmacovigilance	**Product Liability**
US	FDA led and funded 'Unitary' system with licensing Relatively poor industry compliance	Relatively high liability threshold No liability for unknown and unknowable design defects Relatively high expected damages
EU	EMA collaborative with industry 'Plural' system with licensing Relatively good industry compliance	Relatively low liability threshold Potential liability for unknown and unknowable design defects Relatively low expected damages

Continuing in Section 3.3, I now set out the system divergences. This first requires me to consider the regulation of pharmacovigilance and product liability, and their relationship with licensing, using the public interest theory of regulatio

85 Ibid.

86 Cavaliere, A. Product Liability in the European Union: Compensation and Deterrence Issues. *Eur J Law Econ* 18, 299–318 (2004). https://doi.org/10.1007/s10657-004-4275-0

3.3 Public Interest Approach

In this section I discuss licensing together with pharmacovigilance and product liability, because the three are closely related.[1] Public interest theory stipulates that regulation is enacted to address underlying market failures. In the case of all three this is the same market failure, which results from the same underlying information problem.

3.3.1 Underlying Market Failure and Information Problem

The core market failure addressed by both pharmacovigilance and product liability is overconsumption of products which cause externalities in the form of ADRs,[2] the costs of which may be borne by society, decreasing overall social welfare.[3] Lying underneath this market failure is an information failure: pharmaceutical products pose uncertain benefits for, and uncertain costs (risks) to, human health.[4] The benefit-risk profile of a pharmaceutical product is never known in full due to the possibility of unknown (latent) defects. Some risks of the product may only become known – thus changing the benefit-risk profile of the product – once the product has been used for a long time by many people. This information problem makes it impossible to ensure that all products on the market are perfectly 'safe'.[5] The problem is partially mitigated through licensing,[6] however, no amount of (pre-licensing) clinical trials data can guarantee a positive benefit-risk profile for every possible case of

1 This section therefore builds upon what was written in Chapter Two regarding licensing. I speak in this part about three regulatory 'techniques', fully aware that 'technique' is an unconventional term to use, however it is broad enough to logically refer to all three things separately and together.

2 The possibility that 'unsafe' products will be consumed is not the only way in which social welfare may be reduced as a result of a suboptimal regulatory system. It is at least equally problematic that 'safe' products will not become available on the market: either because market access is denied or delayed through an excess of caution by agencies charged with market access licensing, or because firms are deterred from innovating due to the high costs of developing new products. Society may not have the time for clinical trials to be completed prior to market access being granted to a safe product. Often, the product is needed as a matter of urgency. The social benefits forgone by delaying or denying market access to safe products may far outweigh the social costs of ADRs caused by unsafe products. These social benefits may include not only benefits to human health, but also collateral benefits which are instated where human health is secured. The COVID-19 pandemic is another sharp reminder of this, and one which may prompt changes to regulatory systems worldwide. Lockdowns were put in place to secure human health, yet the lockdowns were predicted to cost the global economy around $4,000,000,000,000 USD. *Estimate as of 4 April 2020 https://time.com/5814933/coronavirus-pandemic-cost-4-trillion/...* The potential for a new vaccine to harm human health had to be weighed against the economic cost of not making the vaccine available.

3 This Section adopts a public interest approach and thus it is assumed that the agency wishes to maximise overall social welfare.

4 By costs, I mean the percentage risk that an adverse health outcome will result, multiplied by the monetized value of that outcome. I call this the benefit-risk profile here.

5 And it also makes perfect labelling impossible.

6 Because a license for market access would only be granted based on clinical trials data, collected pre-licensing, which showed the product to be safe and effective.

consumption of the product.[7] An agency must therefore make a choice based on the imperfect information which it has at the licensing stage. Unless the information problem is solved entirely, it is always possible that products will become available on the market which decrease overall social welfare.[8] It is also possible that products which would have increased social welfare are denied access to the market.

3.3.2 Licensing

Through a requirement of prior approval for market access, products are prevented from reaching the market if they would cause externalities which might lead to a reduction in overall social welfare.[9] Thus a regulatory agency is given the task of collecting and/or aggregating a public good:[10] information on the safety and efficacy of new pharmaceutical products.[11] The agency also has the second role of analysing the data, in that it weighs the benefits and risks of the product, to determine whether the product is safe and effective. The public interest justification for this role to lie with a regulatory agency is that the quality of the analysis will be best when the greatest possible amount of data is available to analyse. Also, that analysis should be undertaken by an actor with specific skill, expertise, and experience in analysing it, because this raises the likelihood that the information will be analysed accurately. The third role of the agency in licensing is that of certification. The grant of the license communicates information to the whole of the market in a simple form, certifying that the product is safe and effective by the standards of the expert agency. This certification, too, is a public good.[12]

3.3.3 Pharmacovigilance

Pharmacovigilance is the monitoring of products to 1) gather information about them and 2) manage risk accordingly. Narrow pharmacovigilance is a technical exercise focused on the first part of that definition. Broad pharmacovigilance – which I return to below when setting out the SPI system - encompasses both parts of the definition. The information gathering

7 Or rather, the costs to the sponsoring firm of proving that data would be so high as to deter any pharmaceutical innovation. On top of this lies the problem that data collected in the setting of pre-market-access clinical trials is not a perfect (or even a very good) indicator of the effects of the product when used in clinical practice.

8 Because they possess latent defects which impose externalities.

9 This can happen because the product has a defect which means it harms everyone who uses it. Or, it may be safe for most people if used correctly and thus in the licensing process information will be mandated for provision to doctors or direct to consumers enabling the latter to use it safely. That latter function can also be achieved through use of the prescription system which requires a doctor to match a specific class of consumers to the product before consumers are permitted to purchase and consume it.

10 This information has public good qualities by reason of it having value to all and by being non-rival and non-excludable.

11 In the form of pre-licensing market clinical trials data.

12 Being non-excludable and non-rival, and thus public interest theory provides a justification to place this task in the hands of a regulatory agency.

element of broad pharmacovigilance is justified by the information problem described above. The aim of broad pharmacovigilance is to maximise the sum of the costs and benefits from pharmaceutical products. This includes minimising externalities whilst ensuring that safe products are made available on the market.[13] Broad pharmacovigilance is based upon five pillars, all overseen by the agency. Below, the five pillars are listed, and a brief description is given of what is involved for each pillar.

1. Information collection and aggregation.
2. Information analysis.
3. Planning for risk management.
4. Risk management.
5. Risk communication.

Information collection and aggregation implies the establishment of a database recording data related to ADRs. To that database, interested actors add data from pharmacovigilance studies, which include those studies taking place both before and after the grant of a license for market access. Information analysis focuses on analysis of the aggregated data. In the earlier stages this informs the risk management plan for the pharmaceutical product. In the latter stages it focuses on applying cost benefit analysis principles to potential decisions to communicate risks to consumers and doctors, and more severe regulatory decisions such as market withdrawal. Planning for risk management is most relevant in the earliest stages where the small amount of data is used by the agency as a basis to direct further research and place restrictions, if necessary, upon human testing. As the product progresses through the process, the risk management plan is repeatedly updated based on the latest data, at the discretion of the agency. Risk management includes the agency having the sole authority to permit trials in humans, and wider market access, as well as to mandate further trials from the sponsoring firm either before or after the grant of a license. It also includes the power to mandate the wording of the product label, to permit marketing of the product for additional or fewer indications, and to exercise control over claims that may be made about the product in detailing or direct to consumer advertising. The legal power to require withdrawal of the drug from the market also exists. The aim of risk communication is to provide fully accurate and up to date information on pharmaceutical product risks, as quickly as possible, to doctors and consumers who would then be enabled to make decisions themselves.[14]

13 Assuming that a cost benefit analysis of the use of the product is positive in at least some circumstances, then in practice this means that a product is permitted to remain on the market only for use in certain indications (health conditions), in certain classes of patient and/or subject to certain restrictions on its use, spelled out on the product label and/or communicated directly to doctors and consumers. Where latent defects in the product emerge – often many years after release to the market – pharmacovigilance would be concerned to communicate this information as widely as possible.

14 See Segal, Eleanor S., Cecile Valette, Laurence Oster, Luc Bouley, Catarina Edfjall, Peter Herrmann, Massimo Raineri, Mary Kempff, Saundra Beacham, and Cinda van Lierop. "Risk management strategies in the postmarketing

3.3.4 Product Liability

Product liability is targeted at pharmaceutical firms, seeking to deter the bringing of unsafe products to the market. Deterrence[15] is ensured by the possibility of compensatory awards. Some argue that compensation, not deterrence is the primary goal of product liability law.[16] Compensation[17] and deterrence have related public interest justifications. However, it is already doubtful whether deterrence can be effective in the case of pharmaceutical products with unknown and unknowable defects, and the extent to which compensation may be justified on public interest grounds depends upon the availability of social insurance and private insurability against liability awards.[18]

Standard of Liability

Landes and Posner[19] have described how *strict* liability for products (generally) is socially efficient. In a Coasean world of no transaction costs and perfect information, where the only consumers of products are those who purchase them, then the producer and consumer would negotiate a price which reflected the true cost of the product including the risks of physical harm consequent upon use of the product. Under these conditions it would not matter upon whom 'liability' was placed nor under what circumstances. The optimal level of the product would always be produced and consumed.[20]

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period." Drug safety 28, no. 11 (2005): 971-980. See also Hartford, Craig G., Kasia S. Petchel, Hani Mickail, Susana Perez-Gutthann, Mary McHale, John M. Grana, and Paula Marquez. "Pharmacovigilance during the pre-approval phases." Drug safety 29, no. 8 (2006): 657-673.

15 There are a two widely pleaded justifications for tort liability (generally) which will be dwelled upon here. The first is compensation and the second is deterrence. The second is focused upon safety, i.e., ensuring that firms produce products which are optimally safe and that consumers consume an optimal amount of those products such that accidents caused by products do not lead to a reduction in overall social welfare. Wedded to that goal is the possibility of spreading the risks of product accidents through insurance, and thus the insurability of risks. The first goal, compensation, is concerned with providing for the injured party. This may have a corrective justice rationale: i.e., making the victim whole again. But it may also have a distributive justice rationale if one could successfully argue that it is cheaper and more equitable for the producer of the product which injured an individual, to provide financially for the care and maintenance of that injured individual instead of the state or his/her savings providing for these things financially.

16 See Chapter Six for more information and explanation.

17 The compensatory element of product liability may also be justified on related but separate public interest grounds, in that injuries caused by pharmaceutical products may leave the victim in a position where they become a burden on family or friend who must support them. The injuries thus reduce the productivity, to society, of both the victim and those close to them. Compensatory awards can avoid this, and because the producer of pharmaceutical products can pass on the costs of liability (or insurance) through the price of the product, the losses can be spread effectively. This justification becomes particularly important where there is no or only a weak system of social insurance in place.

18 Finally, whilst the administrative costs of product liability are likely to be low relative to market access licensing and pharmacovigilance, transaction costs are likely to be very high.

19 Landes, William M., and Richard A. Posner. "A positive economic analysis of products liability." *The Journal of Legal Studies* 14, no. 3 (1985): 535-567.

20 In this world, however, there would be distributional outcomes which might be rejected in the real world. Producers, for example, may reap most of the gains from the unsafe products whilst consumers bear the losses.

The Coasean world assumes the ability between consumer and producer to bargain over price. This is not the case in the real world. Moreover, it assumes perfect and symmetrical information, whereby the consumer will have as much knowledge of the safety risks of the product as will the consumer. Finally, it assumes that the consumer (purchaser) is the end user. Again, none of these are really the case. Take a product such as an electric heater. The producer, having developed the product, has much better information than the consumer regarding its risks. If the consumer is unaware of the risks and sees the price of the product, he or she will fail to add an extra sum to that price to account for his or her expected harm from the product. As such, too much of the product will be bought and sold, too many accidents will happen, and social welfare will be reduced not increased by the availability of the product. Therein lies the initial justification for placing strict liability in tort upon the producer. By doing so, the producer is pushed to add the expected costs of accidents to the price of the product. Moreover, because the producer is assumed to operate in a competitive marketplace, price competition incentivises the producer to produce the safest version of the product, as the safest version will be the cheapest version. Then, because the cost of accidents is reflected in the price, an optimal quantity of the product is purchased and consumed by consumers. Thus, social welfare is enhanced and not reduced.

Applying this to pharmaceutical products, clearly public interest theory justifies strict liability in the case of warning defects, where the risks of the product are known. In the case of unknown and unknowable design defects, however, strict liability will not mean that the risks of the product are already reflected in the purchase price because the risk is not known by the producer, and un-insurability and a stifling of innovation may result from the imposition of strict liability.

Defences

The final observation above means that in the situation where the defect was unknown and unknowable, the public interest requires that there is a 'development risk defence'. In the case where the defect was unknown but knowable then there should be liability whereby the firm is incentivised to discover the defect before marketing the product. However, the relevant standard would be negligence, not strict liability.[21] On the learned intermediary doctrine/defence, the role of the doctor is crucial in solving the underlying information problem. Some products will be safe only for a relatively small number of consumers with a relatively small range of conditions and with medical histories which meet certain criteria. In all other circumstances the product may be unsafe. Doctor matching of consumer to product is necessary in these circumstances to avoid negative externalities. The information involved is too complex for non-expert consumers to receive it direct from a pharmaceutical firm. Hence, certain products are placed in a prescription only (PO) sale classification category and – instead of information being provided directly to the consumer on the product label or

21 Another approach which has been suggested is that of 'prospective overruling'. In this case, it is suggested, a court could enunciate legal principles regarding the relevant standard. For example, a latent defect with a drug may be discovered and a court may hear a case. It may decide that the firm is prima facie strictly liable for defective design but, because the defect was literally undiscoverable at the time the product entered the market, the firm will not be held liable retrospectively. In this case, the new standard having been set in the case, this standard would apply henceforth *See* Faure, Michael G. "Economic Analysis of Product Liability." *Faure, MG,"Economic Analysis of Product Liability", in Machnikowski, P.(ed.), European Product Liability. An Analysis of the State of the Art in the Era of New Technologies, Antwerp, Intersentia* (2016): 619-665.

insert – the product can only be consumed under the guidance and supervision of a doctor. Thus, if information and warnings have been provided to the doctor and the product has been placed in the prescription-only category, externalities should be avoided so long as the doctor acts competently based on that information. This is the justification for the learned intermediary defence in strict liability design defect cases, and negligent failure to warn cases, against pharmaceutical firms.[22]

Damages

The public interest rationales for *punitive* damages are potentially threefold:[23] 1) to deter behaviour in cases of intentional concealment of wrongdoing, 2) to overcome the rational apathy problem, or 3) to force swift remedial action on the part of a producer.[24] Clearly, punitive damages are warranted in case 1) because strong deterrence is required to offset the low probability of detection due to concealment. In relation to 2), punitive damages can act as an incentive to claimants to make claims where it seems that the costs of bringing the claim outstrip the value of compensatory damages.[25] Alternatively, punitive damages may ensure that a sufficient financial burden is imposed on the producer despite not all claimants being able to successfully bring and succeed in their claims, in order to set incentives correctly. In relation to 3) the logic is that where a latent defect in a pharmaceutical product has become apparent, but the regulatory agency has not yet decided to withdraw that product from the market or, having made that decision already, lacks the resources to enforce it: then, in this case, the threat of punitive damages will incentivize the firm to take the product off the market unilaterally, and thus avoid crushing liability awards. Punitive damages do, therefore, find a solid justification in public interest theory in the cases outlined above. However, where punitive damages are determined by juries, they are unpredictable. The costs associated with the uncertainty may lead to difficulties obtaining third-party liability insurance.

Procedure

Class action suits may assist in overcoming the rational apathy problem and reduce the transaction costs associated with multiple claims regarding the same product. Public interest theory justifies class action litigation.

Insurance

The ability of the tort system to spread losses so that they are not crippling to any individual or firm is premised on the insurability of the risk in question. Certain risks, including the risks associated with developing innovative pharmaceutical products, are difficult to insure

22 See Bordes, Ozlem A. "The Learned Intermediary Doctrine and Direct-to-Consumer Advertising: Should the Pharmaceutical Manufacturer Be Shielded from Liability." U. Det. Mercy L. Rev. 81 (2003): 267.

23 See Owen, David G. "Punitive damages in products liability litigation." Michigan Law Review 74, no. 7 (1976): 1257-1371 and Owen, David G. "The evolution of products liability law." Rev. Litig. 26 (2007): 955.

24 See Viscusi, W. Kip, Steven R. Rowland, Howard L. Dorfman, and Charles J. Walsh. "Deterring Inefficient Pharmaceutical Litigation: An Economic Rationale for the FDA Regulatory Compliance Defense." Seton Hall L. Rev. 24 (1993): 1437.

25 As it is important that all those with a claim bring their claim for the incentive setting characteristics of liability to be effective, and punitive damages might play an important role in encouraging this.

against.[26] This again justifies the inclusion of a development risk defence in any system of strict liability for design defects in pharmaceutical products.[27]

3.3.5 Suggested Public Interest System

The SPI system would limit the availability of product liability claims only to cases where the defendant firm had intentionally concealed information from the regulatory agency. In this case punitive damages would be made available against the firm. Otherwise, the SPI system would rely entirely upon broad pharmacovigilance to solve the underlying market failure. With pharmaceutical firms incentivised to provide all relevant data truthfully and promptly to the regulatory agency, then that agency – fully furnished with the data – is in a better position to manage the risks posed by pharmaceutical products than are the courts through liability rules, for the reasons set out above. The SPI system is shown in Table 24 below.

Table 24 Suggested Public Interest System

	System = Pharmacovigilance + Product Liability	
	Pharmacovigilance	**Product Liability**
SPI	Broad pharmacovigilance	Limited application
	Integrated with licensing	*Liability and punitive damages where concealment*
	Gatekeeping problem avoided	**Overdeterrence avoided**

There are two further reasons to suggest this as the system best justified by public interest theory. The first is that the integration of licensing with pharmacovigilance avoids Carpenter's 'gatekeeping' problem. The second is that only limited application of product liability avoids overdeterrence.

Gatekeeping Problem

Where broad pharmacovigilance is used, there would be only one committee at the agency dealing with both pre-licensing and post-licensing pharmacovigilance. As such, the *market-access* licensing decision would not be given *undue* significance. The focus placed by agencies on this licensing decision reflects what Carpenter calls the 'gatekeeping' problem. The undue significance afforded to market access licensing lies vis a vis other decisions which must be made under the risk management pillar of broad pharmacovigilance. Those decisions include,

26 Moreover, it has been argued that product liability leads to a preference for third party over first party insurance in a way which makes it very difficult for insurers to pool risks, and thus makes insurance unavailable, frustrating the loss spreading function of liability. See Priest, George L. "The current insurance crisis and modern tort law." Yale Lj 96 (1986): 1521.

27 See also Prentice, Robert A., and Mark E. Roszkowski. "Tort Reform and the Liability Revolution: Defending Strict Liability in Tort for Defective Products." Gonz. L. Rev. 27 (1991): 251.

for example: permission to move from animal to human testing; permission to amend the approved indication on the label; or, the decision to switch the product from prescription only to general sale classification. The significance itself is evidenced by the cost incurred at the market access licensing stage, and the very significant amount of time taken for a pharmaceutical firm to take a product past this stage: in the US, for example, an average time of 10 years to market access licensing, with the pivotal trials costing a median of 19m USD, and the overall costs of development between 2-3bn USD.[28] From the perspective of the firm, the 'gatekeeping' approach (i.e. the undue significance attached to the market-access licensing decision) incentivises firms merely to satisfy the agency and 'get past the gate'. Once past the gate, the firm is not too concerned about what the agency thinks. Given the nature of the ongoing information problem with pharmaceutical products set out above, this arrangement is far from satisfactory.

The product needs scrutiny from the moment of its conception to the end of its life cycle. Ongoing scrutiny is the only way in which the probable risks posed by the drug can be identified at the earliest stage, and thereafter research into the product can be effectively focused. Once the product is past the gate, this is only the stage at which the real data *first* becomes available (data from the clinical practice – or real-world - setting). At this stage, therefore, a full risk management plan needs to be in place identifying where further research needs to be done and what needs to be focused upon.

Overdeterrence

Much of the literature on the overdeterrence issue focuses on whether (in the US) State tort liability rules should be considered 'pre-empted' by federal regulation in the form of FDA approval and FDA mandated labelling. The case is made strongly[29], by Kip Viscusi[30] that there should be pre-emption.[31] According to him, where the licensing agency already errs on the side of caution, then the addition of product liability will lead to overdeterrence and will drive socially beneficial products off the market, or deter them from being launched on the market.[32]

Therefore, a choice should be made between the systems. Judges and juries look only at the facts and the cases before them, and these institutional constraints focus the attention of the decision maker upon the claimant only, and not on the needs of society. The FDA, on the other hand, considers the bigger picture. The FDA has expertise which makes it better at

28 DiMasi, Joseph A., Ronald W. Hansen, Henry G. Grabowski, and Louis Lasagna. "Cost of innovation in the pharmaceutical industry." Journal of health economics 10, no. 2 (1991): 107-142.

29 See Mildred, Mark. "Pharmaceutical products: the relationship between regulatory approval and the existence of a defect." European Business Law Review 18, no. 6 (2007): 1267-1282. See Jackson, Gregory C. "Pharmaceutical product liability may be hazardous to your health: A no-fault alternative to concurrent regulation." Am. UL Rev. 42 (1992): 199.

30 Viscusi, W. Kip, (1993).

31 See also Mottes, Lisa M. "The Need for Federal Preemption of State Tort Claims in the Context of New Drugs and Premarket-Approved Medical Devices." Seton Hall L. Rev. 41 (2011): 723.

32 See also: Polinsky, A. Mitchell, and Steven Shavell. "The uneasy case for product liability." Harv. L. Rev. 123 (2009): 1437. Shavell, Steven. "A model of the optimal use of liability and safety regulation." In Economics and Liability for Environmental Problems, pp. 77-86. Routledge, 2018. Shavell, Steven. "Liability for harm versus regulation of safety." The Journal of Legal Studies 13, no. 2 (1984): 357-374. Shavell, Steven. Economic analysis of accident law. Harvard University Press, 1987. Polinsky, A. Mitchell, and Steven Shavell. "The economic theory of public enforcement of law." Journal of economic literature 38, no. 1 (2000): 45-76.

monetising and weighing the costs and benefits of a new product. Judges and juries do not have this expertise. The FDA and the sponsoring firm negotiate the wording of the new drug label with a view to providing an optimal level of warning to the patient and physician, one which does not over-warn and does not under-warn. Judges and juries focus on what is missing, rather than on what the optimal level of information should be. Concepts in products liability law such as 'defective', and 'consumer expectation' require, in US courtrooms, a definition to be given to them by a jury, which acts as a lawgiver in this sense. This leads to unpredictable outcomes in tort litigation for products liability which can exacerbate the insurance problem raised above. Overall, product liability has institutional constraints which limit its accuracy. The use of product liability on top of licensing regulation is likely to create perverse incentives which harm social welfare. The benefits of pre-emption[33] would include certainty for producers and consumers – which should lead to less litigation and avoidance of the transaction costs of litigation. It would also mean impunity for producers, which would prevent a chilling effect on research and development.

3.3.6 System Divergences

The systems adopted by the US and the EU diverge from the SPI system uniformly. This is shown again in Table 25 below.

Table 25 System Divergence (Pharmacovigilance + Product Liability) US, EU, and SPI

	SYSTEM DIVERGENCE	
	System = Pharmacovigilance + Product Liability	
	Pharmacovigilance	**Product Liability**
SPI	**Broad pharmacovigilance** Integrated with licensing	Limited application
US	**Narrow pharmacovigilance** Not fully integrated with licensing	Full application
EU	**Narrow pharmacovigilance** Not fully integrated with licensing	Full application

However, at the level of the techniques, the transatlantic divergences also exist between the US and EU approaches to pharmacovigilance and product liability, as set out above. Consideration of public interest theory here has helped me to identify the system divergence, too. In the next section I turn to consider whether private interest theory and institutional insights can assist in explaining both the transatlantic divergence and the system divergence.

33 Mildred (2007): Jackson (1992).

3.4 Private Interests: Groups, Organisations, and Institutions

In this section I am considering the groups, organisations, and institutions most proximate to the regulatory positions.[1] I consider how differences in the strength and lobbying power of the groups, as well as key differences in their objectives, have contributed to shaping the regulation as it stands in each jurisdiction. In addition, I consider how bureaucracy behaviour at the relevant organisations has interacted with the efforts of these groups, as well as the extent to which the positions have been shaped by the existence of formal and informal institutions in both. To do so, I must take a historical perspective and consider how the regulation developed in each jurisdiction.

3.4.1 Relevant Interest Groups/Organisations

The relevant organisations are: the FDA, the EMA, and the NAs, and these (and their behaviour) have already been analysed in Chapters One and Two. I say that the most relevant interest groups in the US and the EU are: 1) the pharmaceutical industry and 2) lawyers. The differences between the objectives of lawyers in both jurisdictions, as well as differences in the *way* in which they have influenced lawmaking – as influenced by their institutional frameworks, respectively - have contributed to both the system and transatlantic divergences. Whilst both pharmaceutical industries, in both jurisdictions, represent strong interest groups:[2] in the US, USPI has slightly different objectives to EUPI in the EU. These differences in objectives come about inevitably because of differences in their respective institutional frameworks. This occurs via the mediating effect of the relationships which these institutional frameworks require them to maintain with other actors including: the agencies, consumers, and government, as well as between each other (inter-firm, intra-industry). Those differences in objectives have affected their approaches to their business, and thus their lobbying priorities, which have in turn contributed to the system and transatlantic divergences. This is shown in outline in Table 26 below.

1 Impacting upon the development of the regulation most closely.

2 Clearly there is a large degree of overlap between the two due to mergers and acquisitions. They are not two completely distinct groups. Yet, they are also not completely merged and thus can be written about separately as two groups operating in the context of different regulatory frameworks, and having different objectives.

Table 26 Relevant Interest Groups and Interaction with Institutional Framework

Interest Groups	Institutional Framework Affects…	Contributes to…
USPI	Relationships	
EUPI	Business model and lobbying priorities	Transatlantic divergence
US Lawyers	Impact on lawmaking	System divergences
EU Lawyers	Objectives	

The institutional framework is therefore key to understanding how both interest groups have contributed to shaping both forms of divergence.

3.4.1.1 The Pharmaceutical Industry

Both USPI and EUPI are strong relative to the pharmaceutical industries found in other countries around the world. However, USPI focuses more on *sales* within the US domestic market, outsourcing *manufacturing* to other countries in many cases. In the US, 17-20% of income from pharmaceutical product sales are reinvested in research and development activities making it the most innovative sector of the US economy as of 2014.[3] In the 1990s USPI became the world leader in research, testing, and marketing, and sales surpassing Germany, Switzerland, and France. This, commentators have argued, is due to the knowledge-based innovative driven approach of USPI[4] relative to EUPI.[5] Karamehic et al state: *"…out of ten largest pharmaceutical companies in the world in 2009, five are headquartered in the United States. The largest companies according to sales revenue was Pfizer with US $57 billion, followed by Merck with $39 billion. The third place was held by the Swiss company Novartis with $38.5 billion. In addition, IMS Health made the report of geographic sales by world regions in 2009. The U.S. commands the largest portion with the annual sales of US $300.3 billion (35.9%), and it is followed by Europe with $263.9 billion (31.5%)."* [6]

3 Dorocki, Sławomir. "Contemporary Trends in the Development of the Pharmaceutical Industry in the World." *Studies of the Industrial Geography Commission of the Polish Geographical Society* 25 (2014): 108-131.

4 It is also said to be due to a robust science-based regulatory system and strong intellectual property protections, however these are found also in the EU/EUMS.

5 Karamehic, Jasenko, Ognjen Ridic, Goran Ridic, Tomislav Jukic, Jozo Coric, Djemo Subasic, Mirsad Panjeta, Aida Saban, Lejla Zunic, and Izet Masic. "Financial aspects and the future of the pharmaceutical industry in the United States of America." *Materia socio-medica* 25, no. 4 (2013): 286.

6 In an econometric analysis undertaken in 2019, Lakner and others show the link between research investment and pharmaceutical patents, concluding that investment in research and development (innovation) is necessary in order to maintain competitiveness. Lakner, Zoltán, Anna Kiss, József Popp, Zoltán Zéman, Domicián Máté, and Judit Oláh. "From basic research to competitiveness: An econometric analysis of the global pharmaceutical sector." *Sustainability* 11, no. 11 (2019): 3125.

The innovation in question has been high risk and high reward.[7] The model has been to pursue a shallow but broad portfolio of research and development activities[8] in search of so-called 'blockbuster'[9] products. The major players in USPI compete to develop blockbuster products, which are products which generate more than 1bn USD in revenues per year.[10] These revenues are generated from the *domestic* rather than the international market. Some examples are: Vioxx®, Lipitor® and Zoloft®. USPI's 'blockbuster business model' is facilitated by the US system of pharmaceuticals regulation: which permits DTCA of prescription pharmaceutical products; in which firms receive relatively little or no direct or indirect state aid through socialized healthcare systems (and as such have to compete against each other to capture the domestic market); and which has no direct price regulation, which enables relatively high product prices paid for by private insurance.[11] The incentives to develop blockbuster products have moved USPI towards greater investment in innovation than EUPI.

Meanwhile, EUPI *manufactures* a great deal within the EU and exports around the world. As of 2014 Germany was the world's largest exporter of pharmaceuticals (totalling 14.6% of world exports) followed by Belgium (11.8%). The US does not focus so much on the export sector, with only 8.8%.[12] However, the majority of capital and share transfers – including transfer in ownership and location of research facilities - in the global pharmaceutical sector

7 Karamehic et al. (2013)

8 These research and development activities are costly however: once such a drug was found, the profits obtained by USPI as a result of having market exclusivity for a period would be sufficient to recoup all costs and leave a very healthy profit for shareholders. To the research expenditure were added the costs of promotion – sometimes up to twice the value of the research – resulting in what some consider to be very high prices for these products.

9 Many commentators indicate that this 'blockbuster era' business model is currently dying. Precisely because there is a limit to how many new formulas can be found for blockbuster drugs to treat chronic conditions in elderly patients, and because the market is becoming saturated with very similar products, less and less therapeutically novel. Some argue that USPI will be forced to diversify into other products and/or generics in order to remain competitive globally. Schuhmacher, Gassmann and Hinder tell us that, in response, USPI firms have taken three strategies: *"(A) Activities to reduce portfolio and project risk, (B) activities to reduce R&D costs, and (C) activities to increase the innovation potential."* Schuhmacher, Alexander, Oliver Gassmann, and Markus Hinder. "Changing R&D models in research-based pharmaceutical companies." *Journal of translational medicine* 14, no. 1 (2016): 1-11. Karamehic, Jasenko, Ognjen Ridic, Goran Ridic, Tomislav Jukic, Jozo Coric, Djemo Subasic, Mirsad Panjeta, Aida Saban, Lejla Zunic, and Izet Masic. "Financial aspects and the future of the pharmaceutical industry in the United States of America." *Materia socio-medica* 25, no. 4 (2013): 286. Garnier points out that the recent decline in research and development productivity in the US has led to a loss of 850 billion USD in shareholder value from the top 15 pharmaceutical firms worldwide between 2000-2008. Kesic predicts that in response to this movement the concentration trend in both EUPI and USPI will continue: Garnier JP. Rebuilding the R&D engine in big pharma. Harvard Business Review. 2008 May;86(5):68-70, 72-6, 128. Kesič, Dragan. "Strategic analysis of the world pharmaceutical industry." *Management: Journal of contemporary management issues* 14, no. 1 (2009): 59-76.

10 https://medical-dictionary.thefreedictionary.com

11 This is supported by an analysis undertaken by Grewal et al in 2008 who show that large USPI firm shareholders seek broad but shallow investments in research and development (with a view to discovering a blockbuster drug) rather than the narrow and deep investment approach favoured by small firms. The former approach maximises shareholder value whilst avoiding excessive risk, and the latter is inherently risky. This, it is submitted, is how USPI firms originally took the preeminent position of EUPI in the 1990s. Through having a large appetite for risk across the board, those US firms which survived in their ventures discovered new products so profitable that their path dependent trajectory changed. This occurred at the same time as EUPI firms were locked in a comfortable, collaborative, and relatively non-competitive relationship with each other: with the EUMS, the EUMS treasuries, and the NAs. Grewal, Rajdeep, Anindita Chakravarty, Min Ding, and John Liechty. "Counting chickens before the eggs hatch: Associating new product development portfolios with shareholder expectations in the pharmaceutical sector." *International Journal of Research in Marketing* 25, no. 4 (2008): 261-272

12 Dorocki (2014)

in the last two decades has been between the US and Western Europe, and mostly from Western Europe to the US.[13] Blanc[14] informs that the 2013 Competitiveness report of the European Commission, *"Towards knowledge driven reindustrialization",* stresses the need to address the competitive disadvantage of the EU and the growing EU-US productivity gap. The report *"argues in favour of innovative solutions to maintain its position as a major producer of knowledge."* Various EUMS have reformed their healthcare systems in the 1990s in response to crushing budget pressures resulting from socialized medicine. Some – particularly northern EUMS – have introduced measures to increase competition, which Hutton argued in 1994[15] would be likely to affect returns to EUPI in the long run. In fact, it is most likely to spur greater innovation by a smaller number of EUPI firms, by raising the risks associated with innovation. This is contrary to the pre-1990s position whereby many EUPI firms innovated just a little, in contrast to the US where all major firms innovated a lot.

What accounts for the differences in the approaches of EUPI and USPI today? It has been argued that first mover advantage is key in the pharmaceutical industry. Malerba and Orseniga claim[16] that *"path-dependent processes triggered by increasing returns linked to economies of scale and scope, innovation, marketing, etc. have only a few winners"* leading to the highly concentrated USPI and EUPI sectors that are seen today. Because first mover advantage and path dependence are key it is not surprising that it was the Western EUMS - where the original technology emerged – that originally developed strong pharmaceutical sectors, and that these remained strong and dominated the international pharmaceutical industry for most of the 20th Century. They also argue that changes in political climate have been *"so important"* as to change the *"path dependent trajectory"* in both cases. Here I suggest that the operative political change in the EU/EUMS was the emergence of socialised healthcare systems in Western Europe following the Second World War.[17] Once these systems were established, incentives for EUPI to innovate decreased. Profit motives diminished for EUPI due to direct price regulation which itself was introduced in many EUMS due to budget pressures caused by socialized healthcare. Restrictions on prices however, were offset by guaranteed sales through government departments (national healthcare systems). These factors created a climate in the EUMS in which it made sense for EUPI to cooperate peacefully with government and agencies in the model which Wictorowicz calls, 'corporatist'.[18] There is also the insight[19] that - already occupying a dominant domestic and international position at the mid-point of the 20th century - it was rational for EUPI to profit *satisfice* rather than to seek to profit *maximise*, thus avoiding risk which would threaten that position. The case was the opposite for USPI, which did not have a dominant position at this

13 Ibid.

14 Blanc, Ludivine. *The European Pharmaceutical Industry in a Global Economy: what drives EU exports of pharmaceuticals?*. Vol. 31. Bruges, Belgium: College of Europe, 2015.

15 Hutton, John, Michael Borowitz, Inga Oleksy, and Bryan R. Luce. "The pharmaceutical industry and health reform: lessons from Europe." *Health Affairs* 13, no. 3 (1994): 98-111.

16 Malerba, Franco, and Luigi Orsenigo. "The evolution of the pharmaceutical industry." *Business History* 57, no. 5 (2015): 664-687.

17 And the socialist governments which came to power in those countries like the UK, Germany, France, and Italy.

18 Wiktorowicz, Mary E. "Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France." Journal of Health Politics, Policy and Law 28, no. 4 (2003): 615-658.

19 See Simon, Herbert A. "Theories of decision-making in economics and behavioral science." The American economic review 49, no. 3 (1959): 253-283 and Gordon, Robert A. "Short-period price determination in theory and practice." The American economic review 38, no. 3 (1948): 265-288.

point, and which instead risked the US becoming a dumping ground for surplus EUPI pharmaceutical stock. The incentives on USPI in the second half of the 20th Century were to compete between themselves to capture the domestic market, and to keep EUPI out of it by innovating – i.e., by competing on product quality more than on product price.

The differences in their historic development, and current position, cause EUPI and USPI to have different lobbying priorities as interest groups, and to interact in different ways with government, agencies, and consumers. USPI wishes to protect its business model based on innovation, promotion, patents, and relatively high prices (the 'blockbuster' model). It focuses on the domestic market, but USPI firms must compete with each other, and with regulators, to keep the domestic market and to keep EUPI out of it. To do so they innovate, but they also must deal with the regulator 'at arms-length' instead of voluntarily contributing to the cost of regulatory enforcement through open cooperation, which would place individual firms at a competitive disadvantage relative to others, and/or USPI as a whole at a competitive disadvantage relative to EUPI or to the FDA and consumers. Necessarily, therefore, USPI must be pitted against the FDA and against consumers. Consumers will buy the products of USPI anyway because these are 'essential', and they are heavily DTC advertised. In addition, as set out in Chapter One, an historic alliance has existed between USPI and US Doctors, which enables USPI to distribute its products to consumers via a trusted intermediary, in a mutually beneficial arrangement between the two. This does not mean that consumers 'like' USPI, it is truer to say that US consumers 'tolerate' USPI and its high profits. The adversarial relationship between USPI and consumers also helps to explain why punitive damages and class actions are widespread against USPI: these provide a corrective redress mechanism which allow redistribution of what some see as 'excessive' profits, in a highly salient fashion, from time to time. In relation to specific lobbying objectives, USPI seeks a continued high risk and potentially high reward approach. It is therefore content to accept the risk of high punitive damages awards, but liability must be tied to fault - to avoid crushing liability for the industry - whilst still enabling the blockbuster business model.

The relationship between consumers and EUPI is more estranged. Government health departments and agencies mediate this for the most part. EUPI does not advertise prescription products DTC (within the EU). Its major relationships are with the regulators and governments. So long as EUPI keeps the regulators and government departments happy then the consumers will follow, paying, as they do, for the products through their taxes. Vis a vis the agencies – the NAs and EMA – EUPI cooperates and bargains with them in a corporatist model.[20] EUPI seeks and settles for only a comfortable rate of return on capital in the domestic market, and focuses on the export market at relatively higher prices to remain somewhat internationally competitive. The lobbying objectives of EUPI are to keep things that way – which I call the 'stability' model – therefore EUPI seeks to keep risks low by seeking EU regulation which, for example, tightly controls and harmonises the basis and quantum of liability for defective products in the EU, so that these risks can be insured against. Or, by voluntarily contributing to the costs of regulatory enforcement (e.g. in funding pharmacovigilance studies) in return for an amenable approach by the regulator in licensing new products. The 'blockbuster' model and 'stability' model are set out below in Table 27.

20 Wiktorowicz, Mary E. "Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France." Journal of Health Politics, Policy and Law 28, no. 4 (2003): 615-658.

Table 27 Pharmaceutical Industry in the US and the EU

Institutional Framework	Relationships	Business Model	Lobbying Priorities
United States (USPI) No price regulation Less socialised healthcare DTCA	**Adversarial** Intense competition intra-USPI Arms-length with FDA Tolerated by consumers But: Allied with US Doctors	**Blockbuster Model: USPI** More innovation less manufacturing Blockbuster products Profit maximise	**Embrace risk:** Permit high punitive damages but liability must be tied to fault
European Union (EUPI) Price regulation Socialised healthcare No DTCA	**Corporatist** Avoid intense intra-EUPI competition Cooperate with EMA/NAs Estranged from consumers	**Stability Model: EUPI** More manufacturing less innovation Stable returns on capital in EU Profit satisfice	**Avoid risk:** Harmonise EUMS regulation of product liability Cap total damages but EUPI will act as insurer of last resort for consumers even without fault

3.4.1.2 Lawyers

Here I am most concerned with the impact which lawyers (as an interest group) have on lawmaking.[21] I say their lawmaking impact in both cases is shaped by the institutional framework within which US lawyers and EU lawyers, respectively, operate. They also have slightly different objectives as interest groups which, in turn, are reflective of their institutional frameworks. My analysis of these interest groups is summarised in Table 29[22] (second) below. I later argue that the objectives of the interest groups, and the way in which they affect lawmaking, has contributed to the system and transatlantic regulatory divergence.

21 See Gedde, David S., and Tantatape Brahmasrene. "The role of interest groups in products liability law." Managerial Finance 25, no. 3 (1999): 76-89.

22 See the literature cited in this section for the sources leading me to compile this Table.

Table 28 Two Types of EU Lawyers

EU Bureaucrat Lawyers	Former or current practising lawyers or academic lawyers who are *employed directly* and *in-house* by the EU institutions, agencies, or organs in legal, political, or otherwise bureaucratic roles.
EU Practising Lawyers	Practising lawyers and judges drawn from all EUMS specialised primarily *in the fields* of EU law (e.g. competition law, regulatory law, etc.) before or on both their domestic EUMS courts and the CJEU

Due to the bureaucratic organization of the EU, the interest group of EU lawyers can be seen as comprised of both 'EU Practising Lawyers' and 'EU Bureaucrat-Lawyers' which are former or current practising or academic lawyers (legally trained individuals) who work in or for the EU agencies and organs. This is detailed in Table 28 above.

Table 29 Lawyers and their Impact on Lawmaking in the US and the EU

Institutional Framework	Impact on Lawmaking	Objectives
United States Common law system Inductive reasoning Adversarial procedure	**US Lawyers** As practicing lawyers/judges: bottom-up development of law through case-specific arguments adopted by judges drawn from interest groups of claimant and defendant lawyers	**US Lawyers** Seek to maximise individual fee income and prestige through lobbying as organized groups (e.g. ATLA) or court-based arguments. Seek substantive and/or procedural legal changes to benefit fee income of group
European Union/EUMS Mostly civil law systems Deductive reasoning Inquisitorial procedure EU Bureaucratic organisation EU law must be implemented EU law must be neutral	**EU Bureaucrat Lawyers** As bureaucrats in Council, Parliament, and other organs: drafting law, according to logical, rational, and non-ideological approaches to law-making. Implemented top-down. **EU Practising Lawyers** As practicing lawyers/judges, top-down through interpretation of EU Law before or in the CJEU or national courts in a centralised way leaving little scope for divergent national interpretations.	**EU Bureaucrat Lawyers** Seek to maximise the competences of the organs and the EU by integration 'through' law. **EU Practising Lawyers** Seek to maximise the authority of the CJEU and/or ensure the supremacy of EU law.

Lawyers in the US

I argue here[23] that the adversarial approach and inductive reasoning found in US common law resulted in the emergence of an interest group of practising lawyers which is split evenly along adversarial lines (claimant and defendant) both as attorneys and as judges. The institutional framework of the common law allows this interest group to affect the development of the law in a way which serves its own interest as a whole in the long-run. This is despite the fact that at any given time legal rules may seem to favour one subgroup (e.g. claimant personal injury lawyers) or the other (e.g. defendant personal injury lawyers). The adversarial system leads to a 'back and forth' style of development of the common law. This, due to the uncertainty created over time for users of the legal system, leads to wealth transfers to lawyers (as a whole interest group) in the form of fees paid for advice and representation.

The market for legal services in the US is competitive relative to that of some EUMS.[24] This results in subgroups of lawyers – such as claimant lawyers and defendant lawyers – organising and coordinating as subgroups within the wider interest group. They do so because the US common law itself is institutionally adversarial. They organise both in order to lobby government directly, and to seek legal change by winning judge-made precedent through legal argument in specific cases. Whichever way they are achieved, the changes sought are those which benefit the subgroup by maximising its potential fee income.[25]

By way of example, Gordon, upon considering the history of lawyers in the US[26] writes that claimant lawyers supported strict liability and defendant lawyers supported blanket exemptions from liability for developers of products. Claimant lawyers organised in the 'American Trial Lawyers Association' ('ATLA') *"that lobbied legislatures and argued in courts for broader theories of liability and damage awards. The ATLA portrayed the plaintiffs' lawyers as populist champions, representing the little guy against wealthy and well-lawyered corporations."*[27] However, he continues, *"The defense bar struck back…. in the 1970s and 1980s…. the "tort reform" movement was a huge public relations and political success…"*: in that defendant lawyers managed to roll back strict liability for many classes of defective products. This shows how US lawyers seek - and can achieve - legal changes but, due to the adversarial nature of the system, they counteract each other such that legal change over time does not unduly favour any given subgroup within the overall interest group of US lawyers. This observation is reconcilable with the efficiency of the common law hypothesis[28] however, this process - by which the legal rules change back and forth whilst moving towards the

23 It is my analysis of the institutional framework and the interest group, which is tailored to the specific problem of the development of the regulation of pharmacovigilance and product liability. Of course, many elements of this analysis are taken from the well-established insights of others.

24 Garoupa argued in 2006 that barriers to entry to the legal profession in the US are low relative to many EUMS. In Austria, Germany, Greece, Italy, Luxembourg, and Portugal barriers to entry for the legal profession are 'rigid' for example whilst the United States performs extremely well with relatively low barriers to entry. Garoupa, Nuno. "Regulation of legal and medical professions in the US and Europe: A comparative analysis."

25 This isn't to suggest that there is a conflict of interest with clients, this is the nature of the adversarial system. What lies in the Client's interest often also lies in the lawyer's personal interest.

26 Gordon, Robert W. "Lawyers, the legal profession & access to justice in the United States: a brief history." *Dædalus* 148, no. 1 (2019): 177-189.

27 *"Their cause was aided by the expansions of liability to include strict liability for defective products (such as pharmaceuticals) and changes in the civil procedure rules to favor class actions and multiparty litigation; and by the Supreme Court decision invalidating the bar's prohibition on advertising."* Gordon (2019).

28 See Rubin, Paul H. "Why is the common law efficient?." The Journal of Legal Studies 6, no. 1 (1977): 51-63.

'efficient' rule - involves large wealth transfers from both defendants and claimants to their lawyers. That is due to the bottom-up approach and deductive reasoning of the common law system in which legal change happens because of arguments brought by lawyers in courts instead (for some part) of being handed down from above by legislatures. The 'back-and-forth' between the subgroups of lawyers benefits lawyers (as a whole) due to the fee income from litigating and relitigating. The judiciary – drawn from all subgroups – is happy to participate in this system.

Lawyers in the EU and EUMS

I say that lawmaking at the EU level, and its subsequent top-down implementation from the EU to the EUMS level, are driven by a special subgroup of European lawyers: 'EU Bureaucrat Lawyers'[29] who staff the EU organs and agencies. They have their presence in the 'supranational' sphere[30] and they therefore align their individual objectives specifically with the EU organs rather than with the EUMS from which they are variously drawn. These EU Bureaucrat Lawyers adopt approaches to lawmaking which are ostensibly 'logical, rational, and non-ideological,'[31] and thus are acceptable to all EUMS. Often, the substance of EU law – much of which is regulatory law - is highly technical. Furthermore, the process of lawmaking itself is technocratic. It is left to legal experts and presented to the EUMS governments and legislatures as apolitical. The central actors driving this process are EU Bureaucrat-Lawyers. The EUMS – the majority of which are civil law systems structured around written legal codes - also adopt top-down styles of lawmaking. But, each EUMS has imbued its legal codes with centuries of national legal traditions in interpretation. Also, in all EUMS – as in the US – new legislation is politicised in its scrutiny by national legislatures. EU legislation does not receive such a high degree of scrutiny.[32]

At the EU level, this presented a problem for lawmaking, especially the process of integration-through-law (as it has become known). Vauchez argues[33] that the EU itself *is* law and that the role played by lawyers is *"not peripheral but central to an understanding of law's position within EU polity".*

29 On the ubiquitous presence of lawyers in the EU at the EU agencies and organs see Vauchez, Antoine. "The force of a weak field: law and lawyers in the government of the European Union (for a renewed research agenda)." *International Political Sociology* 2, no. 2 (2008): 128-144.

30 Ibid. This is Vauchez' argument. See also Schepel, Harm, and Rein Wesseling. "The legal community: judges, lawyers, officials and clerks in the writing of Europe." European Law Journal 3, no. 2 (1997): 165-188.

31 Schepel and Wesseling (1997).

32 Gromek-Broc found in 2002 that lawyers in the four largest EUMS (France, Germany, Italy, and the UK) were *"strongly… related to their national cultures and traditions and deeply rooted in their context and environment."* In relation to proposals for harmonization of regulation of these professions (including in the 1998 Lawyers Directive Stephen observes *"Resistance from vested interests… may slow down the moves towards greater efficiency…"*. In addition to the high barriers to entry to the profession within each EUMS there are or were very significant barriers to mobility between each EUMS legal system. Each legal system has strong traditions, is grounded in the national language and is an expression of national identify such that they are difficult to permeate by either lawyers from other legal systems and/or by ideas. Moreover, the civil law systems which abound in most EUMS adopt a strong tradition in which academic lawyers influence the development of the law through juridical writing Gromek-Broc, Katarzyna. "The legal profession in the European Union–a comparative analysis of four member states." *Liverpool Law Review* 24, no. 1 (2002): 109-130. Stephen, Frank H. "The European single market and the regulation of the legal profession: an economic analysis." *Managerial and Decision Economics* 23, no. 3 (2002): 115-125. See e.g. Schepel and Wesseling (1997).

33 Vauchez (2008)

In the early days of European integration, legal academics were consulted[34] on how best to implement the political aims of the project through law. After this, law later developed to become a political model of integration, with the CJEU defining the scope of its own competences. The substance of the law, however, departs a great deal from the national legal traditions of the EUMS. Harm and Wesseling argued in 1997[35] that the conception underlying the EU legal field is a… "*basic mindset, a habitus, socially constructed and maintained, that depoliticises European integration by creating an opposition between a realm of European 'law' as a rational force towards the inevitable and a realm of national 'politics' as the articulation of the illogical, irrational, and ideological."* Thus, academics specialised in the legal traditions of individual EUMS did not publish to the same extent in EU law journals as they did in national legal journals[36] which instead were filled with the writings of academics specialised in a select few disciplines which claimed to characterize law as logical, rational and ideologically neutral. These include, for example: international law, comparative law, political science, competition law, and law and economics, as well as an entirely *sui generis* EU public law.[37] This law was most easily applied to areas where the EU organs had competences to regulate – technical regulation, regulation of markets (e.g. competition) etc. EU bureaucrat lawyers adopt these disciplines to promulgate law acceptable to all EUMS. In doing so, they seek to enhance the status and authority of the organs which they staff, and they seek further integration of the EUMS through law. Whilst the style of lawmaking is technocratic, and the substance of the laws made drawn from those disciplines, it cannot be ideologically neutral. However, the approach taken ensures that it is neutral to an extent which makes it acceptable to all or most EUMS. This explains the emergence of whole fields of EU law which have their own EU level 'branding', but in reality disclose key ideologically non-neutral principles which are so basic that they are acceptable to all or most EUMS. EU consumer protection law is an example of this.

Other lawyers in the EU (in Table 28 and Table 29 above 'EU Practising Lawyers') do not necessarily belong to the supranational sphere, and do not staff the organs, but have their locus in a specific EUMS. These EU Practising Lawyers align their objectives with the objective of the expansion of EU law itself. And, they identify with their EU Practising Lawyer counterparts in other EUMS. These lawyers are responsible – through their judgments and/or their arguments – for the interpretation (rather than creation) of EU law both at the CJEU and before domestic courts. The institutional framework within which they operate enables them to further their objective of enhancing the status of the group to which they belong through

34 Madsen, M., Antoine Vauchez, Alex Jettinghoff, and H. Schepel. "In Lawyers' Circles Lawyers and European Legal Integration." (2005).

35 Schepel and Wesseling (1997).

36 Ibid.

37 As Vauchez states, *"The persistence of this quasi-diplomatic logic in the realm of law shows that, as in most European affairs, legitimacy is still construed in terms of the equal (or, at least, fair) representation of ''national traditions,'' which conditions the fact that the law produced is truly common... This is probably the price to pay for the ''Europeanness'' of EU law; that is, its capacity to convince of its neutrality with regard to the equilibrium between Member States."* Vauchez (2008).

enhancement of the authority of EU law itself. The seminal judgments delivered in *Van Gend en Loos*[38] and *Costa v ENEL*[39] are examples.

3.4.1.3 FDA, EMA, and the NA's

The characterisation set out in Chapters One and Two about the FDA, the EMA and the NA's is adopted here again for the purpose of discussing private interest reasons for the regulation of pharmacovigilance and product liability in the US and the EU. That characterisation is set out again below in Table 30 and Table 31.

Table 30 The FDA, the EMA, and the NAs Key Characteristics (3)

FDA	NAs/EMA
'Direct to Consumer Accountability'	'Double' (NAs) and then 'Treble' (EMA) 'Insulation'
Relative Resistance to Industry Influence	Capture by Default
Politicised Science	Science Excludes Politics

Table 31 Extended Reputation Model Applied to FDA and EMA/NAs (2)

	FDA	EMA/NAs
Reputation	*Consumer Protection/Quick Product Access* *Scientific Expertise (but politicised)*	*Science Based Assessment* *Apolitical*
Main Audience	*Primarily Consumers*	*Primarily Industry and EUMS Ministers*
Industry	*Relative Resistance to Industry Influence*	*Industry Capture by Default*
Doctors	*Safety gatekeeping* *(US doctors accommodate consumers)*	*Reliance on doctor matching* *(EU/EUMS doctors advise consumers)*
Consumers	*Highly responsive/directly accountable* *(activist US Consumers)*	*Less responsive/lack of accountability* *(passive, institutionalised EU consumers)*

In the sections below I set out how these interest groups and organisations have affected the development of pharmacovigilance and product liability in the US and the EU.

38 Judgment of the Court of 5 February 1963. NV Algemene Transport- en Expeditie Onderneming van Gend & Loos v Netherlands Inland Revenue Administration. Reference for a preliminary ruling: Tariefcommissie - Netherlands

39 Judgment of the Court of 15 July 1964. - Flaminio Costa v E.N.E.L.. - Reference for a preliminary ruling: Giudice conciliatore di Milano - Italy. - Case 6/64.

3.4.2 United States

3.4.2.1 Pharmacovigilance

Analysis of the role of USPI and the FDA can assist in explaining the **transatlantic** divergence in pharmacovigilance by helping to explain the reasons why the US has adopted an 'adversarial' approach to pharmacovigilance activities.

USPI

The FDA-led approach to pharmacovigilance is best understood by considering the relative resistance to industry influence (which is characteristic of the FDA) as a result of direct-to-consumer accountability. USPI is not accustomed to cooperating with the FDA for mutual gain, and is not expected to do so.[40] Shareholders of USPI – interested in maximizing profits through innovation – are not interested to see USPI cooperate closely with the FDA. Thus, in the case of pharmacovigilance, USPI will cooperate with the FDA up to the point that[41] the product is given a license – including by making commitments to undertake post-market studies - but thereafter will not voluntarily do so to any great extent e.g. in conducting Phase IV trials.

USPI promotes its products heavily to consumers through DTCA however, the identify of any individual firm is rarely a part of that marketing strategy, which focuses closely on the qualities of the product itself. The firms themselves, within USPI, are all relatively negatively perceived[42] by US consumers[43] which does not affect the business of any one given firm in relative terms. Neither would it be likely to, because consumer boycotts are unlikely in the case of (particularly prescription only) pharmaceutical products. Thus, there is no need to seek better relationships with the FDA (and therefore with consumers) if this would mean USPI having to incur more cost through greater levels of regulatory compliance. The relationship between USPI and US consumers – already cold – relies on third party mediation. That happens through the FDA: in which case US consumers will tolerate the profits taken by USPI for so long as USPI continues to provide essential products and is seen to be kept 'in check' by the FDA. However, where the FDA has demonstrably not 'kept the gate' US consumers will tolerate (what some would see as) the excesses of USPI for so long as there is the corrective mechanism of product liability lawsuits (and potentially large punitive damages awards) to redistribute those profits to US consumers.

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40 Moreover, given the high level of intra-USPI competition, to break ranks with others in USPI and instead seek a more amicable relationship with the FDA would merely mean that the firm gets outcompeted by other firms.

41 Carpenter (2006).

42 See Harris Interactive. Available from URL: http://www.harrisinteractive.com/news/allnewsbydate.asp?NewsID=1206 [Accessed 2009 Aug 6] See Kaiser HealthPoll Report. Views on prescription drugs and the pharmaceutical industry [online]. Available from URL: http://www.kff.org/healthpollreport/feb_2005/index.cfm [Accessed 2008 Apr 20] and See Olsen, A.K., Whalen, M.D. Public Perceptions of the Pharmaceutical Industry and Drug Safety. Drug-Safety 32, 805–810 (2009). https://doi.org/10.2165/11316620-000000000-00000

43 Firms in USPI are not so interested in maintaining a positive image amongst US consumers, they accept that they are demonized, however their products are so in demand that this does not seriously affect their business.

Thus, the US courts can be viewed as the backup mediator of the relationship between consumers and USPI. In this case, in the domain of consumer perception, whether it was the failure of the FDA or of USPI or neither (a truly latent defect), consumers are happy to blame USPI and take punitive damages before allowing their perceptions to return to equilibrium. The possibility of punitive damages arguably, therefore, permits the continuance of the innovation-based blockbuster model, by providing a strong and salient redress mechanism in the eyes of consumers. The equilibrium is also maintained with respect to the FDA because even where it was the FDA's fault, the lack of federal pre-emption means there will still be a product liability case to answer, and consumers are thus nudged to blame USPI instead of the FDA, the latter which consumers can continue to trust. In addition, as product liability takes place in the adversarial common law system whereby consumers must seek evidence of and prove causation themselves, there is little incentive for USPI to assist them in this by cooperating with a pharmacovigilance system which is transparent to consumers. Close cooperation by USPI with the FDA and/or attempts to foster a better image with consumers would be damaging to the competitive efforts of any individual firm in USPI vis a vis other USPI firms.[44]

Any individual firm within USPI - and USPI as a whole - is likely to lobby to maintain the current system of (mostly negligence based)[45] product liability, plus FDA led pharmacovigilance.

FDA

For its part, the FDA wants to keep the pharmacovigilance system unitary to some extent with its licensing system. The FDA seeks to protect its reputation for consumer protection, and thus admitting an earlier licensing mistake is not a welcome scenario. To equalize executive authority between the OSuE and the NDC would risk the FDA contradicting itself more often. The FDA prefers therefore to focus heavily on the market-access licensing decision and get this right. In addition, the FDA wishes to take credit for successes. Therefore, if pharmacovigilance activities were devolved to industry and funded by industry then industry can share in credit taken for discovery of latent defects. Particularly where the FDA licensed the product initially, this will reflect poorly on the FDA in the eyes of the public which is unlikely to be able to draw a distinction between latent and patent product defects. Instead, it will look as though the FDA put consumers at risk, and that industry then protected those consumers.

44 It makes sense then, that if a product defect were to be discovered after market access is granted by the FDA, this should be through the efforts of the FDA, not USPI. In this drama – quite different to that in the EU/EUMS – USPI is the villain, consumer the victim, and the FDA and the courts the heroes. I do not say it was consciously planned that way, but these characters adopted their roles automatically over the decades in a way which fit best with the roles they have always played. The villain has no need to suddenly appeal to the victim and so USPI puts little effort into pharmacovigilance. It pays, anyway, for the licensing and pharmacovigilance activities of the FDA because of PDUFA.

45 Perhaps USPI would prefer federal pre-emption, but the FDA is not necessarily interested in this for the reasons given in the next paragraph, and US lawyers would likely strongly oppose it. In addition, removal of state product liability through preemption would mean that the FDA were even more exacting as a gatekeeper. Overall, USPI is likely to settle for and be happy with a system which exempts it from strict liability for design defects, whilst sporadically lobbying for restrictions upon punitive damages awards.

The FDA therefore seeks to maintain the US pharmacovigilance committee system as unitary with licensing, focusing heavily on the initial licensing decision, and with little input from industry.

3.4.2.2 Product Liability

Analysis of the role of USPI and US lawyers can assist in explaining the **transatlantic** divergence in product liability by helping to explain the reasons why the US courts moved towards strict liability for design defects and then rolled back from this position over time. Analysis of the role of the FDA can assist in explaining the **system** divergence by helping to explain the reasons why the US has not adopted federal pre-emption of State product liability claims.

USPI

I consider first the role of USPI in shaping the regulatory story for product liability in the US. USPI did not want strict liability for pharmaceutical products as it did not want to bear the cost of development risk.[46] To do so would hold back USPI from innovating at a rapid pace and protecting its hold on the domestic market against EUPI.[47] These concerns were exacerbated by jury trials and punitive damages awards.[48] Luckily for USPI the approach of the courts reflected in the Second Restatement, did not require strict liability in the case of unknown and unknowable defects. USPI had already protected itself from negligence-based liability through hiring defendant lawyers to argue for the application of the learned intermediary doctrine in State courts. Doctors in the US, as an interest group, were not too vociferously opposed to this. A strong alliance existed between doctors and USPI in the mid twentieth century. Thanks to the practice of detailing, doctors provided USPI with a domestic distribution system for USPI products through mandatory prescriptions, which USPI and US doctors lobbied for together. Under this system, doctors received detailing benefits from USPI and were able to secure their position as indispensable within the US healthcare system. In exchange for that they and their insurers accepted a large share of the liability risk for defective prescription pharmaceutical products.[49]

Strict liability on pharmaceutical firms for products defective by design – brought about by pro-claimant interpretations of the Second Restatement - threatened the benefits which USPI derived from this system. Thus, later, as claimant lawyers (such as those represented by ATLA) lobbied Congress and State legislatures, and argued in court for these interpretations, USPI responded. It lobbied for a rollback of these developments through its defendant lawyers in US courts. The eventual result was the Third Restatement, and blanket immunity for

46 That is to say, where a latent defect emerged in the product, USPI would prefer that the loss were allowed to lie where it fell – on consumers and their health insurers.

47 Which would be quick to export to the US market and take the higher profits available there than at home where direct price regulation limited returns. Innovation was key to USPIs strategy for holding on to the domestic market and where product liability would stifle innovation - simply through risk – this would suppress USPI vis a vis EUPI.

48 Particularly in the context of a system where USPI was not seen as any sort of friend to consumers and nor – for the reasons given above – was it trying to be seen as such.

49 Bearing in mind that the consumer still had to prove negligence and causation by the doctor in such cases.

pharmaceutical product design defects. Their efforts were very much supported by the insurance industry which was able to create a public policy panic regarding an 'insurance crisis' in the US.[50]

Lawyers

Academic lawyers in the US, being innovative and adhering to a US national legal tradition of legal realism,[51] proposed strict liability for defective products as an efficient legal rule. These abstract conclusions were picked up by claimant lawyers who stood to benefit from adoption of strict liability rules because it would lead to an increase in claimant awards. These would most often be through settlement rather than following trial, but whether through settlement or trial, because claimant personal injury lawyers in the US often work on a contingent fee basis, substantive changes to legal rules which systematically favoured claimants stood to increase the fee incomes of claimant lawyers. Defendant lawyers in personal injury (products liability) cases were not strongly opposed to the rule because they more often worked on retainer, and for large well-resourced corporations. The approach reflected in the Second Restatement was taken up with gusto across the US partly due to the efforts of ATLA who benefitted a great deal from it. In addition, armed with s402A of the Second Restatement and its widespread adoption, ATLA were able to lobby for changes in the civil procedure rules to favour class actions, and multiparty litigation, both of which stood to benefit claimant lawyers considerably.[52]

However, whilst defendant lawyers benefitted to some extent from the increased volume of suits filed against pharmaceutical firms, and thus their increased workload in advice on settlement, this was not as lucrative as the fees to be gained from defending a firm in a full trial. Strict liability made settlement much more likely than trial because the lack of a need to prove breach meant that there was less scope for claimant and/or defendant to proceed to trial strategically, hoping that the other would not discharge the evidential burden. Therefore, USPI, allied with the insurance industry and acting through defendant lawyers, struck back. The fightback culminated in the Third Restatement. In these circumstances, the US bar as a whole had to reach a compromise between its claimant and defendant subgroups, and that compromise would be rubber stamped by the judiciary which make these rules and who are drawn from then US (States) bars. This compromise suited the bar (as a whole) even if it had some distributive effects as between claimant and defendant lawyers. By implementing a system of liability rules for pharmaceutical products which were sometimes based on negligence and sometimes based on strict liability – at different times - the bar ensured more work and more fees for themselves because of the lack of legal certainty. This was quite different to the very clear position taken in the EU PLD, and it meant that relatively more US cases would be required to proceed to trial.

The more recent rejection of the learned intermediary doctrine for pharmaceutical products - particularly where those products have been advertised DTC– is a continuation of the same story. For claimant lawyers the prospect of (the fees from) large class action lawsuits in

50 Priest (1986).
51 See Garoupa, Nuno, and Thomas S. Ulen. "The market for legal innovation: law and economics in Europe and the United States."In Comparative Law and Economics. Edward Elgar Publishing, 2016.
52 Gordon (2019).

relation to blockbuster drugs led them to argue for the rejection of the doctrine in these cases.[53]

FDA

The most interesting question here relates to the system divergence rather than the transatlantic divergence. It is why there is no pre-emption of State product liability claims despite there being licensing and pharmacovigilance undertaken by the FDA. It may seem that the FDA should want to exclude the courts, and lawyers, from straying into the roles for which the FDA wants to claim credit – i.e. protection of consumers. Thus, one might expect the FDA to oppose any form of liability and instead seek a blanket exemption not just from strict liability but from product liability generally for products which it has licensed and in respect of which it oversees through pharmacovigilance. That has not been the case, however. I suggest two reasons why the FDA has not made stronger calls for pre-emption, both founded upon my analysis of FDA behaviour set out above.

The first is that tort liability operates ex-post, after harm has occurred. To ensure compensation for harm is very different in the eyes of consumers from preventing harm, and consumers are unlikely to think in terms of the incentive effects of liability. The reputation of the FDA which it seeks to protect is primarily that of consumer protection. The courts do not, therefore, diminish the status of the FDA much simply by providing an additional mechanism - particularly where it is implied that the USPI firm in some way misled or failed to fully cooperate with the FDA on licensing (an inference easily drawn by a casual observer in such cases, even where not explicit on the facts of the judgment). Secondly, the effects of federal pre-emption would be that where a mistake is made (or, rather, where there was an unknown and possibly unknowable defect), consumers would be more likely to blame the FDA instead of industry for its failure to spot the defect. Hence where a design defect was unknown but knowable, the FDA would much prefer that a court focuses on the failure of the USPI firm to discover the defect and/or its failure to warn of the possibility of a defect than upon the decision of the FDA to grant a license. Undoubtedly, the FDA would also prefer that where a design defect was both unknown and unknowable a court would impliedly absolve the FDA of liability by holding the USPI firm strictly liable. However, USPI and its defendant lawyers have successfully lobbied to ensure that this cannot be the case. In the former case, however, a publicised product liability judgment makes the role of the USPI firm salient to consumers. Even where liability was strict, consumers are likely to interpret the judgment to mean that the USPI firm was to blame. Without the judgment and the salience, the natural culprit would be the FDA. Hence the FDA prefers there to be product liability available on top of FDA licensing and pharmacovigilance.

53 Also, the alliance between US doctors and USPI - which was cemented on the twin bases of the learned intermediary doctrine and the mandatory prescriptions system - has broken down since the moratorium on DTCA was lifted in the 1970s. Now that USPI can appeal direct to consumers to buy prescription products, the justification for sharing liability with doctors has also gone. The learned intermediary doctrine is thus ripe for being dispensed with in the case of such products, yet again the way in which it is being done reflects the tussle between the subgroups claimant and defendant lawyers in the US. Its patchwork abandonment or retention from State to State above all ensures that the legal position is not clear either for claimant or defendant, and thus both are in need of the advice and representation of their lawyers.

3.4.3 European Union

3.4.3.1 Pharmacovigilance

Analysis of the role of EUPI and the EMA/NAs can assist in explaining the **transatlantic** divergence in pharmacovigilance by helping to explain the reasons why the EU has adopted its collaborative approach, with EUPI, to pharmacovigilance activities.

EUPI

Table 31 above summarises the findings from Chapters One and Two which indicate that the EMA (and NAs) find their primary audience in EUPI itself (and the EUMS governments) rather than EU consumers. Wiktorowicz has described this as a corporatist model, based upon bargaining and consultation between the EMA/NAs and EUMS governments on one hand and EUPI on the other.[54] Here, EUPI cooperates with the EMA and can be relied upon to carry out pharmacovigilance because within the corporatist model that exists in the EU, EUPI and the EMA bargain and consult with each other to ensure outcomes which are mutually beneficial. EUPI is happy with this system because EUPI is reliant upon the EUMS for its domestic revenues. This is due to widespread socialised healthcare systems in the EUMS and the prevalence of forms of price regulation not found in the US. There are no incentives for EUPI not to cooperate with either the NAs in the EUMS or the EMA at the EU level because for any individual EUPI firm to do so would likely mean it was excluded from the purchasing decisions of EUMS healthcare agencies. If EUPI acted this way (in order to increase its profits) it would just face more stringent price regulation.

The position of EUPI within the EU/EUMS is therefore stable and comfortable with few incentives to take risks. Money spent on pharmacovigilance activities is money which would otherwise be spent by the EUMS on pharmacovigilance themselves and thus not available to the EUMS to pay EUPI for products. To the extent that there is any disagreement between the EUMS or the EU/EMA and EUPI regarding the findings of post-license studies, these are resolved according to the standard EU approach to disagreements – by allowing science and expert views to have the final say – thus depoliticizing the issue. Therefore, EUPI can and does cooperate well with the EUMS and with the EU in pharmacovigilance. In addition, incentives to innovate and expand have been lacking for EUPI since the creation of the EU up to the turn of the 21st century, since it occupied a preeminent position in the international pharmaceutical sector. Where EUPI wishes to expand and increase profits, it did and does make most sense for it to do so by focusing on exports to other markets.

EMA/NAs

For its part, the EMA does so for the same reasons. It is also the case that the EMA (and the NAs) – not having a particularly high public profile in the EU/EUMS – feels little need to carry out the activities and take credit itself for pharmacovigilance. Credit will be taken by EUMS health ministers for anything that the EMA achieves and similarly government politicians will face public backlash for mistakes made by the EMA. This means that the EMA has little to fear from being closely involved with industry: not that this relationship is particularly visible to

54 Wiktorowicz, Mary E. "Emergent patterns in the regulation of pharmaceuticals: institutions and interests in the United States, Canada, Britain, and France." Journal of Health Politics, Policy and Law 28, no. 4 (2003): 615-658.

the average EU consumer anyway. This also helps to explain the plural system with licensing adopted at the EMA. The EMA is free to contradict itself and make mistakes because 1) such mistakes are unlikely to be salient to consumers and 2) where mistakes are made which are salient to consumers - e.g. where many consumers are harmed – generally it will be domestic EUMS health ministers who take the blame, and bureaucrats at the EMA can always claim that they acted logically, rationally and neutrally under the objective rules of science and expertise. Incentive problems which result from EUPI having control over pharmacovigilance activities are resolved to some extent by the trust of EU consumers in doctors and pharmacists as experts who advise and guide them in the use of medicines, and also through the fact that DTCA of prescription pharmaceutical products is banned across the EU. As was the case with EUPI, therefore, the pharmacovigilance approach adopted in the EU is low risk and comfortable for the EMA and the NAs

3.4.3.2 Product Liability

Analysis of the role of EUPI can assist in explaining the **transatlantic** divergences in product liability by helping to explain the reasons for the relatively low liability threshold and the relatively low expected damages awards (potential damages cap) in the PLD. Analysis of the role of EUPI and EU lawyers can assist in explaining the **system** divergence by helping to explain why the EU adopted the PLD instead of relying entirely upon licensing and pharmacovigilance.

EUPI

According to Van den Bergh[55] the PLD is largely a product of rent seeking, in part by EUPI. EU wide harmonisation of product liability regulation is relatively comfortable and low risk for EUPI, even with the possibility of a very strict liability standard. EUPI knew well before 1985 that not many claims would be brought by EU consumers. EU consumers can rely on socialised healthcare and systems of social insurance to assist them when injured by products. What EUPI was most concerned with when it saw the products (strict) liability revolution in the US in the 1960s and 1970s was that one or more renegade EUMS would be tempted to adopt the US approach or go further. This risked unpredictable damages awards in different EUMS and a 'race to the top' (the strictest liability standard) which may open the possibility of uniform development risk liability across all EUMS. It was the prospects of uncertainty, and patchwork of regulatory environments amongst the EUMS, which EUPI was most opposed to. EUPI thus welcomed harmonisation through the PLD.[56] However, it lobbied for a damages cap[57] and for a development risk defence, both of which – if included – would ensure some certainty and mitigate the worst risk. EUPI had to compromise on this, to some extent, in that both were included but were only optional, with no development risk liability being the default option

55 Van den Bergh, Roger. "Subsidiarity as an economic demarcation principle and the emergence of European private law." *Maastricht Journal of European and Comparative Law* 5, no. 2 (1998): 129-152.
56 Van den Bergh (1998). Van den Bergh, Roger. "Towards an Institutional Legal Framework for Regulatory Competition in Europe." *Kyklos* 53, no. 4 (2000): 435-466.s
57 Faure, (2016).

for the EUMS and the imposition of development risk liability requiring derogation (and justification). EUPI was satisfied with the outcome which – in the median EUMS – would ensure either no development risk liability, or a total damages cap. Overall, the harmonisation led to a level of litigation risk, both in 1985 and in foreseeable decades, which EUPI could manage, and which would allow it to continue with its 'stability' business model. The alternative – whereby all EUMS might have raced to impose both development risk liability and no damages cap – presented a level of litigation risk to EUPI which, given the stability model it was accustomed to, could not be tolerated.

Lawyers

Lawyers at the EU level drafting EU law are the EU Bureaucrat Lawyers described above. The PLD represented an opportunity for these lawyers to enhance the popularity of the EU organs with ordinary EU citizens (consumers) because it was an instrument of consumer protection. Moreover, 'branded' as a uniquely EU instrument of 'EU consumer protection law' and defensible based on approaches to lawmaking – such as law and economics – which were arguably logical and rational, it was also acceptable to the EUMS despite their divergent national legal cultures and traditions. The top-down implementation process and interpretation process of such instruments by EU Practising Lawyers ensured that promulgation of the PLD itself would increase the authority and status of the EU organs at which the EU Bureaucrat lawyers are the staff. The addition of another major instrument to EU law which must be implemented in national EUMS law enhanced the status and authority of EU law to the detriment of national EUMS law, which was desired by EU Practising Lawyers as well as EU Bureaucrat Lawyers.

This then helps to explain the system divergence. One might have expected EU lawyers (particularly EU Bureaucrat Lawyers) to have rallied behind the EMA, and its licensing and pharmacovigilance activities, and thus pushed for an equivalent of pre-emption in the EU. However, the PLD represented an opportunity to expand the authority of the EU in a different and potentially more powerful way: one which was acceptable to EUPI, and which enabled the EU organs (staffed by EU Bureaucrat Lawyers) to appeal directly to EU consumers.

3.4.4 Relevant Institutions

The other relevant institutions have been alluded to in passing above. They include formal institutions pertaining to the legal systems, and social institutions put on a legal footing. The formal legal institutions in the US are: strict liability itself (which has been implemented differently in respect of pharmaceutical products in the US and the EU); the adversarial procedure and inductive reasoning of the common law which account for the flexibility in and relatively rapid changes to the product liability rules in the case of pharmaceuticals and explain how claimant and defendant lawyers have interacted in the US to affect those rules; and punitive damages, jury trials and class action suits which have all raised the liability risks faced by USPI and as such, the 'need' to exempt pharmaceutical products from strict liability for design and failure to warn defects in the US. Finally, on the EU side, again systems of socialised healthcare and price regulation have impacted on the regulation of product liability and pharmacovigilance because these systems bind together EUPI, the EUMS, and the

EMA/NAs in a cooperative corporatist model and obviate the need for EU consumers to make use of product liability law. On that point also, the norm of greater litigiousness in the US is worthy of scrutiny as an informal social institution. Some of these institutions, alongside the groups and organisations discussed above, are considered in Chapter Six.

3.4.5 Summary

Application of private interest theory and institutional analysis has helped to explain both the transatlantic divergence in pharmacovigilance and product liability, and the system divergence.

Analysis of the role of USPI and the FDA has assisted in explaining the transatlantic divergence in pharmacovigilance by helping to explain the reasons why the US has adopted its adversarial approach to pharmacovigilance activities. Analysis of the role of EUPI and the EMA/NAs has assisted in explaining the transatlantic divergence in pharmacovigilance by helping to explain the reasons why the EU has adopted its collaborative approach to pharmacovigilance activities. Analysis of the role of USPI and US lawyers has assisted in explaining the transatlantic divergence in product liability by helping to explain the reasons why the US courts moved towards strict liability for design defects and then rolled back from this over time. Analysis of the role of EUPI has assisted in explaining the transatlantic divergences in product liability by helping to explain the reasons for the relatively low liability threshold and the relatively low expected damages award (potential damages cap) in the PLD.

Analysis of the role of the FDA has assisted in explaining the system divergence by helping to explain the reasons why the US has not adopted federal preemption of State product liability claims. Similarly, analysis of the role of EUPI and EU lawyers has assisted in explaining the system divergence by helping to explain why the EU adopted the PLD instead of relying entirely upon licensing and pharmacovigilance.

3.5 Conclusions

In this Chapter I began by explaining what pharmacovigilance and product liability are, and I set out the transatlantic divergence between the US and the EU approaches to both these regulatory techniques. I then assessed these regulatory positions using public interest theory, concluding that neither is well justified on this basis. This allowed me to develop the SPI system against which I contrasted both the US and EU systems of [pharmacovigilance + product liability], identifying that the two jurisdictions diverge from the SPI approach in a uniform way: the system divergence. Finally, I moved to consider the relevant groups, organisations, and institutions which may have influenced the development of these regulatory positions. I found that private interest theory and institutional analysis helps to explain both the transatlantic divergence and the system divergence to some extent. Further explanation is sought in Chapter Six, from cultural theory, for a variable which consistently explains both the private interest and institutional factors, and which remains consistent in relation to each jurisdiction, respectively, across both divergences here and all divergences considered in this work.

Chapter Four: Sale Classification and Generic Substitution

4.1 Introduction

> *"The Defendants… Boots Cash Chemists… have recently introduced what is called a self-service system… one can see a number of articles such as toilet articles, laxatives, ointments and tonics… The customer when he comes in is invited to take a receptacle and goes round and can choose the articles which he wants. He then goes to one of two desks at the end of the room, and there, admittedly, there is a registered pharmacist …"*
>
> *Pharmaceutical Society of Great Britain v Boots Cash Chemists Ltd.*[1]

A curiosity to Lord Justice Somervell in 1953, *"what is called a self-service system"* proved popular with customers, and Boots[2] later became one of the largest retail pharmacy operations in the world.

Self-service threatened to cut out pharmacists, however, and pharmacists were not happy. The Pharmaceutical Society of Great Britain argued that this retail model contravened sale classification regulation found in the Pharmacy and Poisons Act 1933, which required the supervision of a registered pharmacist for the sale of certain products. The pharmaceutical society argued that a sale contract is formed when the customer puts the item in a basket on the shop floor, and not at the cash register where the pharmacist stands. The Court of Appeal disagreed. It held that the customer makes the offer at the cash register, which is accepted by the taking of payment, and at this point only is a contract formed. It is for this point of law that this case is found on page one of every English contract law textbook.

Some decades ago, the pharmacy *profession*, and *retail* pharmacy, were the same thing. The facts of *Pharmaceutical Society of Great Britain v Boots* show how these interest groups, and their objectives, began to diverge from the middle of the 20th Century. Professional pharmacists had an interest in maintaining their role as advisers and status as experts in pharmaceutical products. Large retail pharmacy became more concerned with maximising its revenues from sale of *"laxatives, ointments and tonics...(etc)."* The two regulatory divergences considered in this chapter are tied together by this theme. I conclude that differences in the relative strength and composition of these interest groups helps to explain the transatlantic divergences in sale classification and generic substitution, but does not do so fully. In Chapter Six I argue that underlying culture provides further explanation via the intermediation of the behaviour of these groups plus relevant organisations and jurisdiction-wide institutions. This Chapter therefore frames the problem of regulatory divergence in sale classification and generic substitution in preparation for the application of cultural theory in Chapter Six.

1 [1953] 1 QB 401 LJ Somervell at 401

2 Now Walgreens Boots Alliance Ltd https://www.walgreensbootsalliance.com/

I begin in Section 4.2 by setting out the divergences: both transatlantic and intra-European Union (EU). Then, in Section 4.3 I evaluate the regulatory positions against the benchmark of public interest theory. In Section 4.4, I adopt a private interest perspective, turning to pharmacists and other relevant interest groups, organisations, and finally the relevance of institutions, to seek further explanation.

4.2 Sale Classification and Generic Substitution

In this Section I begin by giving an overview of what is meant by 'sale classification', 'nicotine replacement products' ('NRPs'), 'herbal remedies' and 'generic substitution'. I then turn to describe the regulatory approaches taken to each in the United States (US) and the EU/EU Member States (EUMS) with a focus on a sample of 14 of the EUMS. I conclude that within the EU there is divergence between a cluster of northern EUMS (the 'NEUMS Cluster') and a cluster of southern EUMS (the 'SEUMS Cluster') as well as between the EU as a whole, and the US. I summarise the regulatory divergences before turning to analyse them using the public interest theory of regulation.

Sale Classification: General

Sale classification is a part of 'selling regulation', which takes effect in between the point at which the pharmaceutical product is placed on the market, and the point at which it is consumed. Aspects of regulation occupying the same space include: mandatory prescriptions, requirements that a product be sold only with specific labelling, and restrictions upon where and by whom the product may be sold. It is the final one of these which I focus on here. Across the EU, the EUMS and the US, there are three potential categories for sale classification and the regulatory agency in each case will decide[3] which of these applies to the product. The first is 'prescription only' (PO). In this case, the product may only be sold in a pharmacy, and only where the consumer presents a prescription written by a doctor. Products placed in the other two categories do not require a prescription.[4] In the first, the product may only be sold under the supervision of a pharmacist: this is called the 'pharmacist supervision only' (PSO) category. In the second, the product may be sold anywhere and without the supervision of a pharmacist. This is called the 'general sale' (GSALE) category.[5] In both cases PSO and GSALE, as with the PO category, the product will still need a license from the regulator for market access. This means that there is a fourth category: 'unlicensed' (U). In this case the product may be sold anywhere, without a prescription and without supervision from a pharmacist.[6]

3 At the time of market access licensing.

4 Non-prescription products are sometimes referred to as 'over the counter', or 'off-prescription' products but normally in this Chapter I will use the terminology set out in Table 32 below.

5 Products in the GSALE category are still pharmaceutical products and thus usually have mandatory labelling.

6 And usually without labelling mandated by a pharmaceuticals regulator, although labelling requirements may be imposed by another regulator e.g. a food safety authority, or a consumer protection authority. Often, in addition, manufacturers may wish to label the product with some information or warnings to avoid tort liability.

The most restrictive form of sale classification regulation is therefore PO, followed by PSO, GSALE, and then U.

Table 32 Sale Classification Categories

Sale Classification Category	Regulation
Prescription Only (PO)	Sale only in pharmacy by pharmacist with prescription from doctor (most restrictive)
Pharmacist Supervision Only (PSO)	Sale only in pharmacy by pharmacist but no prescription from doctor required
General Sale (GSALE)	Sale in any retail outlet with no need for pharmacist supervision or doctor prescription
Unlicensed (U)	Not a pharmaceutical product. Sale anywhere (least restrictive)

The differences are set out in Table 32 above.[7] Whilst an initial category of sale classification is designated with the grant of a license, products may change sale classification categories as more information becomes known about the product and its safety. Usually this will be a move downwards from a more restrictive category to a less restrictive one, but occasionally the move will be in the opposite direction. I refer to this movement process here as 'switching'.[8] Both initial sale classification categories, and switching, are issues discussed in this Chapter under the heading 'Sale Classification: General.'

Sale Classification: Nicotine Replacement Products and Herbal Remedies

As well as considering sale classification generally, I analyse two case studies of specific products. These are two sets of products: NRPs and herbal remedies.[9] These products are or have been regulated for sale classification slightly differently in the US and the EU/EUMS. In the case of NRPs, here I mean specifically 2mg and 4mg nicotine gum and 7mg, 14mg and

7 As one moves from the most restrictive to the least restrictive form of sale classification regulation, the amount of information mandated on the product label will decrease. PO products will not require much information because the doctor prescribing the product has matched the consumer to the product and monitors his/her use. The consumer thus has no need for the information directly. For PSO products, the pharmacist is available to advise the patient at the point of sale. Some direct information provision (through labelling) is needed as the pharmacist will not have detailed knowledge of the consumer's medical history, nor the medical expertise of the doctor. Monitoring is not ensured where there is no prescription and thus the consumer requires some information to assist with self-administration. In the case of GSALE products, one can expect the most information to be provided on the label as the consumer will self-administer the product without pharmacist or doctor expert guidance, nor doctor monitoring.

8 Not to be confused with 'substituting' which I use to refer to generic substitution.

9 The latter are sometimes called 'herbal medicines' or 'botanical medicines' but I try to refer to them here as 'herbal remedies' unless I am speaking about a jurisdiction which legally permits them to be sold as 'medicines'.

21mg nicotine patches. These are shown below in Figure 7[10] with gum on the left and patches on the right.

***Figure 7* 4mg and 2mg Nicotine Gum and 7mg, 14mg and 21mg Nicotine Patches**

NRPs release nicotine into the body. Nicotine is a substance which - according to medical experts - is moderately harmful to the human body, but only if consumed in large quantities[11] which the products shown in Figure 7 do not deliver, even when used constantly. Nicotine consumption can lead to nicotine dependence, but for the body to become dependent, the route of administration for nicotine must normally be fast and direct e.g., by injection (or, to a lesser extent, inhalation through cigarette smoking).[12] The route of administration for NRPs is through the lining of the mouth (gum) or through the skin (patches). The delivery of nicotine from NRPs takes place slowly, over 12 or 24 hours. NRPs are thus agreed by medical experts to pose a low risk of harm and a low risk of dependence.[13] Compared to cigarette or other forms of smoking both risks (harm and dependence) are low. The beneficial effect of NRPs is that they make the user less likely to experience withdrawal symptoms from nicotine if they were or are tobacco smokers. Those withdrawal symptoms include irritability, hunger, and headaches, and they are known to be the reason why smokers find it difficult to stop or reduce smoking.

The second case study is herbal remedies. These products come from botanical sources. They are unprocessed (non-synthesised) substances which often have a history of traditional use within certain communities. The products which I refer to specifically here have not been and generally cannot be licensed *fully* as medicinal pharmaceutical products in either the EU or the US because they will not pass standards of efficacy required by randomised controlled

10 Images taken from Google search. Nicotinell ® is a branded product from GlaxoSmithKline. Other brands include Niquitin ® and Nicorette ® from Johnson & Johnson (EU) and GlaxosmithKline (US), NiQuitin ® GlaxoSmithKline and Nicoderm ® GlaxoSmithKline.

11 Mishra, A., Chaturvedi, P., Datta, S., Sinukumar, S., Joshi, P., & Garg, A. (2015). Harmful effects of nicotine. Indian journal of medical and paediatric oncology: official journal of Indian Society of Medical & Paediatric Oncology, 36(1), 24–31. https://doi.org/10.4103/0971-5851.151771.

12 See McNeill, Ann, Anne Hendrie, and WHO. "Regulation of nicotine replacement therapies: an expert consensus." (2001).

13 See McNeill, Ann, Jonathan Foulds, and Clive Bates. "Regulation of nicotine replacement therapies (NRT): a critique of current practice." Addiction 96, no. 12 (2001): 1757-1768.

(clinical) trials ('RCTs'). In the EU however, it is possible to register these products under a simplified procedure found in Directive 2004/24/EC [14] and thus sell them as herbal medicinal products based upon traditional use. In Figure 8[15] below on the left is shown the popular herbal remedy 'St John's Wort' in its botanical form. In the middle is the product sold as a dietary supplement, for the US market. On the right it is packaged and sold for the EU market

Figure 8 **Botanical Remedies, Herbal Remedies, and Herbal Medicines**

as a herbal medicinal product. In the third case, there are safety warnings written on the side of the packaging.

Generic Substitution

In addition to sale classification (generally), NRPs and herbal remedies, I also consider transatlantic divergence in the regulation of generic substitution. Generic substitution takes place only in the case of PO products.[16] Where the doctor has prescribed a branded ('originator') pharmaceutical product, the pharmacist dispensing the prescription is permitted or required to replace the branded originator with a product which is a generic version of the same drug. In terms of chemical composition, originators and generic products have the same effect on the human body. The differences between them relate to their branding: normally a new originator product has been developed by a pharmaceutical firm which is granted a market access license for the product. With the license, the firm is rewarded for its innovation with the grant of a period of market exclusivity (a patent) during which no other firm can put a product on the market with the same chemical composition. Generally, the firm enjoying

14 Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use.

15 Images taken from Google search.

16 'Products' here always means 'drugs' but for the purposes of consistency throughout this work I will refer to them as products.

this period of exclusivity will invest heavily in branding – including advertising[17] - the product. When the period of exclusivity ends, then other firms are free to produce products with the same chemical composition but may not copy the branding of the originator product.[18] New tests of efficacy and safety are generally not required to place these generic products on the market. For a generic product to benefit from the expedited licensing process it need only show the regulator 'bioequivalence' to the originator product.[19] The prices of originator and generic products are observed to differ significantly, with generics being cheaper than originators.[20] Table 33 lists some branded originators and their generic equivalents.[21]

Table 33 Examples of Originators and Generics

Originator Product	Bioequivalent Generic Product
Celexa®	citalopram
Coumadin®	warfarin
Prozac®	fluoxetine
Xanax®	alprazolam
Zantac®	ranitidine
Ventolin®	albuterol
Valium®	diazepam

Where I refer to generic substitution, I am referring to its practice in a retail pharmacy in the community, and not to generic substitution which may take place in hospital pharmacies.[22] Generic substitution by the pharmacist is a practice which may be 'regulated'[23] in three different ways: 1) banned, 2) permitted or, 3) mandated. In the first case the pharmacist may not substitute what the doctor has prescribed and must dispense as prescribed. In the second case the pharmacist can substitute the prescribed originator with the generic product, and in the third the pharmacist must do this. In the latter two cases, the consent of the patient –

17 By advertising this will usually mean detailing to doctors and pharmacists but can also in recent decades in the US mean direct to consumer advertising (DTCA).

18 The products put on the market by these firms may use the international non-proprietary name ('INN') of the chemical entity in question, or they may brand the product themselves in a different way to the originator i.e., a 'branded generic' product.

19 Meaning that the generic product has the same effect in the human body as a licensed originator.

20 See Grabowski, Henry G., and John M. Vernon. "Brand loyalty, entry, and price competition in pharmaceuticals after the 1984 Drug Act." The journal of law and economics 35, no. 2 (1992) at pgs. 331-350.

21 List taken from Google search.

22 For obvious reasons, generic substitution applies only to products prescribed by a doctor.

23 Here, as throughout this work, I am using 'regulation' and/or 'regulated' very broadly to include everything from forbidding the practice to mandating it. The case where 'regulation' permits the practice but attaches conditions and/or requirements to it is covered by the category: 2) permitted. The most significant conditions attached to the practice where it is permitted, is that some form of consumer consent is required, and that the doctor can veto the substitution in some way. I do not get into the more detailed minutiae, such as the maintenance of lists of products which may be substituted, and/or the specific formalities associated with a doctor veto, from jurisdiction to jurisdiction. I focus instead on the major differences between the jurisdictions in their 'regulation' of the practice.

either express or implied - is almost always required, and the doctor will normally be able to veto substitution expressly. The differences are summarised in Table 34 below.

Table 34 Mandatory, Permissive and Forbidden Generic Substitution

	Pharmacist	Prescribing Doctor	Consumer
Forbidden	…must always dispense as prescribed.	N/A	N/A
Permissive	…may switch originator for generic product.	…may veto expressly.	Implied or express consent required.
Mandatory	…must switch originator for generic product	…may veto expressly.	Implied or express consent almost always required.

The primary reason for the practice and regulation of generic substitution is cost containment in relation to healthcare budgets, whether private or public. Another reason, correspondingly, is the encouragement of competition within the market for pharmaceutical products.

4.2.1 Transatlantic Divergences

Divergences exist in the EU and the US and between the NEUMS and SEUMS Clusters in how they regulate sale classification and generic substitution. These are summarised below in Table 35.

Table 35 Key Transatlantic and NEUMS-SEUMS Divergences Sale Classification and Generic Substitution

	Sale Classification			Generic Substitution
	General	**NRPs**	**Herbal Remedies**	
US	**Two categories:** (PO) and (GSALE) **Less switching**	**Wide availability (GSALE)** **Narrow indications**	**Dietary supplements (U)** No efficacy claims or safety warnings allowed	**Permissive-express** Pharmacist discretion and express consumer consent
EU	**Three categories:** (PO), (GSALE), (PSO) **SEUMS:** (GSALE) uncommon **NEUMS:** (GSALE) common **More switching**	**Narrow availability** **SEUMS** (PSO), (PO) **NEUMS** (PSO), (GSALE) **Wide indications**	**Medicinal products TUR[24] (PSO) and (GSALE)** Limited efficacy claims allowed, and safety warnings required	**SEUMS:** More often pharmacist discretion. Less often express consumer consent. **NEUMS:** Less often pharmacist discretion. More often express consumer consent.

EUMS Sample and NEUMS and SEUMS Clusters

Space precludes a detailed analysis of all 28 former and current EUMS. I have chosen to focus on those with the largest populations, and those in west and central Europe. In this Chapter I focus on 14 EUMS together comprising more than 80% of the total population of the EU as of 2019. These are: Austria, Belgium, Denmark, Finland, France, Germany, Greece, Italy, Ireland, the Netherlands, Portugal, Spain, Sweden, and the UK.[25] Regarding the NEUMS-SEUMS divergences, I do not claim that the Clusters represent two discrete categories within which (one or the other) every sampled EUMS can be placed. Instead, I claim only a broad pattern

24 'TUR' 'Traditional Use Registration' under Directive 2004/24/EC

25 The analysis here relates to the regulatory position as they stood at the latest in late 2019 before the UK left the EU. The UK is referred to here as an EUMS, but the reader may infer 'former' EUMS.

which seems to correspond with north-south geography. The EUMS are not 'placed' in either category, but rather are 'oriented' towards one Cluster or the other.

At this stage I make an initial placement for working purposes. To do so I use geography, plus the most basic regulatory divergences in sale classification and generic substitution. For sale classification this is whether the EUMS has a GSALE category. I say the NEUMS Cluster has this, and the SEUMS Cluster does not. The second is whether[26] the pharmacist has discretion in the matter of generic substitution. I say in the NEUMS Cluster generic substitution is more often mandatory or forbidden (no discretion) and in the SEUMS Cluster it is or was more often permitted (with discretion). In Table 36 below I undertake an initial orientation of the 14 sampled EUMS based only on these two considerations. It can be observed that the placement also corresponds with geography.

Table 36 NEUMS Cluster and SEUMS Cluster Initial Placement Based on Regulatory Approaches

	GSALE Category (2009)?	**Pharmacist Discretion in Generic Substitution (2010)?**
NEUMS Cluster		
Finland	YES	NO
Sweden	YES	NO
UK	YES	NO
Ireland	YES	NO
Denmark	YES	NO
Austria	YES	NO
Germany	YES	NO
Netherlands	YES	YES
Belgium	NO	NO
Italy	NO	NO
France	NO	YES
Spain	NO	YES
Portugal	NO	YES
Greece	NO	YES
SEUMS Cluster		

The orientation in Table 36 broadly continues to hold when other aspects are considered throughout this Chapter. For example, when, in a later section I turn to consider whether the

26 As of 2009.

EUMS permit pharmacies in chain ownership, those EUMS oriented towards the SEUMS Cluster forbid this, whereas those oriented towards the NEUMS Cluster permit it.

The reason for going behind the EU as a whole and looking at the EUMS level is that in some cases, particularly in this Chapter where sale classification and generic substitution is discussed, there is greater intra-EU divergence amongst the EUMS than there is transatlantic divergence between the US and the EU. The purpose of orienting the sampled EUMS using the two Clusters as above is to assist later in Chapter Six of this work where further

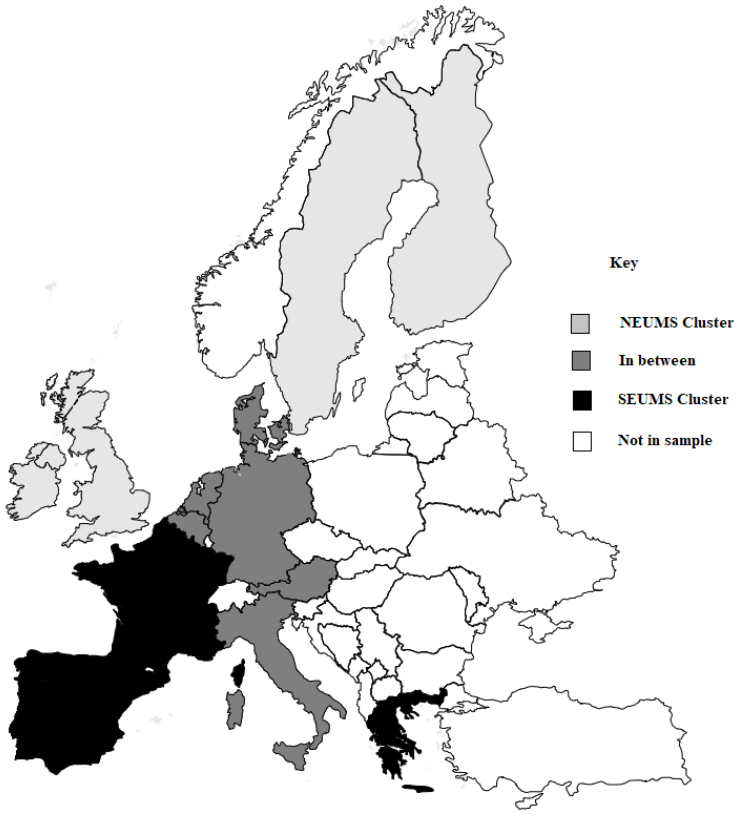

Figure 9 **Initial Placement NEUMS and SEUMS Clusters**

explanation is sought for regulatory divergence by turning to culture. It is argued in Chapter Six that there are broad cultural differences between the north and south of the EU which help to explain the intra-EU divergences. Throughout this Chapter, I refer back to the orienting Clusters to build the case that there are consistent regulatory[27] differences between the NEUMS and SEUMS Clusters. Figure 9 above shows the two Clusters on the map based just upon the considerations at this stage: the same considerations set out in Table 36 above. The shading gradient in Table 36 is also used in Figure 9**Figure 9**.

There are intra-US differences too: for generic substitution, each State sets its own rules, as does each EUMS in the EU. Thus, when discussing generic substitution below I look at the overall picture for both jurisdictions as well as at the State and EUMS level. In the US, most States adopt the same approach and therefore I take this as the position for the whole US without orienting states according to clusters. Between the EUMS there is much more variation in the regulation of generic substitution. This is one reason why it has been

27 And, later, other institutional differences.

necessary to draw attention to the NEUMS and SEUMS Clusters. In the case of sale classification generally, in the US the Food and Drug Administration (FDA) sets the sale classification category for products for all States. Therefore, I do not go beyond the Federal level when looking at sale classification generally, for NRPs or for herbal remedies. In the EU, whilst the European Medicines Agency (EMA) oversees licensing of the products to some extent, often it is National Agencies (NAs) in the EUMS which decide upon sale classification. In this case, therefore, the same approach was taken as for generic substitution: orienting the EUMS approaches using the NEUMS and SEUMS clusters for sale classification (general), for NRPs and for herbal remedies. Although in the case of herbal remedies there is EU-wide regulation which is the focus of the analysis.

4.2.2 Sale Classification General

United States

The US has only two categories of sale classification for products which require a license: GSALE,[28] and PO, plus U where a product does not require a license. Where a product is placed in the GSALE category it may be sold anywhere.[29] A pharmaceutical product will be categorised PO where "…*because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use* [it] *is not safe for use except under the supervision of a practitioner licensed by law…*".[30] PO status is preferred in the US relative to many EUMS where the PSO category is used, either instead of or in addition to GSALE. A study undertaken in 2006 showed that - of six Organisation for Economic Cooperation and Development ('OECD') countries - the US had the highest absolute number and highest proportion of products available PO. This was at about two thirds the level of the leading nation for non-prescription status (New Zealand) and lower than the two EUMS scrutinised in the study: the UK and France.[31] Another study, published in 2014[32] identified

28 General Sale is referred to by the FDA as 'Over the Counter' or 'OTC' but as there are no restrictions upon where the product may be sold, so long as the product conforms with the relevant monograph or has successfully obtained a market access license as a new drug, once it has been placed in the OTC category it may be sold anywhere. See https://www.fda.gov/drugs/questions-answers/prescription-drugs-and-over-counter-otc-drugs-questions-and-answers.

29 This, at least, is the general rule. There are minor exceptions to this on a State-by-state basis. So, for example, for certain (schedule V) substances, there exists the category: pharmacist supervision only. And in certain states – Florida is a notable example - it is possible for a Pharmacist to prescribe certain products. There are other minor exceptions. See Gilbert, Andrew, Deepa Rao, and Neil Quintrell. "A review of pharmaceutical scheduling processes in six countries and the effect on consumer access to medicines." International Journal of Pharmacy Practice 14, no. 2 (2006): 95-104 at pg. 99

30 21 U.S.C. United States Code, 2010 Edition Title 21 - FOOD AND DRUGS CHAPTER 9 - FEDERAL FOOD, DRUG, AND COSMETIC ACT SUBCHAPTER V - DRUGS AND DEVICES Part A - Drugs and Devices Sec. 353 - Exemptions and consideration for certain drugs, devices, and biological products.

31 Gilbert, Rao and Quintrell (2006) at pg. 99-100: *"NZ had the highest number of the identified medicines available without a prescription, 85, followed in descending order by Australia, UK, France, Canada and the US, which had the smallest number (53)".*

32 Gauld, Natalie J., Fiona S. Kelly, Nahoko Kurosawa, Linda JM Bryant, Lynne M. Emmerton, and Stephen A. Buetow. "Widening consumer access to medicines through switching medicines to non-prescription: a six country comparison." PLoS One 9, no. 9 (2014): e107726.

that between 2003 and 2013, the US was one of the slowest nations to switch products out of the PO category. The sample included the US, the UK, Australia, Japan, the Netherlands, and New Zealand. The authors of the study put this down to the existence in the US of a *"single open non-prescription category"* (i.e. GSALE).[33]

European Union and EU Member States

In the EU generally the sale classification category will be decided by the NAs in each EUMS, even if a license for within the EU was granted by the EMA. However, EU legislation[34] does mandate that all pharmaceutical products granted a license within the EU will be given (at least) the status of either 'prescription only' or 'non-prescription' under Directive 2001/83/EC.[35] In Article 71 of that Directive the criteria for allocation to PO status are set out: *"Medicinal products shall only be subject to medical prescription where they: - are likely to present a danger either directly, or indirectly, even when used correctly, if utilized without medical supervision, or – are frequently and to a very wide extent used incorrectly, and as a result are likely to present a direct or indirect danger to human health, or contain substances or preparations thereof, the activity and/or adverse reactions of which require further investigation..."*.[36]

Whilst guidance is given regarding PO versus non-prescription status, when it comes to non-prescription products it is up to the NAs to decide the exact sale classification category.[37] As such, between EUMS, differences can be observed in which categories are used for specific products and in the overall proportion of products placed in each category. Some EUMS insist that all non-prescription products must be sold PSO, whilst other EUMS have a GSALE category too. To illustrate this variation, take the UK and France as examples. In France – where all medicines except for aspirin must be sold only in pharmacies - there are only two categories of sale classification: PO and PSO, with all licensed products assigned to one of the relevant schedules. The least restrictive schedules (Schedule II-III) require at least that a 'licensed person' be present when the product is sold, which means either a pharmacist or a doctor.[38] Prescription products (Schedules I-II) may only be sold in a pharmacy, by a

33 In the words of Gilbert Rao and Quintrell (2006) at pg. 100, "*In countries such as the US where a 'pharmacy-only' schedule does not exist there is a greater tendency for preparations to be held in 'prescription-only' schedules.*"

34 *"Previously the relevant Directive was the Directive for medicines classification (92/26/EEC) which obliges member states to review the legal status of medicines every five years and to allow a drug to be sold without a prescription unless: it is dangerous if used other than under medical supervision; it is frequently used incorrectly; it is a new chemical entity and needs further investigation; or it is usually administered by injection."* Bradley, Colin P., and Christine Bond. "Increasing the number of drugs available over the counter: arguments for and against." Br J Gen Pract 45, no. 399 (1995): 553-556. According to Kanavos, Panos. "Overview of pharmaceutical pricing and reimbursement regulation in Europe." Japanese Pharmacology and Therapeutics 31, no. 10 (2003): 819 it was also the case that EU directives specify that a qualified pharmacist must be present when prescription medicines are dispensed, and that dispensing may only be through licensed pharmacies.

35 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use

36 Article 72 stipulates that all medical products not fitting the prescription in Article 71 shall be treated as non-prescription products These criteria for prescription only status follow from the public interest reasons stated below for the prescription system – i.e. that the product cannot be used safely by the patient/consumer his or herself, and/or that not enough is yet known about the product and thus doctor supervision and monitoring of side effects is required. It also matches in theoretical terms the criteria set out above by the FDA.

37 Kanavos (2003) at pg. 19

38 Gilbert, Rao and Quintrell (2006) at pg. 99-100 at pg. 99

pharmacist with a prescription. The most permissive category in the UK is GSALE and products placed here may be sold anywhere. In terms of the PO and PSO categories, in the UK these match the rules for France's schedule I and schedule II, respectively.[39] Thus, in a study undertaken in 2006[40] France had only one medicine from a predetermined sample available on general sale (aspirin) whilst the UK had six and France had a slightly higher number of medicines available PO: 55 to the UK's 47. Contrast this with the US which in the same study had 66 medicines available PO and 53 available on GSALE to the UK's six.[41] Either the UK or the French approach is adopted in the EUMS sampled here. It follows that throughout the EU many fewer pharmaceutical products are available on GSALE when compared to the US yet fewer are also available PO.

Table 37 Availability of Non-Prescription Products in Sampled EUMS Circa 2009

General Sale Category	No General Sale Category
Denmark	Spain
Finland	Portugal
Germany	Italy
Ireland	Greece
UK	France
Sweden	Belgium
Netherlands	
Austria	

Intra-EU scrutiny falls upon whether a GSALE category exists. Taking the 14 EUMS and looking at the year 2009, the NEUMS Cluster generally embraces a GSALE category, and the SEUMS Cluster generally requires that all non-prescription products be sold under PSO.[42] This is shown in Table 37. It should be noted that those NEUMS with a general sale category all also have a PSO category.

On switching, one study shows that the UK has historically (2003-2013) been quick to do this, and a great deal quicker than the US[43] whilst the Netherlands has been quite slow. Additional studies suggest that the switch out of PO status occurs quicker in countries where a PSO category exists, which includes most EUMS.[44] Compared to the US, therefore, a smaller proportion of products across the EU are available PO. As between those EUMS with a GSALE category and the US, many fewer non-prescription products will be available on GSALE in the EUMS and most will be in the PSO category. The PSO category draws products in from both sides, as illustrated below in Figure 10.

39 Ibid. at pg. 98
40 Ibid. at pg. 100
41 With none available under pharmacist supervision only (because that category does not exist in the US).
42 Kanavos (2003) at pg. 29
43 Gauld et al. (2014) pg. 2
44 Ibid. at pg. 3

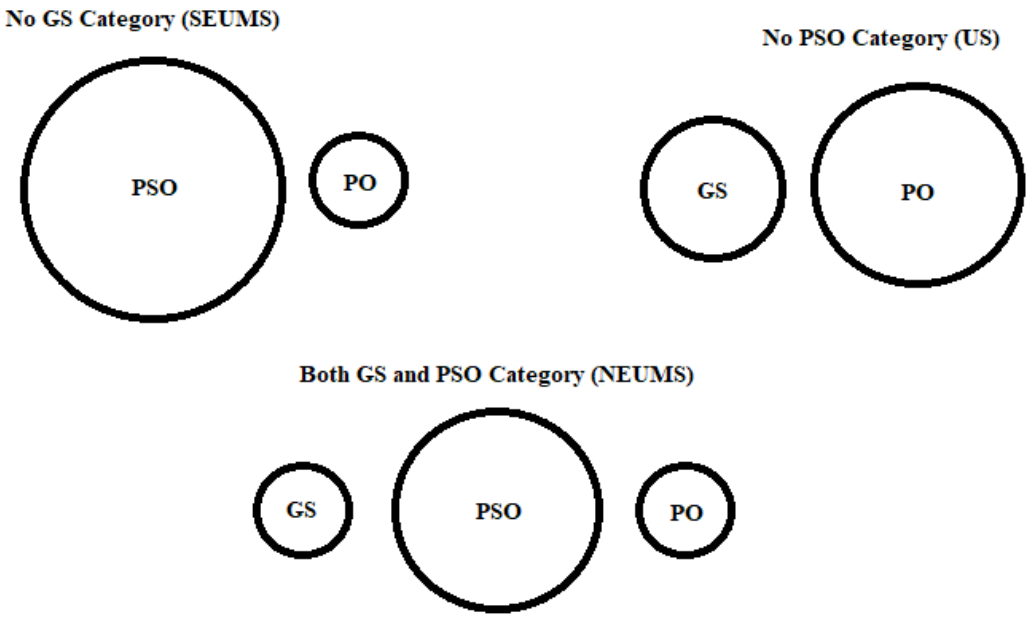

Figure 10 **Effect of PSO Category on Proportion of Products Placed**

4.2.3 Sale Classification: Nicotine Replacement Products

United States

In considering NRPs I look both at availability (sale classification category) and indications/instructions for use. The latter are tied together with the former because the licensing decision is made considering a proposed sale classification category and proposed indications/instructions for use. There are important differences between the US and the EU on both.

Availability

As of 2019 NRPs were licensed and available on GSALE in the US.[45] They were first licensed by the FDA in 1984[46] and in 1996 the FDA approved GSALE availability.[47] Both the original license grant, and the switch from PO to GSALE sale classification, occurred earlier than in many EUMS although the UK Medicines Control Agency (MCA) - its former designation before the Medicines and Healthcare Products Regulatory Agency (MHRA) was first to grant a license to these products out of all agencies in the US and EUMS.

45 World Health Organization. "WHO report on the global tobacco epidemic 2019: Offer help to quit tobacco use." (2019).
46 https://www.drugs.com/monograph/nicotine.html
47 https:// www.fda.gov/ drugs/ drug-information-consumers/ now-available-without-prescription and https:// www.fda.gov/consumers/consumer-updates/want-quit-smoking-fda-approved-products-can-help

Indications/Instructions for Use

Draft guidance to industry published by the FDA in 2019[48] states that NRPs may be developed for certain chronic indications.[49] An indication is a valid reason for using a pharmaceutical product. To make certain claims regarding the product, the firm marketing that product must first gain approval for that indication.[50] The indications listed in the 2019 document are: a) *"smoking cessation"*, and b) *"reduction in risk of relapse"*.[51] According to the guidance, once a product has fulfilled the criteria for these indications - and only then – approval can also be sought for further indications: c) *"reduction of urge to smoke and relief of cue-induced craving in former smokers"*, and d) *"relief of withdrawal symptoms not associated with a cessation attempt."* Both indications c) and d) open the possibility of NRPs being marketed for use by current non-smokers who wish to stay non-smokers, even where their purchase of NRPs is not associated with a new attempt to quit nor (necessarily) with maintaining one. Indication d) suggests that one might use NRPs where one has no intention to quit yet cannot smoke temporarily for whatever reason, such as when taking a long flight.[52]

Up until 2019 the marketing of NRPs for the purposes of temporary quit attempts has not been possible in the US. This is different to the position that has been taken for NRPs by the NAs in the EUMS. The FDA seems more concerned with the addictive potential of NRPs. For example, in the US, after the switch to GSALE occurred, the FDA required a lengthy period of monitoring of abuse and dependence, which was not the case in the UK after the regulator[53] switched NRPs to GSALE.[54]

The differences between the UK and US approaches are illuminating. Doctors and medical experts in the US have long accepted tobacco smoking itself as a disease and thus the FDA accepted *"smoking cessation"* as an indication from an early stage.[55] By contrast, the UK regulator opted for the indication: *"control of withdrawal symptoms during a cessation attempt"*. The effect of this was that the focus was shifted away from smoking abstinence. Thus, whereas in the US the duration of use of the product was strictly limited in its approved instructions for use: e.g., a product granted a license would have to show that it improved chances of four weeks of smoking abstinence starting two weeks after the 'quit date',[56] in the

48 Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products Guidance for Industry https://www.fda.gov/media/121308/download

49 An indication is a valid reason to use a certain product. There can be multiple indications to use a procedure or medication (Wikipedia).

50 That usually occurs in the licensing process though it may later be changed.

51 I.e., to maintain abstinence from smoking after initially breaking the habit.

52 The guidance is clear that indications c) and d) could not be granted on a standalone basis without indications a) and/or b): Smoking Cessation and Related Indications: Developing Nicotine Replacement Therapy Drug Products Guidance for Industry at pg. 8 (emphasis added): *"Additionally, a sponsor that can demonstrate, as a* ***secondary*** *endpoint, that the drug product provides relief of withdrawal symptoms in smokers who are not trying to quit smoking, may be able to include labeling instructions to cover situations in which such individuals are required to abstain and experience withdrawal (e.g., while traveling on an airplane)…* ***FDA does not envision that relief of withdrawal symptoms would be granted as a stand-alone indication for an NRT drug product that has not been shown to be effective as an aid to smoking cessation…"***

53 West, Robert. "Addressing regulatory barriers to licensing nicotine products for smoking reduction." Addiction 95, no. 1s1 (2000): 29-34 at pg. 30.

54 In the UK the switch was made in 1999.

55 West (2000) at pg. 31

56 Ibid.

UK this was not the case. Here, on the product label and insert there was less focus on 'smoke-free time' and more focus placed upon alleviation of the physical effects of nicotine cessation. This was different to the US, where the regulator's view of smoking, nicotine and NRPs is or was based upon an assumption that one should quit completely in the long term, with short-term quit attempts and long-term use of the products implicitly discouraged.[57]

European Union and EU Member States

Availability

The first NRP – Nicorette® gum - was developed in Sweden but initially refused a license by the Swedish Medical Products Agency (MPA) which – like the UK MCA in 1980 - considered smoking itself not to be a disease but a lifestyle choice.[58] The UK agency circumvented that issue by focusing on control of withdrawal symptoms, which were accepted to be a disease. This NRP was registered in Switzerland (1978) and the UK (1980) before licensing in the US in 1984. By contrast (here and discussed fully below) whilst NRPs were a little slow to reach the US market, the US has been quick to switch them to GSALE (out of PO) relative to the EUMS. Whilst in the US NRPs were available on GSALE from 1996, in some EUMS even in 2004 nicotine patches were available only PO.

Table 38 Sale Classification of Nicotine Patches in US and Sampled EUMS 2004 to 2019

2004 (Nicotine Patches)			2019 (Nicotine Gum and Patches)		
GSALE	**PSO**	**PO**	**GSALE**	**PSO**	**PO**
US (1996)	Austria	Greece	US (1996)	Germany	Portugal
	Belgium	France	Finland	Netherlands	
	Denmark	Portugal	UK	France	
	Finland		Ireland	Spain	
	Germany		Sweden	Italy	
	Ireland			Denmark	
	Italy			Belgium	
	Netherlands			Austria	
	Spain			Greece	
	Sweden				
	UK				

57 I call this here the 'abstinence approach'. Having adopted the abstinence approach upon originally licensing NRPs, the US has in 2019 partially embraced a different view, where long term use is considered acceptable based on a secondary indication only: see above.

58 Kalkhoff, Will; Thye, Shane R.; Lawler, Edward J. (2012). "The Birth of Medicinal Nicotine". Critical Perspectives on Addiction (1st ed.). Emerald Group Publishing. p. 79. ISBN 978-1780529318.

Even in those EUMS where the patches had been switched to non-prescription status, they were still available only PSO, as shown in Table 38 above. Even once switched out of PO, consumer access to NRPs in the EUMS was still often restricted through use of the PSO category. The picture in 2019 is also shown – this time for all NRPs including both patches and gum. EUMS where a GSALE category exists have in some cases moved NRPs to GSALE between 2004 and 2019. The exceptions are Germany, Denmark, and Austria.

Indications/Instructions for Use

I set out the possible 'types' of use of NRPs which are disclosed by indications/instructions for use in Table 39 below.[59] By 'type of use' which is permitted by the approved indications and instructions, I am referring to what producers are permitted to print on the label and packaging of the product.

Table 39 Possible Types of Use and Corresponding Indications/Use Instructions for NRPs

Table Adapted from West (2000) at pg. 32

Type of Use	Description
1) Temporary after 'quit date'	Temporary use of NRPs and only to assist in a permanent quit attempt. Duration of use limited to a few weeks after the quit date.
2) Temporary but no 'quit date'	Temporary use of NRPs but for only temporary abstinence from smoking. E.g., on a long flight or a period spent in hospital.
3) Long-Term (after 'quit date')	Long-term use of NRPs to maintain smoking abstinence. May be used for as long as the consumer feels necessary (possibly even for the remainder of life) or may be used sporadically at times where the consumer feels at risk of smoking relapse.
4) Concurrent (with smoking)	Short- or long-term use of NRPs to help reduce tobacco smoking. There is no intended period of abstinence from smoking. May be used simultaneously – e.g. 7mg patch worn every day with the effect that smoker goes from smoking 40 cigarettes per day to only 15.

In the US, despite making NRPs available on GSALE as early as 1996, the adopted indications, taken together with the instructions for use which limited the duration of use to six weeks after the 'quit date',[60] supported only type 1) use. It was not until 2019 that secondary indications have been proposed which seem to support type 2) and 3) use to some extent, whilst type 4) use does not seem supported at all in the US. The indication originally adopted in the UK – *"control of withdrawal symptoms"* –supports both type 1) and type 2) use whilst not expressly supporting type 3) use due to the further reference in the UK indication to, *"associated with a… cessation attempt"*.

Other EUMS had adopted the indication: *"treatment of nicotine dependence"*[61] as of 2000. This indication, as with the UK indication, opens the possibility of both type 1) and type 2)

59 Adapted from West (2000) at pg. 32.
60 This was the language of the instructions: "4 weeks of smoking abstinence starting 2 weeks after the quit date" West (2000) at pg. 30.
61 West (2000 at pg. 30.

use, and this was the case much earlier than in the US. Moreover, as early as 2000, Denmark supported type 4) use, albeit only as a prelude to a quit attempt.[62] In 2001 NRPs were being approved in EUMS and other European countries for temporary quit attempts of type 2) above: in Austria, France, and Norway[63] and were being provided free of charge in hospitals in France to smokers for type 2) use. In terms of type 4) use – Austria and Belgium followed the Danish approach of permitting marketing with concurrent use instructions by 2001.[64] On type 3) use, in 2001 Germany adopted a flexible approach[65] with the weeks-long duration for use stated to be a recommendation only, and longer-term use permitted *"where appropriate"*.[66] The differences between the US and the various EUMS are summarised in Table 40 below.[67]

Table 40 US v EUMS Permitted Types of Use for NRPs According to Indications/Instructions

Type of Use Permitted	US	EU
1. Temporary after 'quit date'	1996	UK: 1999. FR/AUT/DE/BE: by 2001
2. Temporary but no 'quit date'	Proposed 2019	UK: 1999. FRA/AUT: by 2001
3. Long-Term (after 'quit date')	Proposed 2019	DE: by 2001
4. Concurrent (with smoking)	Not permitted	DK/AUT/BE: by 2001

Conclusion

The US makes NRPs widely available on GSALE and did so early relative to the EU/EUMS. Yet, the US is and was more restrictive in terms of indication/instructions for use, effectively limiting these products to type 1) use only until recently. Within the EU/EUMS the availability of these products depends in part upon whether a GSALE category exists. Thus, in some countries - particularly those oriented towards the NEUMS Cluster - NRPs are available on GSALE. In other countries - particularly those oriented towards the SEUMS Cluster - they are available PSO. A small handful of countries which have a GSALE category nevertheless classify

62 Ibid.

63 McNeill, Ann, Anne Hendrie, and World Health Organization. "Regulation of nicotine replacement therapies: an expert consensus." (2001) at pg. 18

64 But again only as a prelude to a quit attempt McNeill (2001) at pg. 18

65 In the summary of product characteristics and instructions for use.

66 The approaches here mirror expert consensus on NRP use versus cigarette smoking. The WHO recommended in 2001, it its paper "Regulation of Nicotine Therapies: an Expert Consensus": at *"9. Regulators should withdraw strong warnings against NRT use and concomitant smoking"* at *"10. Regulators should enable package labelling to be changed to allow smokers to continue to use NR(Ps) after the recommended treatment period if they feel it would help them stay off tobacco. The potential health risks of longer-term use are far less than those associated with resuming smoking"* and at *"8. Regulators should consider allowing NRT use by smokers during periods of temporary abstinence from smoking when the smoker has no choice but to remain in the smoke-free environment (such as in hospital or aeroplanes). In such circumstances, NRT would be used as a treatment for the withdrawal syndrome resulting from compliance with smoke-free policies."* McNeill (2001) at pg. 19.

67 Table 40 is not an exhaustive list and does not show the full current picture across the EU. It is intended to highlight only the difference in timing between the EUMS and the US in relaxing instructions for use and indication to incorporate more types of use for NRPs.

NRPs as PSO. The NAs in various EUMS were quicker than the FDA in the US to accept indications which permitted type 2), 3) and 4) uses.[68]

4.2.4 Sale Classification: Herbal Remedies

United States

In 2002 a survey indicated that 18.6% of US adults use traditional herbal remedies, rising to 33% in 2010.[69] Relative to the EUMS (particularly Germany) and China, there is little demand for herbal remedies in the US. In Germany as of 2010 the figure was 65%[70] and in China, 30%-50% of all 'medicines' consumed were herbal.[71] What sets the US apart from China and the EU is that herbal remedies are not considered to be 'medicine' in the eyes of the FDA or consumers. In terms of sale classification category, herbal remedies are within the U category for the US.

Under the Food Drug and Cosmetics Act 1938 (FDCA 1938) herbal remedies were previously capable of being regulated as foods or food additives,[72] subjecting them to some safety oversight by the FDA but no licensing requirements.[73] Herbal remedies could not meet the efficacy standards required by the licensing system for 'drugs' where the benchmark is set by synthetic products developed in laboratories. So, herbal remedies were instead usually sold as food additives.[74] Under the FDCA 1938 there were certain labelling requirements for food additives, and these provisions led to disputes between the FDA and marketers of food additives and herbal remedies. These disputes led to the passage of Dietary Supplement Health and Education Act 1994 ('DSHEA 1994') under which now most herbal remedies are regulated in the US as dietary supplements and the sale classification category is U.[75]

Under DSHEA 1994 there is no licensing requirement for dietary supplements but: 1) the marketer of dietary supplements containing any new ingredient is required to notify the FDA 75 days before these are marketed, and 2) the label on the product must disclaim: *"These*

68 Medical experts and the WHO – whilst advocating smoking cessation – do not share the US approach to use of NRPs but rather share that adopted in many EUMS. Yet medical experts would support the availability of NRPs on a much wider basis than found in the EU.

69 Liu, Frank Xiaoqing, and J. Warren Salmon. "Herbal medicine regulation in China, Germany, and the United States." Integrative Medicine 9, no. 5 (2010): 54-61 at pg. 55.

70 Users of natural remedies of which herbal remedies are a large part: Liu and Salmon (2010) at pg. 54.

71 Liu and Salmon (2010) at pg. 54

72 Cataxinos, Edgar R. "Regulation of Herbal Medications in the United States: Germany Provides a Model for Reform." Utah L. Rev. (1995): 561 at 561.

73 It was always difficult to classify and regulate herbal remedies as 'drugs' under the FDCA as this requires a broad interpretation to be given to this term in the FDCA. Generally the FDA could only claim to regulate such products as drugs if the product – through its labelling, advertising etc. – seemed to be marketed with the intention that it was *"intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease…"* FDCA section 201 (g) However, given that herbal remedies, if presented as drugs (with that intention) on the market would face licensing requirements and the need to present evidence of efficacy to the FDA this was rarely the case.

74 Section 201 (ff) FDCA any substance *"supplying a vitamin, mineral, or other ingredient for use by man to supplement his diet by increasing the total dietary intake."*

75 Liu and Salmon (2010) at pg. 55.

statements [on the label] *have not been evaluated by the FDA. The product is not intended to diagnose, treat, cure, or prevent any disease"*.[76] There are no FDA monographs[77] for dietary supplements as are required for all licensed non-prescription pharmaceutical products. The focus of the US regulation of dietary supplements is upon avoiding misleading claims of efficacy being made about the products.[78] Safety of dietary supplements need not be proven before these products are marketed.[79] If the putative marketer of herbal remedy wishes to be able to market it as a herbal medicine which can carry claims of efficacy then the marketer must seek a license as a pharmaceutical product through making a new drug application to the FDA. In doing so, they will be fully required to establish efficacy and safety. In 2004 the FDA issued a document: *"Guidance for Industry Botanical Drug Products"*[80] which sets out some limited special guidance to assist in seeking licensing approval of herbal remedies through the New Drug Application (NDA) process.[81] In 2016 this guidance was updated to cater also for an NDA for proposed herbal medicines with less serious indications which would be sold GSALE. This guidance is not a new regime specific to herbal products in the same way as the regulation found in the EU even if significant efforts have been made by the FDA to make allowance in the NDA process for the unique characteristics[82] of herbal remedies. Subsequently, many herbal remedy products in the US will remain marketed as dietary supplements and regulated under DSHEA 1994.

European Union and EU Member States

Prior to EU Directives and Regulations in 2001 and 2004, herbal remedies had been regulated for many years under national legislation.[83] Germany, has had the most detailed independent

76 Ibid. at pg. 58

77 Monographs are a detailed written scientific record of everything known about a pharmaceutical product.

78 Liu and Salmon (2010) at pg. 58.

79 Starr, Ranjani R. "Too little, too late: ineffective regulation of dietary supplements in the United States." American journal of public health 105, no. 3 (2015): 478-485.

80 https://www.fda.gov/files/drugs/published/Botanical-Drug-Development--Guidance-for-Industry.pdf updated in 2016.

81 At this stage the special guidance related to proposed herbal medicines for serious indications (sold PO). In 2006 the first herbal remedy was approved as a herbal medicine (a licensed product) by the FDA. Whilst the 2004 guidance - as updated in 2016 - brought the US more in to line with the German (and from 2004, European) position, for most of history and for much longer than was the case in several EUMS, herbal remedies in the US were consigned to the U category and sold as dietary supplements. If they made claims of efficacy they would often be forced off the market by the FDA. Even now, since the 2004 and 2016 guidance the bar of efficacy is set very high for herbal products which are wished to be sold as licensed herbal 'medicines'and are thus permitted to make claims of efficacy about the product for treatment of diseases and conditions. Liu and Salmon (2010) at pg. 58.

82 I.e. the difficulty in isolating the key active ingredient, and the difficulty of proving consistency of effectiveness over batch quality even where the herbal remedy has been in use for a long time and seems to be generally accepted by people as effective.

83 In the UK the market for herbal remedies was almost completely unregulated prior to the 2001/2004 Directives with a study from 2011 showing that many herbal remedies lacked key safety information: Raynor, David K., Rebecca Dickinson, Peter Knapp, Andrew F. Long, and Donald J. Nicolson. "Buyer beware? Does the information provided with herbal products available over the counter enable safe use?." BMC medicine 9, no. 1 (2011) at pg. 94. In the Netherlands herbal remedies were sometimes marketed as food supplements and sometimes as homeopathic medicines: Anquez-Traxler, Christelle. "The legal and regulatory framework of herbal medicinal products in the European Union: a focus on the traditional herbal medicines category." Drug information journal

system of regulation for herbal remedies throughout the 20th century.[84] It defined herbal remedies as medicinal products under the Medicines Act of 1976. To undertake the task of regulating herbal remedies the Bundesgesunheitsamt ('BSG') created a special committee: Commission E, which contained a range of experts from medicine, pharmacy, toxicology, and representatives from the pharmaceutical industry. Up to 2010 the Commission has published 380 monographs covering 360 plant species.[85] Prior to the Commission E procedure herbal medicinal products were widely demanded and used in Germany, a situation which can be traced back to an Imperial Decree of 1901 permitting certain botanical products to be sold outside of pharmacies.[86] Commission E evaluates the safety and efficacy of herbal medicines using the same principles as the general licensing committee of the BSG for other medicines save for one key difference.[87] There is an additional way for a product to evidence efficacy. Commission E accepts evidence of traditional use as *supplementary* to experimental data. The Commission E system therefore partially 'grandfathers' certain herbal remedies.

EU-Wide Approach

The Commission E system served as the model for an EU-wide approach adopted in the following decades. At the EU level there now stand two relevant Directives. First Directive 2001/83/EC[88] under which herbal medicines can be authorized in the conventional way but employing *"well-established use"* as the legal basis for efficacy, and making use of

45, no. 1 (2011): 15-23 at pg. 15. In France traditional use was regulated to some extent in Cahier. No. 3 of the *Agence francaise de securite sanitaire des produits de sante*. In Austria, there existed a list of herbal remedies and associated excipients which constituted a 'traditional' status: Hooyenga, Pieter A., Renger F. Witkamp, and Kees Groen. "Herbal products: Marketing strategies and legislation." International Journal of Green Pharmacy (IJGP) 3, no. 4 (2009) at pg. 271. In Belgium, a simplified registration procedure was floated as early as 1994. In Sweden, the concept of a natural remedy was determined to mean a medicinal product in which the active ingredients derive from natural sources that have not been processed too highly and consist of part of a plant or animal, bacterial culture, mineral, salt, or salt solution: Hooyenga, Witkamp and Groen (2009) at pg. 271.

84 Compared to the US, in the EU the production and development of herbal remedies has flourished, particularly in Germany where much research into herbal remedies is sponsored by pharmaceutical companies or carried out under grants by universities. Germany has the largest market in the EU for herbal remedies – worth 3.5 billion USD in 1996. According to studies undertaken in the 1990s 70% of German doctors prescribed herbal remedies and until 2004 herbal remedies were reimbursed under German social health insurance. Cataxinos (1995) at pg. 561. Liu and Salmon (2010) at pg. 54. The high demand for herbal remedies from consumers and the medical industry in Germany has been the driver behind the development of these products and the regulatory system described below has contributed a great deal to the wide availability and popularity of these products within Germany Important because demand for product has driven regulation and existence of regulation has driven demand. Cataxinos (1995) at pg. 561.

85 Liu and Salmon (2010) at pg. 57.

86 The reason for the introduction of these herbal medicines provisions in 1976 was expert disagreement over the safety and efficacy of herbal remedies. Commission E monographs have presented a way of providing consumers with a definitive scientific consensus on questions of safety and efficacy. The reason why there was such expert disagreement over safety and efficacy is arguable due to the nature of the products themselves. And this lies for the same reason as in the US for so long herbal medicines were frozen out by the NDA procedure (due to the stringent requirements of RCTs), that is: efficacy in the case of herbal remedies means something quite different to efficacy in the case of synthetic medicines. Yet, it is not true to say that one is effective and the other is not. Cataxinos (1995) at pg. 561.

87 Accordingly *"the process has been described as requiring "reasonable certainty" rather than "absolute proof" of safety and efficacy – which is what is required by the US FDA in relation to new drug applications."* Cataxinos (1995) at pg. 561.

88 Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

bibliographic data to support claims of efficacy.[89] The second and more significant is Directive 2004/24/EC[90] under which these can be authorized based on *"traditional use".* The 2004 Directive substitutes the conventional requirement of RCT data with evidence of traditional use.[9192] Unlike the 2001 Directive it effectively dispenses with the need for clinical trial data altogether, at least for the purposes of proving efficacy.[93] In doing so it goes further than the German approach under Commission E and much further than the FDA approach introduced by the 2004/2016 guidance in the USA. The 2004 Directive establishes 'Traditional Use Registration' ('TUR'). In order to obtain TUR a herbal medicine must show proof of 30 years of safe use, at least 15 years of which must be within the EU.[94] These periods may be *"substantiated with references to sales information, textbooks, expert reports of pharmacists, herbal experts and medicals or historically used national pharmacopoeias."*[95] This efficacy standard diverges very substantially from the *"absolute proof"* of efficacy required by the FDA on an NDA in the US.[96]

The 2004 Directive led to many products previously marketed within the EU as food additives or dietary supplements being licensed as TUR herbal medicines. The 2004 Directive permitted the registration of such products in all member states.[97] TUR herbal medicines may only be given the non-prescription sale classifications of GSALE or PSO.[98] Limited efficacy claims for TUR herbal medicines are permitted in the following form: *"Traditional herbal medicine for use in … [indication]…, exclusively based on long standing use."*[99] Whilst a TUR product under the 2004 Directive will only be able to gain this registration if it is proposed to treat an indication which is mild and thus the product will not be a prescription product, it is for the NAs in each EUMS to decide the final sale classification category.

Those products which cannot satisfy the requirements set out in the 2004 Directive (30 years of documented traditional use with 15 in the EU), must seek full market authorisation through

89 However, that bibliographic data – as with the 1976 German Medicines Act – was not dispositive, only probative, and clinical trials data would also be required to receive a license.

90 Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use

91 Liu and Salmon (2010) at pg. 57.

92 The effect of the 2004 Directive is also that Commission E monographs produced under the German system prior to 2004 now stand as a basis for the 2004 established Herbal Medicinal Products Committee to produce EU level monographs for herbal medicinal products/herbal remedies. See Liu and Salmon (2010) at pg. 57.

93 To be eligible for this registration, the following criteria must be met: The manufacturer should demonstrate product quality by complying with the principles of Good Manufacturing Practices, it should demonstrate product safety by providing bibliographic data, and it should demonstrate product efficacy by providing evidence of at least 30 years of traditional medicinal use, including at least 15 years in the EU.

94 Liu and Salmon (2010) at pg. 58.

95 Hooyenga, Witkamp and Groen (2009)

96 Ibid. at pg. 271.

97 Hooyenga, Witkamp and Groen (2009) at pg. 271.

98 Ibid.

99 The 2004 Directive also created the Herbal Medicinal Product Committee of the EMA which produces, 'Community monographs' for herbal medicines, often based upon earlier German Commission E monographs. This should assist and has assisted in ensuring some consistency between EUMS as to how sale classification is determined in each. Anquez-Traxler (2011) at pg. 17.

the 2001 Directive procedure under Article 10 of that Directive.[100] Herbal remedies which cannot gain TUR under the 2004 Directive or the more stringent 2001 Directive procedure[101] will likely be regulated in the EU as food supplements – as is usually the case in the US. Those products cannot make efficacy claims, as set out in Directive and Regulation 2002/46[102] and 1924/2006[103] and they are regulated by the European Food Safety Authority.

Conclusion

The crucial difference between the jurisdictions is that in the EU herbal remedies are sometimes accepted as 'effective' even where they would not be considered effective according to the RCT standard which is applied to synthetic products.[104] This different standard has been made possible by giving herbal remedies separate treatment in a separate legal regime with standards and procedures specific to herbal rather than synthetic products. By contrast, in the US the FDA continues (despite the 2004/2016 guidance) to treat the two types of products in fundamentally the same way, for the purposes of licensing, i.e., the same standards are applied to both herbal products and synthetic products in order for either to be permitted to bear efficacy claims.

4.2.5 Sale Classification: Summary

Table 41 is displayed below to summarise the regulatory positions taken in the EU (including the NEUMS and SEUMS Clusters) and the US, respectively, on sale classification.

100 Hooyenga, Witkamp and Groen (2009) describe this process as follows: *"This includes preclinical safety testing and clinical trials to prove efficacy and safety in humans. In some cases, well-documented safety data are available and no additional preclinical safety testing is required. Herbal Medicinal Products with a long history of use often have been subject of scientific investigation. When the product has a recognized efficacy and an acceptable level of safety, the applicant may apply for marketing authorization under the precondition of well-established use according to 2001/83 article 10. In this situation, the applicant may not have to perform additional safety or efficacy tests. In addition to scientific evidence supporting the well-established use, it is required that the herbal product is in medicinal use in the EU for at least 10 years. A bibliographical application may be sufficient for marketing authorization. Scientific evidence to support well-established use may come from scientific literature databases, historical textbooks and monographs. It is especially recommended to use information provided in a community monograph (if available) or monographs from the European Scientific Cooperative On Phytotherapy or World Health Organization. Requirements on data submission to substantiate well-established use are set out in Directive 1999/83. Herbal medicinal products that have a history of use do not always fulfil the requirements for well-established use. In particular, the evidence may not be sufficiently documented. To allow these products on the market, herbal medicinal products may have access to the market under the registration procedure as traditional herbal medicinal products (but of course in that case they need to prove 30 years traditional use and 15 within the EU)."*

101 In the latter case these products may be PO products.

102 Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements.

103 Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods.

104 Another way of putting this would be to say that these products simply are not effective in a scientific sense. But, that they are socially accepted as effective particularly in some parts of Europe.

Table 41 Key Transatlantic and NEUMS-SEUMS Divergences Sale Classification

	Sale Classification		
	General	**NRPs**	**Herbal Remedies**
US	**Two categories:** (PO) and (GSALE) **Less switching**	**Wide availability (GSALE)** **Narrow indications**	**Dietary supplements (U)** No efficacy claims or safety warnings allowed
EU	**Three categories:** (PO), (GSALE), (PSO) **SEUMS:** (GSALE) uncommon **NEUMS:** (GSALE) common **More switching**	**Narrow availability** **SEUMS** (PSO), (PO) **NEUMS** (PSO), (GSALE) **Wide indications**	**Medicinal products TUR (PSO) and (GSALE)** Limited efficacy claims allowed, and safety warnings required

4.2.6 Generic Substitution

United States

There is no uniform federal regulation of generic substitution and *"the politics and economics of substitution"* have *"played out at the state level"*[1] ever since the practice emerged. Regulatory differences between states are therefore to be expected. Those States which - due to demographics - have a greater consumption of medicines, would experience more healthcare budget pressure and therefore move towards mandatory substitution. This is the case in Florida and Nevada, both with ageing populations. Substitution in these States is mandatory (as it is in eight other states), meaning the pharmacist must make the substitution so long as the generic product is in stock, and the prescribing doctor has not vetoed substitution. Substitution is not mandatory but merely permissive however in most States.[2] When it comes to consumer consent, no State allows a pharmacist to undertake generic substitution where the consumer expressly opposes it, but some states do allow pharmacists to infer consent without expressly receiving it (i.e., implied consent): Washington, Oregon, Massachusetts, Rhode Island, New Jersey, New Mexico, Alabama, and Tennessee. In all States

1 Song, Yan, and Douglas Barthold. "The effects of state-level pharmacist regulations on generic substitution of prescription drugs." Health economics 27, no. 11 (2018): 1717-1737 at pg. 1719.
2 Ibid.

a doctor can veto substitution by writing: 'dispense only as prescribed' on the prescription itself.[3]

Table 42 below summarises this. What is important to note for the reader is that regulation of generic substitution here described as 'mandatory' does not mean that the consumer has no choice. The labels 'mandatory', 'forbidden' and 'permissive' apply to the pharmacist only. Therefore, to ensure clarity, where I refer below to a system which is permissive upon the pharmacist but in which the implied consent of the patient is sufficient, I call this 'permissive-implied'. Where the express consent of the patient is required, I call it 'permissive-express'. The same rule applies for 'mandatory-express' and 'mandatory-implied'. None of this nomenclature relates to the doctor, who may always veto expressly, in all jurisdictions which I have considered.

Table 42 Mandatory, Permissive and Forbidden Generic Substitution and Consumer Consent

		Pharmacist	Prescribing Doctor	Consumer
Forbidden		Must always dispense as prescribed	N/A	N/A
Permissive	Express	May switch originator for generic product	May veto expressly	Express consent required
	Implied	May switch originator for generic product	May veto expressly	Implied consent suffices
Mandatory	Express	Must switch originator for generic product	May veto expressly	Express consent required
	Implied	Must switch originator for generic product	May veto expressly	Implied consent suffices

Some States have adopted mandatory-implied regulation of generic substitution. These include Washington, Oregon, Massachusetts, Rhode Island, and New Jersey. Other States take the mandatory-express approach: Kentucky, Hawaii, and Florida. Permissive-implied is adopted in New Mexico, Alabama, and Tennessee. By far the most states - 36 of them including five of the six most populous: California, New York, Texas, Pennsylvania, and Illinois – have adopted the permissive-express approach.[4] The permissive-express approach maximises both consumer and pharmacist choice. The pharmacist has discretion whether to offer the consumer a choice between an originator and a generic product at two different prices.[5] The consumer then has the choice whether to take the more expensive branded originator or the cheaper generic product. The consumer bears at least some part of the price

3 When it comes to doctors, "*Physicians in all states can block substitution, usually by ticking a box on the prescription pad that reads "dispense as written"* Wouters, Olivier J., Panos G. Kanavos, and Martin McKee. "Comparing generic drug markets in Europe and the United States: prices, volumes, and spending." The Milbank Quarterly 95, no. 3 (2017): 554-601 at pg. 559.

4 Song and Barthold (2018) at pg. 1717-1737.

5 So long as the doctor has not specifically vetoed this on the prescription pad.

differential directly through their health insurance deductible or co-payment. In the case of the socially insured in the US, where Medicaid or Medicare claims are made then limits are placed on the extent to which the schemes will reimburse consumer payments to the pharmacist.[6] This system ensures that the consumer reveals her willingness to pay for the originator in her consumption decision.[7] Thus, the regulation existing in over three quarters of the US States and covers most of the population of the US, is a system which maximises choice for consumer and for pharmacist. In economics this is described as 'first party ordering of preferences' because the parties who bear the costs, and reap the benefits, of the private bargain also make the choice over the substance of the bargain.

Table 43 Regulation of Generic Substitution in Most Populous US States

State	Population in 2019 (m)	Regulation of Generic Substitution 2006-2018	
		Pharmacist Discretion	Consumer Consent
California	40	Yes: Permissive	Express
Texas	29	Yes: Permissive	Express
Florida	22	No: Mandatory	Express
New York	19	Yes: Permissive	Express
Pennsylvania	13	Yes: Permissive	Express
Illinois	13	Yes: Permissive	Express
Ohio	12	Yes: Permissive	Express
Georgia	11	Yes: Permissive	Express
N. Carolina	11	Yes: Permissive	Express
Michigan	10	Yes: Permissive	Express
New Jersey	9	No: Mandatory	Implied
Virginia	9	Yes: Permissive	Express
Washington	8	No: Mandatory	Implied
Arizona	7	Yes: Permissive	Express
Total (14)	213m (330m total US)		

6 This ensures that the socially insured too, have their choice maximised. They may insist on the more expensive originator product, but they will be reimbursed only to the level of the generic product price.

7 And thus effectively her willingness to pay for the brand itself given that originator and generic are certified as bioequivalent by the FDA.

In Table 43 above[89] I set out the position taken in relation to both pharmacist discretion and consumer consent for the period 2006-2018 in the 14 most populous US States.

European Union and EU Member States

In the UK, it was at the time that the US states were rolling back their anti-substitution laws that the possibility of utilizing generic substitution to assist in the control of healthcare budgets was tabled in government, around 1983. Despite this, the UK opted for using generic prescribing[10] instead of specifically permitting or mandating generic substitution.[11] It was first raised in the context of an incentive scheme in the Netherlands in 1988,[12] although generic prescribing had already taken a strong foothold there before generic substitution arrived on the scene.[13] It was first permitted in Spain in 1990.[14] Partly in response to its (apparent) success in raising market penetration by generic products in the US generic substitution was rolled out across EUMS throughout the 1990s.[15] The form of implementation in the EUMS was in constant flux throughout the 2000s. Sweden introduced mandatory generic substitution in 2002, and Finland in 2003. Italy introduced permissive substitution in 2001 and made it mandatory by 2002[16] expanding it to a wider range of products in 2005. Whilst I do not go beyond 2010 in the analysis below, this process continued in to the 2010s. Ireland introduced permissive generic substitution in 2013 and Spain made generic substitution mandatory in 2012. As of 2017, there were 13 EUMS (and European Free Trade Association ('EFTA') countries) in which substitution was mandatory, 14 in which it was permissive and 5 in which it was forbidden.[17]

8 Shrank, William H., Niteesh K. Choudhry, Jessica Agnew-Blais, Alex D. Federman, Joshua N. Liberman, Jun Liu, Aaron S. Kesselheim, M. Alan Brookhart, and Michael A. Fischer. "State generic substitution laws can lower drug outlays under Medicaid." Health affairs 29, no. 7 (2010): 1383-1390.

9 Finally, in terms of how widespread generic substitution is in the US, research shows that it happens more often in the case where consumers are socially insured than when they are privately insured. It happens more often in the case of medication for chronic (long term) conditions – and thus more often in the case of elderly consumers over younger consumers. Where substitution is permissive (as of 2002) in 80% of cases pharmacists would perform the substitution after gaining the consumer's consent. Mott, David A., and Richard R. Cline. "Exploring generic drug use behavior: the role of prescribers and pharmacists in the opportunity for generic drug use and generic substitution." Medical care (2002): 662-674.

10 This is where the doctor is incentivised (often strongly) to prescribe using the INN.

11 Posner, John, and John P. Griffin. "Generic substitution." British journal of clinical pharmacology 72, no. 5 (2011): 731.

12 https://www.cmladvocates.net/download/educational-material-for-patient-advocates/scientific-papers/generics/436-2012-royal-dutch-pharmacists-association-guideline-for-generic-substitution/file

13 Pechlivanoglou, Petros, Willem Jan van der Veen, Jens H. Bos, and Maarten J. Postma. "Analyzing generic and branded substitution patterns in the Netherlands using prescription data." BMC health services research 11, no. 1 (2011): 89.

14 Mondelo-García, Cristina, Elvia Mendoza, María-Jesús Movilla-Fernández, and Carmen Coronado. "Perceptions of pharmacists and physicians on generic substitution in a financial crisis context in northwestern Spain: a qualitative study." Health Policy 122, no. 12 (2018) at pg. 1316-1325.

15 Johnston, Atholl, Roland Asmar, Björn Dahlöf, Kate Hill, David Albert Jones, Jens Jordan, Michael Livingston et al. "Generic and therapeutic substitution: a viewpoint on achieving best practice in Europe." British journal of clinical pharmacology 72, no. 5 (2011): 727 at pg. 727.

16 https://www.gabionline.net/layout/set/print/Country-Focus/Italy/Policies-and-Legislation

17 Wouters, Kanavos, and McKee (2017) at pg. 554.

There is no EU-wide regulation of this practice, it lies entirely with the EUMS. In this section I consider in detail the 14 EUMS which I have chosen to focus on throughout this Chapter. In relation to these 14, whilst I consider how the regulation developed over time, the analysis is anchored in the year 2010. Through the decades all EUMS have gradually moved towards forms of regulation which further limit pharmacist discretion, the requirement for patient consent, and in some cases the doctor's ability to veto. However, it is in 2010 that patterns - consistent from the late 1980s through until the early 2020s - are clearest to see.

It should be noted that simply comparing the regulation of generic substitution in each EUMS or polity is unlikely to show the whole picture, as there are many other options available to the regulator for controlling healthcare expenditure and encouraging generic penetration. One major difference between the EU and the US is that in the EU all but three EUMS (Denmark, Germany and - formerly - the UK) impose direct controls on the prices of pharmaceutical products (drugs) which obviate the need for budget control through generic substitution.[18] On top of this lie the other potential options for reducing healthcare expenditure including: (aimed at doctors) the encouragement of or insistence upon generic prescribing, and prescribing monitoring and audits, (aimed at pharmacists) regressive margins and claw-back schemes and (aimed at consumers) co-payments and coinsurance or flat/tapered fees for dispensing prescriptions.[19] Finally, measures which encourage the entry of generic products on to the pharmaceuticals market in the first place (i.e. supply side competition measures) may have affected availability and prices and thus affected demand and regulation of generic substitution. These exogeneous differences are important to bear in mind later when considering explanations for differences in the regulation of generic substitution. Similarly, general background differences must be borne in mind.[20] Thus, it cannot be expected to see very clear patterns in the regulation of generic substitution, as it is impossible to hold all other factors constant.

Nevertheless, it is submitted in this section that broad differences can be identified both between the NEUMS and SEUMS Clusters and between the EU as whole and the US. These are as follows.

1. That the EUMS were much later to regulate generic substitution than their US counterparts.
2. That once the practice was regulated in the EUMS, these have been much more willing (than is the case in the US) to interfere with first party ordering of preferences.[21]
3. That interference with the discretion of the pharmacist took much longer to materialise in the SEUMS Cluster than in the NEUMS Cluster.

18 Ibid.

19 Kanavos, Panos, Joan Costa-Font, and Elizabeth Seeley. "Competition in off-patent drug markets: Issues, regulation and evidence." Economic policy 23, no. 55 (2008): 500-544 at pg. 509

20 In the words of Wouters, Kanavos, and McKee (2017): *"There are vast differences between countries in terms of regulatory structures, lobbying powers of special-interest groups, patent-litigation systems, political economies of health care systems, and perceptions of generics among patients and health care professionals. Such differences influence the adoption and effectiveness of policies."*

21 By mandating substitution by the pharmacist and/or to taking away the requirement of express consent from the consumer.

4. That implied consumer consent is accepted more often in the SEUMS than in the NEUMS Cluster.

Generic Substitution Circa 2010 in the 14 EUMS Sampled

In **Austria** generic substitution is forbidden. In practice this means that the express consent of the prescribing doctor is required before the pharmacist may substitute.[22] Austria instead focuses on measures which relate to pricing and reimbursement to increase generics uptake.[23] In addition, doctor generic prescribing targets are used.[24] Consumers are not normally informed about the products (generic or originator) and the differences between them including prices, and they pay a fixed prescription fee (flat rate).[25] In **Belgium** generic substitution is also forbidden.[2627] A law was passed in 1993 which would permit generic substitution with the express consent of both, but this never received royal assent. However, where the physician prescribes by the international non-proprietary name ('INN') the pharmacist may dispense a generic or the originator subject to a price constraint and the consent of the consumer.

Generic substitution in **Denmark** is mandatory, meaning that the pharmacist must dispense the cheapest version of the medicine if it is in stock. However, the express consent of the consumer must be obtained and he or she may refuse without giving a reason.[2829] Since 2003 **Finland** has enacted mandatory generic substitution.[30] The pharmacist must substitute the prescribed medicine *"with the cheapest product or close to the cheapest product (i.e. the product to be offered should be within a specific price range, also known as the price corridor/band)."* [31] The express consent of the consumer must be obtained.[32] Generic substitution has been permitted (but not mandated) in **France** since 1999. Where the doctor writes a prescription using either a brand name or an INN the pharmacist may substitute a cheaper medicine unless this is specifically vetoed by the doctor.[33] It seems that if the doctor

22https://www.gabionline.net/layout/set/print/Country-Focus/Austria/Policies-and-Legislation

23 Simoens, Steven, and Sandra De Coster. "Sustaining generic medicines markets in Europe." Journal of Generic Medicines 3, no. 4 (2006): 257-268.

24 However, in terms of generic prescribing physicians are not permitted to use the INN to prescribe and must stipulate either the originator (brand) name or the generic name on the prescription.

25 https://www.gabionline.net/layout/set/print/Country-Focus/Austria

26 OECD 2015 https://www.oecd-ilibrary.org/docserver/health_glance-2015-69-en.pdf

27 https://www.gabionline.net/Country-Focus/Belgium/Policies-and-Legislation

28 https://laegemiddelstyrelsen.dk/en/reimbursement/prices/medicinal-product-groups-substitution-groups/generic-substitution-questions-and-answers

29 https://www.gabionline.net/Country-Focus/Denmark

30 Hassali, Mohamed Azmi, Alian A. Alrasheedy, Andrew McLachlan, Tuan Anh Nguyen, Saleh Karamah Al-Tamimi, Mohamed Izham Mohamed Ibrahim, and Hisham Aljadhey. "The experiences of implementing generic medicine policy in eight countries: a review and recommendations for a successful promotion of generic medicine use." Saudi pharmaceutical journal 22, no. 6 (2014) at pg. 491-503.

31 Ibid.

32 Nokelainen H, Lämsä E, Ahonen R, Timonen J. Reasons for allowing and refusing generic substitution and factors determining the choice of an interchangeable prescription medicine: a survey among pharmacy customers in Finland. BMC Health Serv Res. 2020;20(1):82. Published 2020 Feb 3. doi:10.1186/s12913-020-4894-3

33 Dylst, Pieter, Arnold Vulto, and Steven Simoens. "Analysis of French generic medicines retail market: why the use of generic medicines is limited." Expert review of pharmacoeconomics & outcomes research 14, no. 6 (2014) at pgs. 795-803.

has not vetoed substitution specifically on the prescription, then the consumer's consent may be implied. In the case that the consumer does not wish for substitution to occur it is incumbent upon him or her to request the doctor to make a veto.[34] Having said this, where the pharmacist does undertake substitution then the pharmacist must tell the consumer about the substitution. In this case, and if the pharmacist is unwilling for whatever reason to dispense the originator, then the consumer can walk away from the transaction and go back to the doctor to request a veto.[35]

Since 2002 generic substitution in **Germany** has been mandatory on the pharmacist – in relation to certain products he or she must substitute and dispense the lower cost product (of generic or originator) unless the doctor forbids it. Where INN is used to prescribe, pharmacists must dispense one of the three cheapest versions of the medicine available.[36] The express consent of the consumer is required.[37][38] Generic substitution in **Greece** is permitted but not mandated on the pharmacist.[39] As one of many measures demanded by the Troika in response to Greece's sovereign debt crisis in the late 2000 and early 2010s, measures were introduced in 2012 targeted at physicians mandating prescribing by INN in some cases, to reduce overall public health expenditure. Further measures were introduced in 2017 targeted instead at pharmacists, aiming to financially incentivise switching (which remained voluntary for the pharmacist). The patient's express consent is required for the pharmacist to make the substitution and/or to provide either the generic or the originator where INN is used to prescribe.[40] From 2001 until 2002 **Italy** adopted permissive generic substitution, however it was quickly changed in 2002 to become mandatory upon pharmacists. The pharmacist must substitute the cheaper generic unless the doctor has specifically prohibited it, or the consumer is willing to pay the price difference. Therefore, express patient consent to the substitution is required. **Ireland** forbade generic substitution

34 Beauvais V, Marque A, Ferté G, et al. Factors influencing the use of the "not for generic substitution" mention for prescriptions in primary care: a survey with general practitioners. BMC Health Serv Res. 2018;18(1):850. Published 2018 Nov 12. doi:10.1186/s12913-018-3652-2

35 Studies indicate that doctors in France are highly opposed to generic substitution. In 2012 one study found that one in five French prescriptions contained a 'Not for Generic Substitution' mention. Some have attributed low rates of generics prescribing by French doctors (in 2013 only 12.3% of prescriptions were being written by INN by French physicians) to cultural attitudes regarding what is seen as an incursion on their prescribing freedom. In addition, French doctors seem to have reservations over the quality of generic medication. A 2012 study found that only 43% of French physicians believed that generics possessed the same quality as originators. The corresponding figure for pharmacists surveyed was 89% and for patients 75%. Dylst, Vulto, and Simoens (2014) at pgs. 795-803.

36 Simoens and De Coster (2006) at pgs. 257-268.

37 Schreyögg, Jonas, Klaus-Dirk Henke, and Reinhard Busse. "Managing pharmaceutical regulation in Germany: overview and economic assessment." (2004).

38 One noteworthy aspect of the German approach – and some would say the most successful – is the use of prescribing budgets provided to physicians based around practice-specific prescription targets (from 1998 onwards), *"Physicians surpassing their individual target by more than 15% received written notice informing them to reconsider their prescribing practices. Physicians exceeding 125% of the medicine budget were required to refund the difference between the actual budget and 115% of the target budget in the absence of a justification for the budget deficit."* Simoens and De Coster (2006) at pgs. 257-268.

39 Yfantopoulos, John N., and Athanasios Chantzaras. "Drug policy in Greece." Value in health regional issues 16 (2018) at pgs. 66-73.

40 Karampli, Eleftheria, Efstathia Triga, Vasiliki Tsiantou, Kostas Athanasakis, and John Kyriopoulos. "Views of physicians and patients with chronic conditions on generic medicines in Greece after the introduction of measures to promote their consumption: findings from a qualitative study." GaBI J 5 (2016) at pgs. 9-20.

until 2013 when the Health (Pricing and Supply of Medical Goods) Act[41] was passed. Ireland's former prohibition on the practice followed the approach taken in the UK where generic prescribing was (and is, there) the preferred approach to incentivising the uptake of generics. The 2013 Act allowed pharmacists to substitute medicines which have been confirmed as interchangeable by the Irish regulator. This is subject to a doctor veto and express consumer consent.

Generic substitution has long been practiced in the **Netherlands**; however, the old requirement was that the pharmacist had to *actively* obtain the express consent of the prescribing doctor first.[42] In 1998 that requirement was relaxed so that active consent need not be obtained in every case but is now done through the making of general agreements between pharmacies and doctors' surgeries. Express patient consent is required, and doctors may still expressly veto substitution.

Generic substitution is permitted but not mandatory, upon the pharmacist in **Portugal**.[43] Express consumer consent is required. Pharmacists have few financial incentives to dispense generics, but the effect of consumer co-payments is such as to incentivise patients to not refuse substitution where it is offered. Moreover, doctors in Portugal are incentivised to prescribe by INN. In **Spain** from 1990[44] to 2011[45] generic substitution was permissive[46] upon pharmacists, however in 2011 it was made mandatory upon pharmacists as was generic prescribing also made mandatory upon doctors. In the context of Spain's heavily socialised healthcare system, consumer consent to the substitution could be implied when generic substitution was permissive on the pharmacist. Under the regime from 2011 onwards (mandatory substitution) it remains implied, and in fact the consumer cannot obtain the more expensive product by offering to pay the difference. The pharmaceutical market in **Sweden** was reformed in 2002 and generic substitution is now mandatory.[47] Thus, the pharmacist must substitute the cheapest available generic for the prescribed pharmaceutical product so long as the consumer expressly agrees and so long as the doctor has not vetoed it. If they refuse, then consumers must pay the difference to obtain the originator.[48]

The **UK** does not permit generic substitution and instead relies upon generic prescribing, which had great success in increasing generics uptake in the UK between 1983 and 1993.[49] Whilst proposals have been raised in the decades since[50] to introduce permissive generic substitution, this has never taken place. Measures targeted at doctors include financial and non-financial incentives to prescribe generically and the use of technology to assist in

41 http://www.hpra.ie/homepage/medicines/regulatory-information/generic-and-interchangeable-medicines
42 Pechlivanoglou et al (2011) at pg. 89.
43 https://www.gabionline.net/Country-Focus/Portugal
44 Ley 25/1990 del Medicamento
45 Real Decreto Ley 9/2011 de Medidas para la Mejora de la Calidad y Cohesion del Sistema Nacional de Salud
46 https://www.pharmaceutical-journal.com/spain-approves-generic-substitution/20002521.article
47 Granlund, David. "Price and welfare effects of a pharmaceutical substitution reform." Journal of Health Economics 29, no. 6 (2010) ay pgs. 856-865.
48 Hassali et al. (2014) at pgs. 491-503.
49 Posner, John, and John P. Griffin. "Generic substitution." British journal of clinical pharmacology 72, no. 5 (2011) at pg. 731.
50 Duerden, Martin G., and Dyfrig A. Hughes. "Generic and therapeutic substitutions in the UK: are they a good thing?." British journal of clinical pharmacology 70, no. 3 (2010): 335-341 at pg. 335

prescribing and to nudge towards responsible prescribing practices and to provide feedback on own prescribing practices.[51]

Looking at the overall picture, the information provided above for each EUMS is summarised in Table 44 below. The forms of regulation are represented also in Figure 11 below.

Conclusions

Looking at comparisons between the EU and the US, there is a clear divergence between the approaches taken in most of the US States against those taken in the EUMS. The key differences are the extent of pharmacist discretion and the acceptable form of consumer consent. None of the most populous 14 US States forbid generic substitution and only three of these make it mandatory – comprising a population of 39 million out of the 213 million in the 14 States combined.

Table 44 Status of Generic Substitution in Selected EUMS Circa 2010

EUMS	Population 2016 (m)	Regulation of Generic Substitution in 2010	
		Pharmacist Discretion	Consumer Consent
Germany	82	No: Mandatory	Express
France	67	Yes: Permissive	Implied
UK	65	No: Forbidden	N/A
Italy	61	No: Mandatory	Express
Spain	46	Yes: Permissive	Implied
Netherlands	17	Yes: Permissive	Express
Belgium	11	No: Forbidden	N/A
Greece	11	Yes: Permissive	Express
Sweden	10	No: Mandatory	Express
Portugal	10	Yes: Permissive	Express
Austria	9	No: Forbidden	N/A
Denmark	6	No: Mandatory	Express
Ireland	5	No: Forbidden	N/A
Finland	5	No: Mandatory	Express
TOTAL	405m (Total EU 510m)		

By contrast in the EU sample nine EUMS give no discretion to the pharmacist, comprising a population of 254 million out of the 405 million total for the 14 EUMS. Overall, therefore, the US provides more discretion to pharmacists in the matter of generic substitution. On consumer consent, implied consent is permitted in two of the US States comprising a total population of 17 million. In the EU it is also permitted in two EUMS, but their combined population is 113 million. The US therefore prioritises express consumer consent to a greater degree than the EU. The differences are summarised below in Table 45.

51 Hassali et al. (2014) at pgs. 491-503.

Table 45 Regulation of Generic Substitution in the US and the EU

	Generic Substitution
US	**Permissive-express** Pharmacist discretion and express consumer consent
EU	**SEUMS:** More often pharmacist discretion. Less often express consumer consent. **NEUMS:** Less often pharmacist discretion. More often express consumer consent.

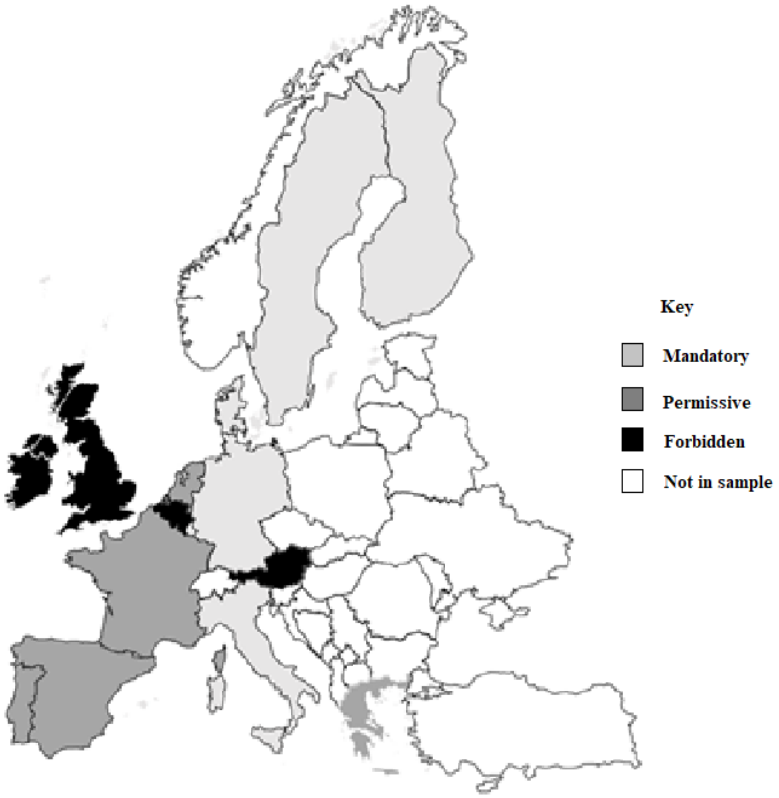

Figure 11 **Pharmacist Discretion in Generic Substitution Selected EUMS (2010)**

4.2.7 Summary

To summarise, the full US-EU and NEUMS-SEUMS divergences across both aspects of regulation are set out again in Table 46 below.

Table 46 Key Transatlantic and NEUMS-SEUMS Divergences Sale Classification and Generic Substitution

	Sale Classification			Generic Substitution
	General	**NRPs**	**Herbal Remedies**	
US	**Two categories:** (PO) and (GSALE) **Less switching**	**Wide availability (GSALE)** **Narrow indications**	**Dietary supplements (U)** No efficacy claims or safety warnings allowed	**Permissive-express** Pharmacist discretion and express consumer consent
EU	**Three categories:** (PO), (GSALE), (PSO) **SEUMS:** (GSALE) uncommon **NEUMS:** (GSALE) common **More switching**	**Narrow availability** **SEUMS** (PSO), (PO) **NEUMS** (PSO), (GSALE) **Wide indications**	**Medicinal products TUR** **(PSO) and (GSALE)** Limited efficacy claims allowed, and safety warnings required	**SEUMS:** More often pharmacist discretion. Less often express consumer consent. **NEUMS:** Less often pharmacist discretion. More often express consumer consent.

I now consider the regulation of sale classification and generic substitution using the public interest theory of regulation. In doing so I relate back to the actual forms of regulation in the US and the EU/EUMS, respectively.

4.3 Public Interest Approach

4.3.1 Sale Classification

Market Failure

For sale classification regulation, the relevant market failure results from an information problem. The problem here is the unknown and unknowable benefits and risks of pharmaceutical products. The specific market failure is the overconsumption of products which impose negative externalities (injuries) upon society or underconsumption of products which produce benefits for society.

In addition to market access licensing, pharmacovigilance, and products liability, selling regulation is used to tackle this market failure - as shown below in Figure 12. Selling regulation includes the prescription system, sale classification, and mandatory labelling. These are all linked, and all apply once the product is already on the market. At this stage, enough is known about the risk benefit profile of the products to be sure that the product has a positive risk-benefit profile for at least some classes of consumer. The prescription system and thus the PO category use doctor oversight to ensure that only these classes of consumer can consume the product.

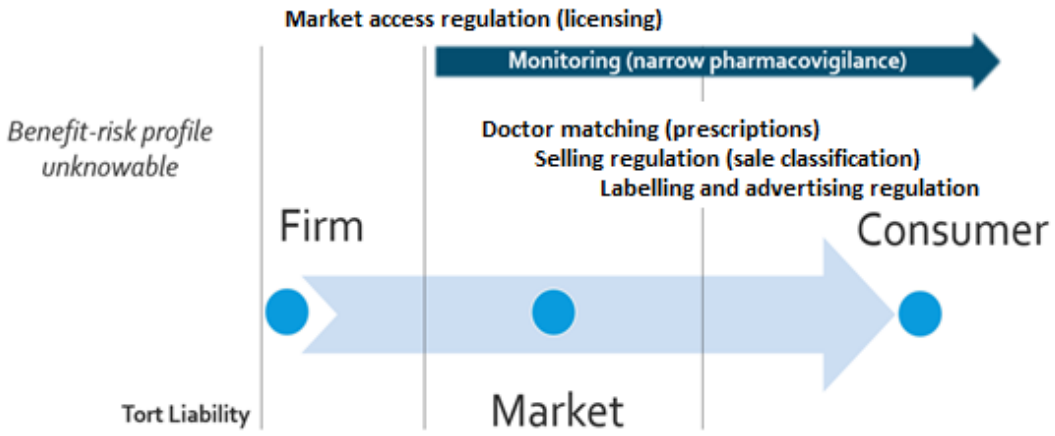

Figure 12 **Info Problem: Licensing, Pharmacovigilance, Product Liability, Selling Regulation**

What is left (after the prescription system accounts for use of the PO category) are products for which enough information about the risk-benefit profile is known to be sure that for not just some but for *most* classes of consumer the risk-benefit profile of the product is positive. Direct provision of information through mandatory labelling and/or pharmacist supervision minimises externalities in the case of these products. In choosing between GSALE plus detailed information provision, and the PSO category with less information provision plus pharmacist supervision, two things are relevant. Firstly, the likely extent of information

already known about the product: if the product has not yet been long enough on the market, then the regulator may wish to restrict availability to the PSO (or PO) categories until more information is known. Second, whether information provided directly can be fully understood by the consumer - without the monitoring/guidance of a doctor or pharmacist - so that consumers can self-administer without costly externalities being generated.[1]

Then also, one must consider the costs to society associated with the form of the regulation itself. The most permissive form of regulation – U - will be the cheapest because there are no system or administration costs related to regulating the product itself. The most stringent form of sale classification regulation – PO - will be the most expensive to society in terms of system and administration costs. PSO and GSALE lie somewhere in between. Consumer self-administration of widely available pharmaceutical products is the most beneficial system for society, so long as this arrangement does not lead to externalities costlier than the savings made on system and administration costs. Public interest theory would indicate, then, that the agency should place a product in a category where[2] the cost savings of placing the product in the more permissive category outweigh the costs incurred from any externalities which may result from use of the more permissive category.[3]

4.3.1.1 General

It can be assumed that the differences in the rate of switching – between the US and EU/EUMS – is attributable to the existence of the PSO category in Europe. Does the existence of a PSO category further the public interest in the way described above? Indeed, it does. The PSO category cuts the costs incurred from externalities associated with wider availability of the product (versus the GSALE category) because the product is dispensed under the supervision of a pharmacist who is available to provide guidance. At the same time, the PSO category is likely to be cheaper for society because it cuts out the costs involved to the consumer and the doctor of consulting and obtaining a prescription. It seems then, that the EU approach (particularly NEUMS) is most readily justified by public interest theory.

4.3.1.2 Nicotine Replacement Products

When assigning monetary costs to externalities one might adopt an 'expert' view based on medical science. Expert medical consensus holds that NRPs are not very harmful to the human body even when used incorrectly. Therefore, by this view, the externalities associated with

1 The former problem links into the discussion (above and below) regarding pharmacovigilance, and it may be relevant to sale classification where it comes to the possibility of a product switching between classes. Thus a product may start out as a prescription only product, then after used for some time and – subject to the oversight of pharmacovigilance monitoring – it becomes less and less likely that a latent safety defect will emerge – it will then move to the PSO or GSALE categories.

2 Taking in to account the likely extent of information known about the benefits and risks of the product, and what that information is.

3 The latter takes in to account the risk that not enough information about the product is known yet (latent defects) and the risk or reality that consumers will not understand direct information provision.

these products are small. The same expertise holds that the benefits of these products are large. Studies show that even when used concurrently with cigarettes or other forms of smoking NRPs cause the user to smoke less and - given the well documented harms caused by smoking[4] - the positive risk-benefit profile of NRPs is not in doubt. As there are only small externalities associated with NRPs, and considerable costs associated with doctors' consultations and prescriptions[5] one would not expect the products to be available PO. In choosing between PSO and GSALE sale classification, GSALE is expected where this exists. As the products have been used safely for over 40 years, regulatory agencies can be near certain the benefit-risk profile of NRPs is positive in most cases. Pharmacist supervision can add little to the easily understood information written on the label of NRPs, and even if a consumer does not follow these instructions the harm which they can do to themselves is minimal. Moreover, as cigarettes are available widely in the EU and the US in supermarkets, petrol stations, vending machines, bars, and restaurants, one would expect NRPs to be just as widely available.

Also adopting an expert medical view, all four potential types of use/indications should be permitted, because the harmful health effects of cigarette smoking are much greater than any harms which can be caused by NRPs.

This presents a puzzle, as outlined in Table 47 below. I return to this puzzle in Chapter Seven.

Table 47 Puzzling Regulation of Sale Classification NRPs US and EU

	Availability	**Use**
Expert View/Public Interest	**Wide**	**Wide**
United States	Wide	Restricted
European Union	Restricted	Wide

4.3.1.3 Herbal Remedies

Herbal remedies should carry safety warnings in the view of medical experts.[6] That is because they can interact with synthetic medicines and with each other and are capable of being abused. Such warnings would help to minimise externalities associated with use, and these are particularly needed where the products are widely available without pharmacist or doctor supervision (either U or GSALE). The expert medical view on efficacy is that herbal remedies

4 Which are mostly due to the other ingredients in cigarette smoke such as tar and carbon monoxide.

5 And given that studies show NRPs yield higher success rates when made available off prescription than when on PO Gilbert, Andrew, Deepa Rao, and Neil Quintrell. "A review of pharmaceutical scheduling processes in six countries and the effect on consumer access to medicines." International Journal of Pharmacy Practice 14, no. 2 (2006): 95-104 at pg. 97.

6 Bent, Stephen. "Herbal medicine in the United States: review of efficacy, safety, and regulation." Journal of general internal medicine 23, no. 6 (2008): 854-859 at pg. 854

should not carry efficacy claims. These remedies cannot show the standards of efficacy in RCTs which are normally required by medical experts for new drug market access licensing.

Again, as with NRPs, there is a difference between the expert public interest view and the approaches taken in the US and the EU. This is shown in Table 48 below.

Table 48 Puzzling Regulation of Sale Classification Herbal Remedies US and EU

	Safety (warnings)	Efficacy (claims)
Expert View/Public Interest	**Label warnings**	**No efficacy claims**
United States	No warnings	No efficacy claims
European Union	Label warnings	Limited efficacy claims

4.3.2 Generic Substitution

Market Failure

A different market failure may justify generic substitution and its regulation. The market failure here results from monopoly. Monopoly market structure is caused by a lack of competition from generics against originators *after* the patent of the originator has expired.[7] That in turn is caused by consumer[8] brand loyalty to originators. In addition, the market failure is exacerbated by a failure of prices to correctly signal consumers' willingness to pay for drugs (generic or originators). This causes demand for drugs to be inelastic to changes in price. The combined consequences are that the drug (generic or originator) is under consumed and is sold at too high a price (see also below on price failure). That additionally has distributive effects.

Price Failure

I deal first with the price failure, which has been argued to cause drug price inflation. Price theory stipulates that the price of any product will represent the intersection of supply and demand. Suppliers of the product will be willing to supply a certain quantity of the product at the given price and consumers of the product will be willing to buy the same quantity of the product at that price. Thus, in equilibrium, there is a specific quantity of the product supplied and demanded at a given price. This assumes that the quantity demanded by consumers at the equilibrium price does represent consumers' actual willingness to pay for that quantity of the product. That, in turn, assumes that the market actor choosing the product, the one consuming the product and the one paying for the product are the same. In the case of PO drugs these are not the same actor. The consumer consumes the product, but it is the doctor

7 Before the patent expires, the monopoly market structure is caused by the patent. After expiry of the patent, a monopoly structure persists due to brand loyalty.
8 Arguably also doctor brand loyalty.

who chooses the product and often, an insurer will pay.[9] As demand for the product is inelastic to price this means that the price of the product can rise to some degree without the quantity demanded dropping by a similar proportion. Therefore, pharmaceutical firms have incentives to raise the prices of originator products to maximise revenues from the product.

Brand Loyalty as a Barrier to Generic Entry

Brand loyalty develops during the period of market exclusivity granted with the patent. Consumers and doctors become familiar with the product and have no incentive to switch to a cheaper generic product once it enters the market because the consumer and doctor are not paying the full price of the product which they consume and choose, respectively. This also represents a barrier to market entry to generic competitors to originator products.[10]

Effects on Market Structure

The existence of this barrier to entry means that the market for the drug in question has monopoly characteristics.[11] The pharmaceutical product market structure is – without brand loyalty and with the possibility of generic entry – one of monopolistic competition, whereby branded originators enjoy some power over price but should be deterred from raising prices too high by the threat of 'hit and run' entry from generic competitors. Monopolistic competition is marked by some brand loyalty, however the effect of brand loyalty must be kept in check by the threat of hit and run entry. Where brand loyalty to one supplier deters entry and competition then the market structure moves from monopolistic competition to oligopoly or monopoly.

This is shown below in Figure 13. On the left is the market for the drug where competition exists in the market i.e., the originator patent has expired but there is no brand loyalty and generic products face no barrier to entry. Note that the demand curve is inelastic due to the price failure. Any given pharmaceutical firm will produce the drug (originator or generic) at point q where its marginal cost of production is equal to price, which lies at the intersection of supply and demand. In the market overall the quantity q(C) will be demanded at the price p(C) where all firms supplying the drug (generics or originator) are supplying it at marginal cost. If the originator firm raises its price too high it will make zero revenue because other

9 Danzon, Patricia M., and Eric L. Keuffel. "Regulation of the pharmaceutical-biotechnology industry." In *Economic Regulation and Its Reform: What Have We Learned?*, pp. 407-484. University of Chicago Press, 2014 AT PG. 407-408.

10 See Morton, Fiona M. Scott. "Barriers to entry, brand advertising, and generic entry in the US pharmaceutical industry." international Journal of industrial Organization 18, no. 7 (2000): 1085-1104.Danzon, Patricia M., and Michael F. Furukawa. Cross-national evidence on generic pharmaceuticals: pharmacy vs. physician-driven markets. No. w17226. National Bureau of Economic Research, 2011. Berndt, Ernst R., and Murray L. Aitken. "Brand loyalty, generic entry and price competition in pharmaceuticals in the quarter century after the 1984 Waxman-Hatch legislation." International Journal of the Economics of Business 18, no. 2 (2011): 177-201. Weiswasser, Elizabeth Stotland, and Scott D. Danzis. "The Hatch-Waxman act: History, structure, and legacy." Antitrust LJ 71 (2003): 585.

11 The market structure in the pharmaceuticals sector normally is likely to be oligopoly or monopolistic competition (contestable). See Danzon and Keuffel (2014) at 412.

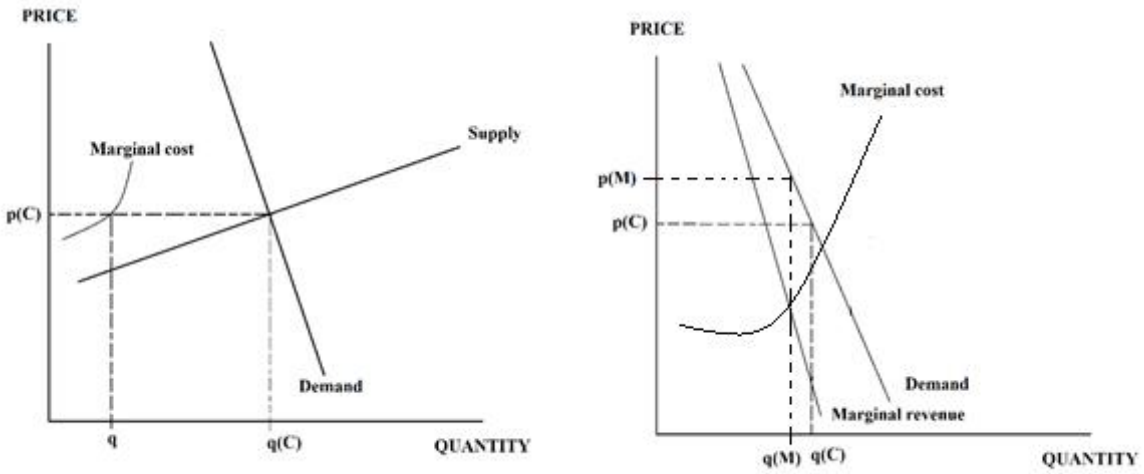

Figure 13 **The Monopoly Effects of Barriers to Entry Post Patent Expiry**

firms will supply the generic product for the competitive price, and consumers will choose the generic version only, having no brand loyalty to the originator.

Post patent-expiry brand loyalty[12] deters hit and run entry by generics and gives the producers of originator products power over the price of those products. On the right of Figure 13 there is consumer brand loyalty to the originator product and a resulting barrier to entry to generics. Again, the situation is shown post patent expiry. Here, there is no threat of hit and run entry from generics thus the originator firm produces the amount q(M) which is where its marginal revenue is equal to its marginal cost.[13] In doing so the originator firm increases its revenues rather than decreasing them by raising its prices above the competitive market price. The effect is that the smaller quantity q(M) of the drug is consumed by society at the higher price of p(M). This means that fewer of both originator and generic products will be consumed than in a competitive or contestable market. This is costly to society due to the foregone benefits of consumption. It also has distributive effects. Where social or private insurers pay for the products, drug prices can reach levels where they become a burden on society and health insurance becomes unavailable or unaffordable. This redistributes wealth from the pockets of consumers, taxpayers, or premium payers to pharmaceutical companies.

Innovation and Dynamic Efficiency

The market exclusivity period which gives rise to brand loyalty itself can be well justified by public interest theory.[14] To remove this period of exclusivity would remove incentives to innovate. As the development of new pharmaceutical products poses huge positive externalities to society in the long run, it would be costly to society not to incentivise their development.

12 Grabowski, Henry G., and John M. Vernon. "Brand loyalty, entry, and price competition in pharmaceuticals after the 1984 Drug Act." The journal of law and economics 35, no. 2 (1992): 331-350. Costa-Font, Joan, Caroline Rudisill, and Stefanie Tan. "Brand loyalty, patients and limited generic medicines uptake." Health policy 116, no. 2-3 (2014): 224-233.

13 Bear in mind that the firm may have inflated its marginal cost by huge investment in advertising, for example.

14 Schumpeter, Joseph Alois. Das Wesen und der Hauptinhalt der theoretischen Nationalökonomie. Duncker & Humblot, 1908. Magazzini, Laura, Fabio Pammolli, and Massimo Riccaboni. "Dynamic competition in pharmaceuticals." The European Journal of Health Economics, formerly: HEPAC 5, no. 2 (2004): 175-182.

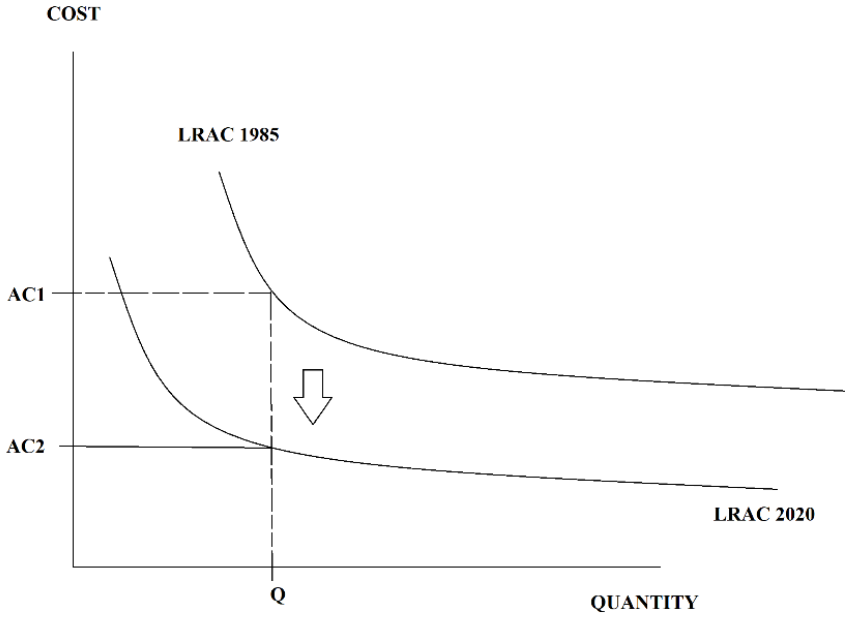

Figure 14 **Dynamic Efficiency and Innovation in the Pharmaceutical Sector**

This is shown above in Figure 14. With research, pharmaceutical firms can produce more effective drugs than they can with the existing state of knowledge. This investment in research leads to a shift in the long run average cost curve ('LRAC') to produce pharmaceutical products over time. The LRAC shifts in Figure 14 above from the 1985 position to the 2020 position such that in 2020 the quantity Q can be produced at the cost AC2 much lower than the 1985 cost AC1. It is therefore in the interests of society that investment be made in research. The free rider problem exists, however, when it comes to private production of knowledge (research). Once the product is on the market there is no way to prevent a competitor from free riding on the research efforts and duplicating the product without incurring the research costs. This possibility removes incentives to innovate by investing in research. Some legal protection is therefore justified to ensure that private investments in research can be recouped. That legal protection comes in the form of the patent.

Yet, with patents and market exclusivity comes the problem of brand loyalty. Public interest theory would best justify a regulatory approach which protects incentives to innovate but ensures that once the costs of research and development have been recouped by the pharmaceutical firm, the market is open to competition.

Generic Substitution

Generic substitution is a way to tackle these underlying market failures by cancelling out brand loyalty to originators post patent-expiry and/or by remedying the price failure by substituting the doctor's choice with that of the consumer.

In its weakest form – permissive-express –it operates according to the market principle of first party ordering of preferences. In that case it does not solve the problem of brand loyalty but – where[15] the consumer bears some part of the additional cost of the originator product – it solves the price failure because it replaces the doctor's choice of product with the consumer's

15 Through co-payments or deductibles etc.

choice and payment. The effect of solving the price failure is that consumers will reveal their willingness to pay in their consumption choice between generic and originator. Prices between the two versions of the product will then converge. This will have the effect of lowering barriers to entry to generics which stand a greater chance of gaining a foothold in the market despite brand loyalty to originators, where generic substitution is not forbidden. Permissive-express generic substitution also solves the brand loyalty problem to some extent simply by facilitating the pharmacist in making the consumer aware that a cheaper generic version of the prescribed drug is available.[16] The effect of permissive-express generic substitution regulation is likely to be that some consumers pay for and consume higher priced originators and the remaining consumers pay for and consumer the lower priced generics. The prices of the two versions of the drug are likely to differ slightly. Brand loyalty has not entirely disappeared, and some consumers have a willingness to pay for the brand. In essence then permissive express generic substitution will likely lead to the desired market structure of monopolistic competition, whereby the suppliers of branded originators possess some power over price however, where they raise prices too much, many consumers will switch to generics products (or 'branded generics') - which are capable of hit and run entry.

In its strongest form – mandatory-implied – the brand loyalty problem is solved completely because the preferences of the doctor, the consumer and the pharmacist are overridden. The price failure is not remedied, however, as now instead of the consumer choosing and paying the regulator chooses and an insurer pays – which was much the same situation in terms of the price failure as before, when the doctor chose, and the insurer paid. Where mandatory-implied substitution is in place there are not only no barriers to entry to generics, but instead entry is facilitated. The effect of such strong regulation is likely to be a sharp decrease in the prices of originator products and increase in the price of generic products. The two may equalise. However, because substitution is mandatory-implied and there is not first party ordering of preferences, this will mean that some consumers who would have chosen to consume (and pay for, through their deductibles etc) originators, in a system where their consent was required expressly, will instead consume generics resulting in welfare losses to consumers (to the extent these attached subjective surplus value to branded products). In addition, some pharmacists who prefer to sell originators are forced to sell generics instead and - in theory - some will leave the market. Mandatory-implied generic substitution may therefore be a good policy tool for sharply decreasing healthcare expenditure however, it is not allocatively efficient and will not likely result in a market structure of competition or monopolistic competition.

Where generic substitution is forbidden, the problem of brand loyalty and the price failure remains. As such, public interest theory would best justify generic substitution regulation in the form permissive-express.

United States and European Union/EU Member States

Assessing the EUMS and the US systems against this, the US system seems to match well with it. In most States generic substitution is permissive-express. That includes all the 14 most populous States save for Florida, Washington, and New Jersey.[17] In the EUMS the picture is

16 It may be that the brand loyalty resides most in the prescribing doctor who chooses the originator product, and permissive express substitution moderates this by incorporating the choice of the consumer.

17 Totalling a population of 39 million (2019) out of a total population of 213 million in all 14 States.

different. Only in three of the EUMS sampled is generic substitution permissive-express: the Netherlands, Greece, and Portugal. When it comes to the discretion of the pharmacist those EUMS oriented towards the SEUMS Cluster more often give, or gave for longer, discretion to the pharmacist. This, however, is counteracted by a tendency to allow implied consumer consent. Those EUMS oriented towards the NEUMS Cluster more often insist upon express consumer consent, but this is counteracted by more commonly mandating or forbidding generic substitution.

4.3.3 Public Interest: Conclusions

In this section I have approached sale classification and generic substitution from a public interest perspective whilst being cognisant of the fact that what lies in the public interest may depend upon underlying group preferences. I have identified, in theoretical terms, the market failures which may justify the existence of these two forms of regulation. I have concluded that the position taken in the EU/EUMS regarding sale classification (three categories, and more switching) seems better justified by public interest theory than the position taken in the US system (two categories and less switching). Additionally, I concluded that, where public interest theory itself is linked to expert medical consensus it would justify specific forms of sale classification regulation for the two case studies: NRPs and herbal remedies. In this case, NRPs should be made widely available (GSALE classification) and for all types of use. Neither the US nor the EUMS take this approach because the EUMS more often restrict availability of NRPs (whilst allowing broad indications) and the US disallows broad indications but makes NRPs widely available. In the case of herbal remedies, where this approach is adopted, products should not be permitted to make efficacy claims and should not be sold as medicines (i.e., they should be in the U sale classification category). These products should, however, carry safety warnings even where not sold U. Yet in the EU/EUMS, whilst safety warnings are mandated, limited efficacy claims are also permitted. In the US, these products generally may not make any efficacy claims nor carry safety warnings. As to generic substitution, it was concluded that it was the US system which seemed better justified by public interest theory. This is because it (largely) adopts the permissive-express approach and allows for first party ordering of preferences. Across the EUMS, this approach is departed from widely, the reasons for which require further explanation.

Public interest theory has not been able, therefore, to provide a complete explanation for the transatlantic regulatory divergence. Neither has it assisted fully in explaining intra-EU regulatory divergence. In the next section I turn to private interest theory, and institutional insights to identify further potential reasons for both.

4.4 Private Interests, Groups, Organisations, and Institutions

In this section I adopt a private interest approach and take a closer look at which groups and organisations have influenced the form of the regulation in each polity. After this, I consider jurisdiction-wide institutions which may have constrained or widened the options of those groups and organisations. The purpose is to identify whether differences in the strength or lobbying power of groups, the approach taken by organisations and/or the effect of other institutions in each jurisdiction or Cluster may provide some further explanation for the regulatory divergence. My primary focus is upon interest groups and their strength. The relevant organisations – the EMA, the NAs and the FDA - have already been discussed in Chapters One and Two. The most important institutions are summarised in the concluding subsection.

4.4.1 Relevant Interest Groups and Organisations

There are three potential interest groups - existing independently but corresponding to each other in both jurisdictions - which may have impacted upon the regulation through lobbying: pharmacists the pharmaceutical industry, and doctors. Then, also relevant, are the organisations of the FDA, the EMA, and the NAs.

4.4.1.1 Retail Pharmacists

Retail Pharmacists: Independent Pharmacy v Large Retail Pharmacy

Here I discuss retail pharmacists as an interest group. That interest group differs between the US and the EU and between the NEUMS and SEUMS Clusters. Retail pharmacists are comprised (in both jurisdictions) of a mixture of 'independent pharmacy' ('IP') and 'large retail pharmacy' ('LRP'). However, this is the case in different proportions for each jurisdiction/cluster.

IP is where the commercial retail interest and the pharmacist are one and the same. IP is owned and run by the pharmacist his or herself and the business is not a part of a chain nor part of a publicly traded company.[1] LRP is not pharmacist-owned and managed but instead employs pharmacists. It is not necessarily limited to pharmacy services, but often maintains large retail premises where, in addition to PO products being dispensed in the pharmacy section, GSALE products, cosmetics, food and many other general merchandise product

1 https://en.wikipedia.org/wiki/Independent_pharmacy

categories are also offered.[2] Within LRP there are a few different business models, and these are shown in a typology in Table 49 below alongside IP and drugstores.[3]

Table 49 Types of Retail Pharmacies in the US and the EU

Type	Product Range	Examples
LRP: **Large Chain Pharmacies/Drugstores**[4]	Specialised in the retail of pharmaceutical products including **U and GSALE** but diversified into some other product ranges including food, cosmetics and other U products. **In pharmacy section: PSO and PO.**	*Walgreens (USA)* *CVS (USA)* *Boots (UK)*
LRP: **Supermarket Pharmacies**[5]	Highly diversified, including **U and GSALE** as well as cosmetics, food, and most of the most common consumer goods. **In pharmacy section: PSO and PO**	*Walmart (USA)* *Tesco (UK)*
LRP: **Chain Pharmacies**[6]	Usually **GSALE, PSO and PO** products. No further products.	*Benu Apotheek (NL)* *Kronans Apotek (SWE)* *Super-Pharm (POL)*
IP: **Independent Pharmacies** [7]	Usually **GSALE, PSO and PO** products. No further products.	
Drugstores[8]	**U and GSALE.** Never PSO or PO. In addition: cosmetics/food	*Rossman (DEU)* *Etos (NL)*

Where I refer, here, to LRP I am referring collectively to 1) large chain pharmacies/drugstores, 2) supermarket pharmacies and 3) chain pharmacies. When I refer to IP, I am referring to the fourth type in Table 49 above. Retail pharmacists in the US are dominated by LRP. Retail

2 Brand franchises may fall in to this category to some extent. The FDA (2001) defines 'independent pharmacies' as those retail pharmacies with three or fewer stores. By contrast, 'chain pharmacies' the FDA defines as those with four or more stores.

3 It is important to note that where I refer to retail pharmacy, whether independent or large retail pharmacy, I do not include mere drugstores, where PO products cannot be dispensed.

4 Large retail chains with large retail premises. National or international presence. Contain a separate pharmacy section employing licensed pharmacists.

5 Large supermarket chains with large retail premises. National or international presence. Contain a separate pharmacy section employing licensed pharmacists.

6 Here this is defined as any chain with four or more branches. The difference from large chain pharmacies/drugstores is the smaller product range.

7 Privately owned by pharmacist. May be under a franchise.

8 Specialised in the retail of pharmaceutical products except for PO products: so GSALE and sometimes PSO. In addition, food and cosmetics. Generally, does not employ licensed pharmacists. Generally numerous stores in numerous locations.

pharmacists in the EU are comprised of a mixture of LRP and IP. In the SEUMS Cluster IP dominates the interest group of retail pharmacists.

In the US in 2016 CVS and Walgreens accounted for circa 29% of total prescription dispensing revenues and Walmart appeared in the top five[9] by prescription dispensing revenue.[10] Between 1980 and 2000 the US moved from a market structure of independent drugstores dispensing prescriptions from family doctors to an oligopolistic structure (for prescription dispensing) dominated by national chains. As of 2017 only 35% of retail pharmacies in the US were privately owned independent pharmacies[11] and even then, of that 35%, 25% were owned by an owner who owned more than one pharmacy (in 2014)[12] with 32% owning two or more.

This lies in stark contrast to the EU, where in many EUMS the regulatory position is still that a retail pharmacy dispensing PO products may not form part of a chain and must be owned and operated by an IP individual pharmacist. Taylor, Mrazek, and Mossialos (2004) state: *"In much of Europe, only pharmacists can purchase or establish pharmacies, and in many instances, a pharmacist cannot own or be responsible for more than one pharmacy. Such regulations inhibit the formation of large managed pharmacy chains such as those most typically found in the UK and North America."*[13] According to a 2015 report by James Dudley[14] chain pharmacies were not allowed at all in France[15], Spain, Finland, Greece, Austria, Hungary and Slovenia. In Bulgaria, Denmark, Germany, and Italy one pharmacist is not allowed to own and operate more than four pharmacies. On the other hand, in the Netherlands, Norway, Sweden, Slovakia, Belgium, the Czech Republic, Poland, Romania, Switzerland, Ireland and the UK, chain pharmacies are allowed.[16] The situation in the sample of 14 EUMS is provided in Table 50 and Figure 15.

9 www.ncpanet.org/digest

10 https://marketrealist.com/2017/10/walgreens-versus-cvs-comparing-pharmacy-giants/

11 https://www.nationalcooperativerx.com/independent-vs-chain-pharmacies

12 https://ncpa.org/independent-pharmacy-today

13 Taylor, David, Monique Mrazek, and Elias Mossialos. "Regulating pharmaceutical distribution and retail pharmacy in Europe." Regulating pharmaceuticals in Europe: striving for efficiency, equity and quality. Copenhagen, European observatory on health systems and policies, 2004a (2004): 196-121 *quoted in* Písek, Jaroslav. "How Strong are the Pharmacy Chains within the EU?." In *INPROFORUM 2017*.

14 Summarised in https://www.prnewswire.com/news-releases/over-half-of-europes-pharmacies-are-grouped-into-wholly-owned-or-affiliated-to-chains---says-new-report-300188788.html

15 E.g. *"The pharmacist must be the owner of the community pharmacy of which they are the licensee. The pharmacist can only be the operator of a single community pharmacy as they are bound by an obligation of personal practice but may invest in the capital of two other private practice pharmacy companies."* See https://epheu.eu/france-more-about-pharmacy

16 These restrictions (in the first list) relate to pharmacies where PO products may be dispensed. This means that some EUMS appearing in the list where chain pharmacies (or more than four) are not allowed may have very large drugstore chains selling everything except PO products. Germany is one example where Rossman operates 2,196 stores, DM 1,997, Muller 566 and Budnikowsky 192 as of 2020.

Table 50 Regulation of Chain Pharmacies Selected EUMS Circa 2017

Forbidden	More than Four Forbidden	Permitted
France	Denmark	Netherlands
Spain	Germany	Sweden
Finland	Italy	Belgium
Austria		Ireland
Greece		UK
Portugal		

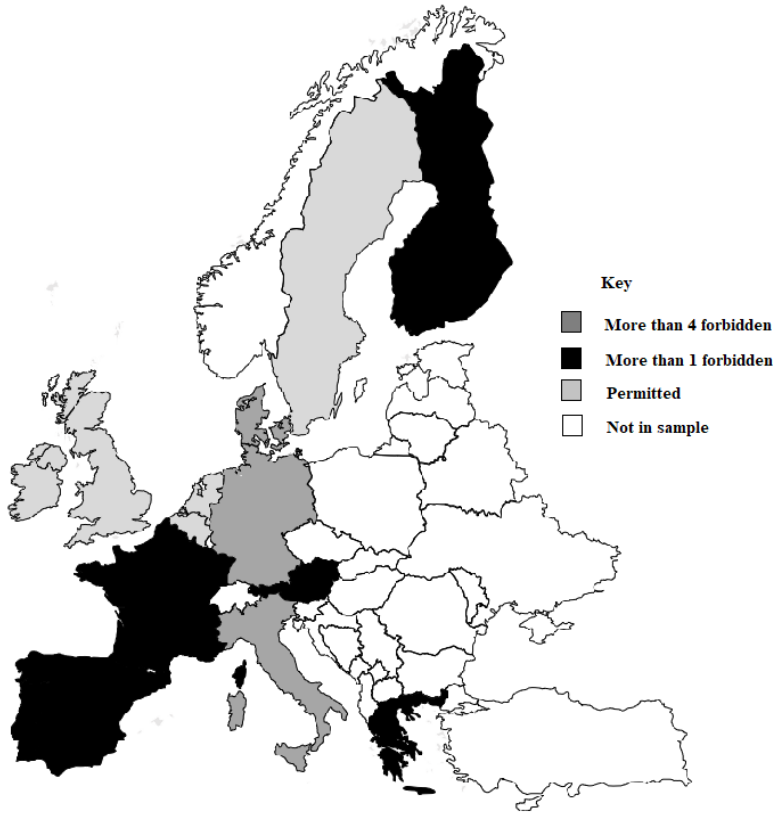

Figure 15 **Regulation of Chain Pharmacies Selected EUMS Circa 2017**

Apart from the anomaly of Finland, there is a strong correlation between the SEUMS Cluster as defined at the beginning of the previous section and those EUMS where chain pharmacies are not allowed or are restricted to a small number.[17]

17 The UK was a clear exception to the general EU position. For example in England between 2001 and 2011 'Retail-driven large multiples' and non-retail driven large multiples (which we call here Large Chain Pharmacies/Drugstores), small multiples (chain pharmacies) and supermarket pharmacies together accounted for 61.5% of new pharmacy licenses issued, which overall number itself increased steeply from 2005-2011 (9,736 to 10,951 respectively compared to a 9,756 and 9,736 in 2001 and 2005 respectively. As of 2019 there were 14,000

For the EU, according to the 2017 study,[18] there were 160,000 retail pharmacies and 16.7% of these were wholly owned by chains (LRP). According to the 2015 study this was 13.3% in the 20 countries sampled and three large publicly traded companies: 1) Celesio 2) Walgreens Boots Alliance and 3) Phoenix were (in 2015) in ownership and control of 35% of the pharmacies in that 13.3% subset. Even though it is only roughly half of the EUMS in Table 50 above which forbid chain pharmacies, in the remainder of the EUMS it is only a small number where LRP dominates. In only four EUMS did LRP hold 80% or more of pharmacies: Sweden, Estonia, Lithuania, and the UK.[19] In Italy only 9% of pharmacies are held by LRP.[20] If one removes UK data from the whole of the EU then the market share held by large retail pharmacy stands at 10.4% compared to 65% in the US. The conclusion drawn here is that retail pharmacists in the US are dominated by LRP whilst in the SEUMS Cluster they are dominated by IP. This is summarised below in Table 51.

Table 51 Composition of Retail Pharmacists as an Interest Group US & EU/EUMS (IP/LRP)

	Large Retail Pharmacy (LRP)	Independent Pharmacy (IP)
United States	Strong	Weak
NEUMS	Moderate	Moderate
SEUMS	Weak	Strong

Pharmacists who work in retail pharmacy either work in employment for LRP or independently in IP. The objectives of the former are commercial whereas those of the latter are both commercial and non-commercial. LRP employs professional pharmacists but is also comprised of a much larger operation including capital interests, and those non-pharmacy aspects of the business. In the US pharmacists are a relatively weak interest group because they are overwhelmingly employed by a highly concentrated market of LRP corporations against which US pharmacists have little bargaining power. In those EUMS oriented towards the SEUMS Cluster, pharmacists are a strong interest group, being independent from LRP which, in the SEUMS Cluster is weak or non-existent due to the restrictions upon chain ownership meaning that most pharmacists work as IP. In Spain, France, and Italy in particular

retail pharmacies in the UK and the market was highly concentrated with the 12 biggest companies holding 49.2% of the market. Boots operated 2,376 pharmacies and was/is the biggest player in the Large Chain Pharmacies/Drugstores market holding a 33.3% share of the market in which outfits with 100 or more pharmacies operated. Following behind this are a mixture of Large Chain Pharmacies/Drugstores including: Lloyds pharmacy (Chain pharmacy), Well (Chain pharmacy), Rowlands (Chain pharmacy), Tesco (Supermarket pharmacy), Sainsbury's (Supermarket pharmacy), Day Lewis Pharmacy (Chain pharmacy), and Asda (Supermarket pharmacy). In the UK therefore, large retail pharmacy is on the rise and posing fierce competition to independent pharmacy. See https://www.nl.kearney.com/health/article/?/a/the-future-of-community-pharmacy-in-england. See also: https://start.askwonder.com/insights/need-know-turnover-major-pharm-store-chains-following-countries-uk-france-italy-n1t3dko2e. See also Písek (2018).

18 Písek (2018).

19 Ibid.

20 It should be noted that in those EUMS where chain pharmacies are forbidden, there are co-operative solutions adopted whereby independent pharmacies cooperate with each other to benefit from economies of scale and superior purchasing power, Denmark and Germany are notable examples where this system is widely adopted. This does not, however, change the fact that pharmacies in these countries remain independent pharmacies which are pharmacist owned and operated.

pharmacists have successfully protected their professional independence, avoiding integration with LRP, and remaining IP. In those EUMS oriented towards the NEUMS Cluster, pharmacists have successfully maintained high incomes relative to the SEUMS Cluster and to the US but relative to the SEUMS Cluster (only) have protected less well their independence from LRP.

One way to assess the relative strength of pharmacists as an interest group in the jurisdictions/clusters is to look at the characteristics of the profession itself.[21] Olson says that an interest group will be successful where it is small, well-organised and focused on a single issue.[22] As such, when it comes to pharmacists, I look for a relatively small overall number of pharmacists working in a relatively small number of pharmacies. Another method which has been used when assessing professions as an interest group is to consider the extent to which they have successfully lobbied for regulation which lies in the benefit of the profession.[23] This is the rent-seeking hypothesis – taken from Tullock (1967),[24] Becker (1983),[25] Buchanan, Tollison & Tullock (1980)[26] and Buchanan and Tullock (1962).[27] It comes from capture theory and Stigler's economic theory of regulation.[28] In the case of pharmacists I consider the barriers to entry to the profession in the form of educational requirements, as well as examples of other forms of barrier to competition and restrictions upon the overall number of pharmacists. As a crude measure of how effective these have been, I consider how the median salaries of pharmacists in the US and EUMS compare to the average salary in those countries. Table 52 shows some data on the US and the sampled EUMS.[29]

Pharmacists in the US

Most pharmacists in the US belong to the American Pharmacists Association[30] based in Washington DC. Of the 297,100 pharmacists in the US in 2014, 65% of these worked in retail pharmacies, and most of these were salaried employees.[31] Entry to the profession requires a Doctor of Pharmacy degree followed by successfully passing the North American Pharmacist Licensure Examination.[32] Including the bachelors level study which must take place before

21 See, for example, Philipsen, Niels. *Regulation of and by pharmacists in the Netherlands and Belgium: an economic approach*. Vol. 45. Intersentia nv, 2003.

22 Olson, M. "The Logic of Collective Action: Public Goods and the Theory of Groups (Cambridge, MA: Harvard)." (1965).

23 For an empirical analysis of this type of rent seeking see Faure, Michael, Jörg Finsinger, Jacques Siegers, and van den R. Bergh. "Regulation of Professions: A Law and Economics Approach to the Regulation of Attorneys and Physicians in the US, Belgium, the Netherlands, Germany and the UK." (1993).

24 Tullock, Gordon. "The welfare costs of tariffs, monopolies, and theft." *Economic Inquiry* 5, no. 3 (1967): 224-232.

25 Becker, Gary S. "A theory of competition among pressure groups for political influence." The quarterly journal of economics 98, no. 3 (1983): 371-400.

26 Tullock, Gordon, James Buchanan, and Robert Tollison. "Efficient Rent-Seeking: Toward a Theory of the Rent Seeking Society." Texas A&M University Press (1980): 97.

27 Buchanan, James M., and Gordon Tullock. "The calculus of consent (University of Michigan Press, Ann Arbor, MI)." (1962).

28 Stigler, George J. "The theory of economic regulation." The Bell journal of economics and management science (1971): 3-21.

29 OECD (2015), "Pharmacists and pharmacies", in Health at a Glance 2015: OECD Indicators, OECD Publishing, Paris. DOI: https://doi.org/10.1787/health_glance-2015-67-en

30 https://www.pharmacist.com/about-apha

31 United States Bureau of Labor Statistics

32 There are requirements and regulations at the State level also

embarking on the Pharm.D degree, and including mandatory vocational training, it takes eight years (at least) to qualify as a practising pharmacist in the US.[33] Educational barriers to entry in the EU are low compared to the US.[34] The US has 92 practising pharmacists per 100,000 population, slightly above the OECD average of 82 and above the EUMS average of 83.9 but well below that of the highest EUMS: Belgium (121), Spain (119), Italy (116) and France[35] (112).

The US has well below the OECD average number of retail pharmacies per 100,000 population at 10.4 (OECD average 24.7) and well below the EUMS average of 26.5. To assist with the analysis here I have calculated a ratio of pharmacists to pharmacies. In the US this stands at 9.11 pharmacists per pharmacy. The average of the EUMS in this sample is much lower at 3.17. Taken in conjunction with the high number of retail pharmacies in the EUMS sampled, this suggests that in the EU a greater proportion of pharmacists are working in small, independent pharmacies (IP). The reason I arrive at this conclusion is because, despite having a small number of pharmacists overall (per 100,000 population) in the EUMS sampled, these pharmacists work in more pharmacies – over twice as many as in the US. Some of the surplus US pharmacists may be working in research, or in hospital pharmacies, but well over half (65%) work in retail pharmacies. The conclusion can be reached that more of the US pharmacist are working in larger pharmacies located in urban centres. This also corresponds with the data given in the last section, which indicates that LRP dominates retail pharmacy in the US.

33 It seems anomalous that US pharmacists would have a longer period in education and yet fewer responsibilities in their profession. I believe that the difference is partly due to a general difference between the US and the EU regarding time taken to complete professional education. Lawyers in the US, for example, also spend much longer in professional education than many of their European counterparts.

34 There is EU-wide regulation concerning the minimum duration of education and training for professional pharmacists (5 years) found in Article 44 of Directive 2005/36/EC the European Parliament and of the Council of 7 September 2005 on the recognition of professional qualifications.

35 France provides a typical example of the regulation restricting multiple ownership of pharmacies: *"The pharmacist must be the owner of the community pharmacy of which they are the licensee. The pharmacist can only be the operator of a single community pharmacy as they are bound by an obligation of personal practice but may invest in the capital of two other private practice pharmacy companies"* https://epheu.eu/france-more-about-pharmacy. See Arrêté du 15 mai 2011 relatif au nombre de pharmaciens dont les titulaires d'officine doivent se faire assister en raison de l'importance de leur chiffre d'affaires [Decree of 15 May 2011 on the number of pharmacists pharmacy owners need to have, based on their turnover], including amendments until September 2018 (in French). Paris: Journal Officiel de la République Française; 2011: 6 August (SANM9101766A). See also https://www.legifrance.gouv.fr/codes/texte_lc/LEGITEXT000006072665. See finally *https://epheu.eu/france-more-about-pharmacy*

Table 52 Summary Statistics on Pharmacists and Pharmacies in US, EU, and Sampled EUMS

	Pharmacies[36]	Pharmacists[37]	Ratio[38]	Pharmacist Income[39]	Years Education[40]
OECD average	**24.7**	**82**	**3.32**		
United States	**10.1**	**92**	**9.11**	**141%**	**8**
Average EUMS	**26.5**	**83.9**	**3.17**	**165%**	**5**
Belgium	43.9	121	2.76	164%	5
Ireland	37.5	111	2.96	202%	5
Poland	35.7	74	2.07	124%	5
Portugal	28	84	3	130%	5
UK	22.1	83	3.76	235%	5
Netherlands	11.7	21	1.79	216%	5
Sweden	13.3	76	5.71	119%	5
Denmark	3.9	51	13.08	143%	5
Italy	29.9	116	3.88	158%	5
Germany	24.8	64	2.58	175%	5
Austria	15.4	71	4.61	173%	5
France	34	112	3.29	146%	5
Spain	47.2	119	2.52	162%	5

Turning to incomes,[41] I have worked out a crude measure of pharmacist median income for the purposes of comparison with the EUMS sampled. This is done by[42] taking information from online salary websites as to the median income for pharmacists in each country and

36 Number of retail pharmacies per 100,000 population 2013 or nearest year (OECD 2015)
37 Practising pharmacists per 100,000 population 2015 or nearest year (OECD 2015)
38 Number of pharmacists per pharmacy per 100,000 population.
39 The median pharmacist salary expressed as a percentage of the average national salary (salary and income data taken from salary comparison websites).
40 The number of years required to train and qualify as a pharmacist in that country, taken from Wikipedia.
41 It is important to be cautious about this as it is always difficult to be certain of approximating overall annual income due to a lack of reliable data, and cross-country comparisons are difficult because in one country pharmacists may be able to supplement their salary income with other services on the side or bonuses from health insurers etc, whilst in another they may not. On this point see Philipsen, Niels J., and Michael G. Faure. "The regulation of pharmacists in Belgium and the Netherlands: in the public or private interest?." Journal of Consumer Policy 25, no. 2 (2002): 155-201.
42 https://www.careerexplorer.com/careers/pharmacist/salary

information regarding the average salary in each country[43] and expressing the former as a percentage of the latter. In the case of the US, this is 141%, thus the median pharmacist earns 141% of the average US salary. This is quite low relative to the average of the EUMS sampled (165% of average salary) and very low compared to the Netherlands (216%) the UK (235%) and Ireland (202%).

That is confusing given that a minimum eight years of study and training are required to become a pharmacist in the US, compared to only five years across the EU. High educational requirements are a barrier to entry which should restrict the number of people entering the profession, yet the US has higher than the OECD (and the EUMS sampled) average number of pharmacists per 100,000 population. Restrictions upon entry should lead to a low number of pharmacists overall and higher earning per pharmacist. Look, for example, at the Netherlands which has a similar number of retail pharmacies per 100,000 population to the US (11.7 NL v 10.1 US) yet a much smaller number of pharmacists (21 per 100,000 population versus 92 per 100,000 population US). The effect of this restriction seems to show in the earnings of Dutch pharmacists (216% of average Dutch income).

I suggest again that the reason is that in the US, lots of pharmacists are working in a relatively small number of LRP establishments or supermarket pharmacies like Walgreens, CVS, and Walmart. By contrast, I believe, the Dutch pharmacist work mainly in independent pharmacies (or small chains). These small pharmacies in the Netherlands are more likely to be owner operated. Thus, the owner pharmacists are taking a greater share of the profits of the pharmacies than pharmacists working for large retail pharmacy in the US because these profits are not being distributed to financial investors and/or equity shareholders or used to pay salaries of support staff or invested in corporate expansion etc. In addition, these pharmacies are never likely to be short of business because clearly in the Netherlands there are restrictions upon supply of pharmacies and pharmacists and therefore a lack of competition.[44] This explains high pharmacist incomes in the Netherlands: restrictions upon supply have created supernormal profits pocketed largely by Dutch pharmacists.

By contrast, in the US, large chain pharmacies/drugstores, supermarket pharmacies and chain pharmacies (all LRP) are employing many licensed pharmacists as salaried workers to dispense medications. Whilst there is a restriction on the supply of pharmaceutical dispensing services (i.e. pharmacies) in the US vis a vis the OECD average,[45] there is an oversupply of pharmacists on the labour market meaning these command only a low wage. It could be that the supernormal profits gained by the pharmacy owner/operators in the US from the restriction on supply of pharmacies is being pocketed there by non-pharmacist actors whilst the professional pharmacists take only their contracted salary, over which they have little bargaining power due to the oversupply of pharmacists. Therefore, in the US it is LRP which benefits from the restrictions upon supply, and not pharmacists themselves.

43 http://www.salaryexplorer.com/salary-survey both in local currency

44 This can be deduced from the small number of pharmacies per 100,000 population. See also Philipsen and Faure (2002) where the point is substantiated in detail.

45 And the average of certain EU MS sampled such as Belgium and Spain: see the number of pharmacists per 100,000 population.

Pharmacists in the SEUMS and NEUMS

In those EUMS oriented towards the SEUMS Cluster IP are a particularly strong interest group relative to in the US. This view is borne out by the data in Table 52. Belgium, France,[46] Spain, and Italy all have a high number of pharmacists per 100,000 population (121, 112, 119 and 116 respectively: OECD average 92 and EUMS sampled average 83.9/US 82). They also - unlike their counterparts elsewhere in Europe which also have high numbers of pharmacists - have a high number of retail pharmacies per 100,000 population: 43.9, 34, 47.2 and 29.9 respectively (OECD average 24.7/EU MS sampled average 26.5/US 10.1). This means that their ratio of pharmacists to pharmacies is mostly on the low side relative to the OECD average: 2.76, 3.29, 2.52 and 3.88 respectively (OECD average 3.32) and very low indeed compared to the US figure of 9.11. This – taken together with the widespread ban on chain pharmacies - strongly suggests that for those EUMS oriented towards the SEUMS Cluster there are a lot of small pharmacies, mostly independent and separate from each other, owned, and operated by a small number of pharmacists. Due to the oversupply of both pharmacists and pharmacies, salaries are not particularly high in the SEUMS Cluster - at least relative to the rest of the EUMS Sampled. They are: 164% (Belgium), 146% (France), 162% (Spain) and 158% (Italy).[47] These SEUMS pharmacists do have a better relative income than their US counterparts (US: 141%). But, it seems that NEUMS pharmacists have been best at lobbying for regulations which protect their income.

However, pharmacists in the NEUMS Cluster have not lobbied for protection of their independence from LRP. Indeed, the countries with the highest relative income ratio: the UK, the Netherlands, and Germany, all permit multiple ownership of pharmacies, although Germany only up to four. The highest – the UK – is (was) also the (then) EUMS with the greatest domination by LRP. This is different to the situation in the US, where the domination of pharmacists by LRP seems to have ended up leaving pharmacists with median incomes low relative to the EUMS sampled. Some NEUMS resemble the plight of US pharmacists. In Sweden and Denmark where chain pharmacies are permitted[48] median pharmacist incomes are low relative to the EUMS average.

Conclusions

I have identified a relatively consistent pattern in Italy, Spain, and France where IP are prevalent, where restrictions on supply of pharmacists and pharmacies have not been as

46 France has also sought to tackle oversupply of pharmacists through restrictions on the number of students who may study pharmacy in any given year. In addition, the number of pharmacies permitted to obtain licences are limited by the Code de la santé publique (Articles L.5125-3 and following) with a quota of 2500 inhabitants of a settlement required to obtain the first license and 4500 thereafter for each additional license. These restrictions on the number of community pharmacies allowed, and the number of pharmacy students permitted, are perhaps a response to an oversupply of both pharmacies and pharmacists in France, given the overall figure of 34 retail pharmacies per 100,000 population in France (OECD average 24.7, and 112 pharmacists per 100,000 population (OECD average 82). It is the case that pharmacies in France are present within easy reach of most people, and that pharmacists play a key role in communities and in the provision of certain aspects of healthcare. This approach is the same in much of the south of the SEUMS Cluster: whilst attempts are made to restrict supply of pharmacies and pharmacists there is still oversupply of both (relative to the OECD average, to the NEUMS Cluster and to the United States), yet professional pharmacists appear to have successfully lobbied to maintain their independence from large retail pharmacy through the regulation disallowing chain pharmacies.

47 Compare the EUMS sampled average of 165%, and the UK (235%) the Netherlands (216%) and Ireland (202%).

48 In Denmark not more than four.

successful for pharmacists as they are in the north of Europe, and where chain pharmacies are not permitted, and thus LRP does not dominate retail pharmacy. In the north of Europe, restrictions on supply have been more successful in raising median incomes, and pharmacists seem to have taken relatively more of this surplus. I summarise this analysis of pharmacists in the US, the EU, and the NEUMS/SEUMS Clusters below in Table 53.

Table 53 Retail Pharmacists as an Interest Group in the US, EU, and EUMS

	Retail Pharmacists Strength as Interest Group	Independence of Retail Pharmacists
United States	Relatively Weak	Dominated by LRP
NEUMS	Relatively Strong	Sometimes dominated by LRP (e.g. UK/SWE) Sometimes relatively independent from LRP (e.g. NL)
SEUMS	Relatively Strong	Generally independent from LRP

Directly comparing the SEUMS with the US and some NEUMS, I believe there has been a trade-off faced by pharmacists between ensuring their independence from LRP and maximising their incomes. This is because independence seems to lead to oversupply of pharmacies and pharmacists, leading to high levels of intra-retail pharmacists competition, which results in relatively low median incomes.[49]

4.4.1.2 Doctors, the Pharmaceutical Industry and Agencies

Up to this point I have considered the most important interest group for the private interest analysis which follows – pharmacists (whether they operate as IP or are dominated by LRP) - in both the US and the EU and the NEUMS and SEUMS Clusters. Now I touch upon the major remaining interest groups: doctors, and the pharmaceutical industry, and organisations: the FDA, EMA and NAs.

I previously argued[50] that doctors in the US, having avoided 'capture' by agencies and social healthcare systems, represent a strong interest group relative to their EU counterparts.[51]

49 Oversupply of pharmacies seems to result *from* the independence requirement for pharmacies. This is because usually only a large company with sufficient financing will be able to place a very large pharmacy in an urban centre serving a large population and staffed by multiple licensed (salaried) pharmacists. Because in the SEUMS pharmacies must often be owner operated, this is not possible, and instead multiple small pharmacies spring up. The resulting lost economies of scale lead to an oversupply of pharmacists and thus lower relative median incomes per pharmacist. In the US large economies of scale and a small relative number of (large) retail pharmacies) make the retail pharmacy business very profitable but most of that surplus is taken by large retail pharmacy (investors, shareholders etc) and the remainder is shared out between quite many (salaried, employed) pharmacists.

50 See Chapter 2: Licensing and Direct-to-Consumer Advertising.

51 But also, that their lack of capture by such agencies and systems has caused them to have to compete for patients in the US, which has led to consumer/patients being a strong interest group in the US relative to the EU.

Doctors in the US have historically been targeted[52] by the US pharmaceutical industry (USPI), through detailing: the advertising of pharmaceutical products directly to doctors. It is argued here that this has led to an historical alliance between doctors and USPI in the US. Doctors, not being salaried and in the employment of agencies and social healthcare systems, were free to supplement their income with benefits from USPI detailers. USPI itself benefitted from this because it meant that doctors were more likely to prescribe the products being advertised by the detailer. This alliance between doctors and USPI was at its height when the prescriptions system was introduced, and I argue below that the concept of PO medicines was introduced for the mutual benefit of doctors and USPI. This was to the detriment of consumers and IP pharmacists, but arguably to the benefit of LRP pharmacists. This alliance was partially prompted by products liability law in the US, which placed a heavy burden on USPI. The pharmaceutical industry was able to share this burden with doctors through the 'learned intermediary' doctrine and the prescription system.[53]

Table 54 Doctors in the US and EU/EUMS and Relationships/Autonomy (2)

	US	**EU**
Autonomy v the State (hospitals/agencies)	High	Low
Autonomy v Pharmaceutical Industry	Low	High
Autonomy v Consumers	Low	High
Consumer Autonomy	High	Low

By contrast, in the EU doctors have been captured by agencies and social healthcare systems – as set out fully in Chapter Two. Subsequently their freedom to develop such an alliance with the pharmaceutical industry in the EU (EUPI) was weak relative to the situation of doctors in the US. As such EUPI has focused its efforts upon lobbying (or collaborating with) the EU Commission and EU organs or the NAs instead of focusing their efforts upon doctors directly.[54]

That has resulted in a relatively hierarchical relationship between patients and doctors in the EU but a relatively egalitarian relationship between doctors and patients in the US where patient autonomy/choice is paramount.

52 See Manchanda, Puneet, and Elisabeth Honka. "The effects and role of direct-to-physician marketing in the pharmaceutical industry: an integrative review." Yale J. Health Pol'y L. & Ethics 5 (2005): 785.

53 This was the historical approach, at the time that mandatory prescriptions were introduced in the mid-20th Century. On the other hand, in recent decades, the alliance between doctors and the pharmaceutical industry has weakened, partly because of the lifting of the moratorium on DTCA, which has enabled the pharmaceutical industry in the US to reach directly to consumers to advertise their products. Consumers in the US share an egalitarian relationship with their doctors due to the (independent) doctors needing to compete to maintain their patient base and thus the effectiveness of DTCA is ensured because consumers/patients will reliably seek the prescription from the doctor who will usually oblige (within reason). The pharmaceutical industry in the US, it was argued, has been benefitted a great deal in products liability law by the 'learned intermediary' doctrine, whereby the prescribing doctor will normally bear the liability burden in the case of prescription-only medicines – where there is little safety information on the product label because the product is only used under the supervision and monitoring of the doctor. Effectively, the pharmaceutical industry, through prescription only medicines, has shared the burden of products liability risk with doctors, in exchange for the benefits which they gave to doctors through detailing etc.

54 Detailing to doctors, and to pharmacists is and has been endemic in the EU/EUMS of course, but it is submitted that detailing to pharmacists has been more widespread in the EU than in the US because pharmacists in the EU

I summarise the analysis of US and EU doctors, and USPI and EUPI, in Table 54 and Table 55 again above, and below, respectively.

Table 55 Pharmaceutical Industry in the US and the EU (2)

Institutional Framework	Relationships	Business Model	Lobbying Priorities
United States (USPI) No price regulation Less socialised healthcare DTCA	**Adversarial** Intense competition intra-USPI Arms-length with FDA Tolerated by consumers BUT: Allied with US Doctors	**Blockbuster Model: USPI** More innovation less manufacturing Blockbuster products Profit maximise	**Embrace risk:** Permit high punitive damages but liability must be tied to fault
European Union (EUPI) Price regulation Socialised healthcare No DTCA	**Corporatist** Avoid intense intra-EUPI competition Cooperate with EMA/NAs Estranged from consumers	**Stability Model: EUPI** More manufacturing less innovation Stable returns on capital in EU Profit satisfice	**Avoid risk:** Harmonise EUMS regulation of product liability Cap total damages but EUPI will act as insurer of last resort for consumers even without fault

Finally, I summarise again, in Table 56 and Table 57, below, the characterisation of the FDA, EMA and NAs and their relationships with the other relevant actors, which I set out at length in Chapters One and Two.

are able to advise patients on certain medications. Something which is not the case in the US where there are only two sale classification categories, and no PSO category. In addition, because DTCA is not allowed in the EU, the efforts of the pharmaceutical industry in detailing to pharmacists (in addition to doctors) has always had greater relative importance.

Table 56 The FDA, the EMA and the NAs Key Characteristics (4)

FDA	NAs/EMA
'Direct to Consumer Accountability'	'Double' (NAs) and then 'Treble' (EMA) 'Insulation'
Relative Resistance to Industry Influence	Capture by Default
Politicised Science	Science Excludes Politics

Table 57 Extended Reputation Model Applied to FDA and EMA/NAs (3)

	FDA	EMA/NAs
Reputation	*Consumer Protection/Quick Product Access* *Scientific Expertise (but politicised)*	*Science Based Assessment* *Apolitical*
Main Audience	*Primarily Consumers*	*Primarily Industry and EUMS Ministers*
Industry	*Relative Resistance to Industry Influence*	*Industry Capture by Default*
Doctors	*Safety gatekeeping* *(US doctors accommodate consumers)*	*Reliance on doctor matching* *(EU/EUMS doctors advise consumers)*
Consumers	*Highly responsive/directly accountable* *(activist US Consumers)*	*Less responsive/lack of accountability* *(passive, institutionalised EU consumers)*

I now apply these insights regarding the characterisation of these interest group and organisation to seek to explain the regulatory divergences in sale classification and generic substitution.

4.4.2 United States

To recapitulate: the US has only two categories for sale classification: GSALE and PO. In addition, and because of this, it has less switching between those categories and as such a relatively large proportion of pharmaceutical products are classified PO. NRPs are found on GSALE, however, but with historically strict indications and instructions for use which initially did not permit marketing for long term use, temporary cessation attempts and/or concurrent use of these products. Herbal remedies generally are not sold as medicinal products because the standards of efficacy required for a successful NDA to the FDA in respect of these products remains high. As such, most herbal remedies are still sold as dietary supplements and as U products. On generic substitution, the practice and its regulation were adopted relatively early in the US, and most states regulate generic substitution in the form permissive-express.

4.4.2.1 Sale Classification

Sale Classification Generally

Because the US has only two sale classification categories the key aspect of the regulation which requires analysis is the prescription system. The basic legislative basis in the US for compulsory prescriptions and thus creation of the PO category was found in the FDCA 1938. Scholars have disagreed over why precisely the loose language in the FDCA was developed to become the mandatory prescription system known today. Some argued that the prescription system came about in the US due to advances in biomedical sciences which led to an abundance of antibiotics on the market in the late 1940s and 1950s. It was later argued that the introduction of compulsory prescriptions was a power grab by USPI, allied with the FDA in the matter.[55] This account reflects capture theory, with the FDA policies reflecting *"the concerns and interests of the regulated industry"*.[56] Harry Marks argues differently, asserting that it was not a case of capture, but that the FDA acted to introduce mandatory prescriptions to prevent abuse by USPI of a prescription labelling exemption[57] found in regulations from 1944 which imposed mandatory product labelling.

Marks' argument makes more sense given what I have explained above about the relationship between the FDA and USPI- not marked by capture, but instead adversarial. Here I adopt Marks' argument but go further and argue that the introduction of the compulsory prescription system was a collaboration between a coalition of doctors, USPI, and pharmacists (in this case what would later become LRP).

The Development of the Compulsory Prescription System

The compulsory prescription system was fully introduced around 1951 at the time of the Durham-Humphrey Amendment to the FDCA. The Amendment stated that a *"drug could be dispensed 'only upon a written prescription' if because of its toxicity or other potentiality for harmful effect, or the method of its use, or the collateral measures necessary to its use, [it] is not safe for use except under the supervision of a practitioner licensed by law".*[58] Below I set out the relevant interest groups and the impact they had on the adoption of this amendment, starting with USPI, then doctors, and finishing with pharmacists.

US Pharmaceutical Industry

The prescription system benefits USPI in two distinct ways. In the first, prescriptions provide doctors with control over the consumption choice of consumers, in addition to eliminating scope for a pharmacist intermediary to influence this consumption decision. Because there was, at this time, a strong alliance between doctors and USPI in the US -founded upon the practice of detailing - the pharmaceutical industry already had an infrastructure set up through which it could indirectly influence the consumption decisions of consumers through

55 Temin, Peter. "The origin of compulsory drug prescriptions." *The Journal of Law and Economics* 22, no. 1 (1979): 91-105.

56 Marks, Harry M. "Revisiting" the origins of compulsory drug prescriptions"." American Journal of Public Health 85, no. 1 (1995): 109-115 at 109

57 The exemption allowed pharmaceutical firms to avoid providing detailed information on product labels if the label instead indicated that the product was only available for sale upon prescription by a doctor.

58 Marks (1995) at 112.

their doctors. The introduction of mandatory product labelling in the 1944 regulations disrupted this infrastructure because it provided information directly to the consumer. USPI could not so easily influence consumers - through information on a product label which could be compared with information on the label of another product side by side on the pharmacy shelf - as they could influence doctors. USPI therefore wanted to restrict the channels through which information reached the consumer. It therefore lobbied for the prescription labelling exemption in the 1944 regulations and once the exemption was ensured, it made extensive (abusive) use of it.

The second way in which the prescription system benefits USPI relates to liability risks. Product liability concerns followed from having to label every product under the mandatory labelling provisions of the 1944 regulations. USPI relies on the 'learned intermediary doctrine' to shield it from liability in cases where a doctor had been available to monitor and guide the consumer in his or her use of the product. As the doctor always had superior knowledge of the consumer's medical history, normally the doctor would bear (or at least share) liability for any harm caused by the product. This comfortable situation for USPI was displaced by the 1944 mandatory labelling regulations and by 'failure to warn' as a head of liability in US States products liability law. Where no information appeared on a product label because it was subject to doctor prescription, guidance, and monitoring, then the learned intermediary doctrine would shield the pharmaceutical firm from liability. Where information did appear due to mandatory labelling then any deficiency in that information could lead to direct liability of the firm towards the consumer. It was safest for USPI to avoid placing any information on the product label wherever possible. By securing wide exemptions in the form of the prescription labelling exemption and later the compulsory prescription system, USPI ensured that once again the doctor was the learned intermediary.

US Doctors

Doctors also wanted exemptions to the 1944 mandatory labelling regulations which (the exemptions sought by doctors) would provide for PO products subject to doctor monitoring and without detailed labelling. Product labelling, being information direct to consumers, would have the potential to cut out the need for the consumer to obtain the doctor's advice. By contrast, a prescription system made the doctor indispensable. Thus, doctors sought this regulation to protect and strengthen their role as an interest group. Secondly, doctors - at this point strongly allied with USPI - were happy to continue with the system in which information regarding pharmaceutical products flowed from USPI, through doctors, to consumers instead of direct from the industry to the consumer. In return for this, doctors continued to receive the benefits which USPI gave to doctors through the practice of detailing. Doctors stood to bear some of the liability burden for defective PO pharmaceutical products under the compulsory prescription system, however this had also - and almost always, rather than just in the case of PO products - been the case under the pre 1944 system. The new system was preferable to doctors to the system under the 1944 regulations (without exemptions) which threatened to cut out the doctor altogether.

(Some) US Pharmacists

Under the pre 1944 system pharmacists would provide some expert advisory role to patients in the case of products recommended (but back then not necessarily prescribed) by a doctor. Pharmacists were free to sell any product which they were licensed to have in stock, whether or not a doctor had provided formal authority for the pharmacist to do so, in the form of a prescription. It seems like this system should have been preferred by pharmacists maximising, as it did, their scope both to provide advice and sell goods. This changed somewhat after the introduction of mandatory labelling, including the prescription labelling exemption in the 1944 regulations.[59] Many pharmacists were unhappy with the restrictions placed on their ability to sell goods and provide advice and some simply continued to sell prescription drugs without a prescription. Following a US Supreme Court (SCOTUS) decision in 1948, the FDA began to crack down on this behaviour, including a policy forbidding pharmacists to refill prescriptions without the prior written authorisation of a doctor.[60]

The US National Association of Retail Druggists[61] then lobbied the US Congress for the introduction of compulsory prescriptions, to replace the exemption-based system. The problem which the pharmacists had in this case was that (at the time in 1949) it was the manufacturer and not the FDA which decided whether a product would be placed in the PO category – i.e., whether to make use of the prescription labelling exemption. This placed an administrative burden upon retail pharmacists, as they had to carefully control stock and sales to ensure that the regulations were kept to. Yet, one pharmaceutical manufacturer could classify a given product as PO whilst another (with the same product) may classify it off-prescription. The risks of selling (or refilling) a product mistakenly without prescription posed these business-minded pharmacists with a potential liability burden which they wished to avoid. The Durham-Humphrey Amendment - introducing *compulsory* prescriptions - was the result of this lobbying of the US Congress by the pharmacists, assisted by lobbying from the pharmaceutical industry and doctors.[62]

Conclusions: Compulsory Prescriptions System

It can be seen here how US pharmacists were part of a coalition which – along with doctors and USPI – jointly called for the introduction of the compulsory prescription system in the US. However, it was a specific faction within US pharmacists: the business minded pharmacists – seeking to maximise their revenues rather than secure or redeem their previous role as advice givers and experts – who lobbied to cement the 1944 regulations into the Durham Humphrey Amendment.[63] After the introduction of the compulsory prescriptions system in the US, there

59 Marks (1995) at 112
60 Ibid.
61 Ibid.
62 The final regulations set the standard (copied above) which would determine whether or not a product would be classified PO. However, it would remain the pharmaceutical manufacturer which would decide on the application of that standard to the specific product. but that the FDA would challenge this through the courts if necessary. In effect now the FDA licenses based on the proposed sale classification and thus if the proposed sale classification is not restrictive enough then the sponsoring firm will not get a license – this also ensures consistency.
63 Doubtless, there were many less commercially focused pharmacists within that group who would have preferred that both the prescription labelling exemption and mandatory product labelling systems had never been introduced. However, those voices within retail pharmacy had been drowned out in the late 1930s and early

came the rise of LRP to dominate the interest group of pharmacists and the IP pharmacists which had been common prior to the introduction of compulsory prescriptions dwindled in number in the US over the following decades.

The analysis undertaken here helps begin to explain how the US *arrived at* its current regulation of sale classification. This, however, requires further analysis.

US Two Category Sale Classification System Today

To have a GSALE category, and to place all products which are not in the PO category in the GSALE category suits the interests of LRP. This is because having just a GSALE category and a PO category enables LRP undertakings to lower the administrative costs of their business. Their employed pharmacists, working at the pharmacy counter, can take prescriptions and dispense products which are then paid for at the cash register. The other arm of this business – selling the remainder of the product line, including all GSALE products, can occupy the rest of the shop floor. There is no additional training required of the staff in this section of the shop to provide guidance and advice to consumers on the products sold. The safety aspects of these questions are instead left to the mandatory product labelling for the GSALE products. Where a product presents the manufacturer with a risk of liability even with labelling, the manufacturer seeks to classify it as a PO product and details to doctors to get the product prescribed. The costs of the safety regulation under a three-category sale classification system are thus shifted away from LRP and on to USPI in a two-category system, which must be careful with labelling. Where the manufacturer is unsure, the manufacturer can choose to share the product liability risk with doctors by classifying the product as PO.

The introduction of a third category of PSO would mean that staff at the cash register would have to be trained and/or the staff there would have to be licensed pharmacists. Product ranges would have to be split such that PSO products could be easily distinguished from GSALE products and other products sold. The shop floor would have to be designed differently and the overall effect would be that the pharmacy section and the GSALE/other section of these retail premises would have to be split, in such a way that it would make more commercial sense to operate both as wholly separate businesses instead. The US two-category system makes it economical to run a business where all these products are sold together, and the pharmacy counter represents the consumer inducement to enter the retail premises in the first place. This system therefore benefits LRP as an interest group most, and benefits doctors and USPI to some extent too, whilst suppressing the role of the interest group of IP pharmacists who operate as experts and advisors on medicines. That insight matches the conclusion reached earlier regarding the relative strength of these interest groups in the US as set out in Table 53.

Switching

It is the existence of the third category in the EU which accounts for the major differences in switching between the US and EU/EUMS. That is because most products at the least risky (fewer externalities) end of the PO category are found, in the EU, in the PSO category, and vice versa for the GSALE category. The differences in overall switch levels are also explained by this, although I should note that the reluctance to switch out of the PO category in the US

1940s by doctors and the pharmaceutical industry who were strongly allied with each other and who were stronger interest groups overall than pharmacists at the time.

is also likely due to the pharmaceutical industry being shielded from liability in this category due to the learned intermediary doctrine.

Nicotine Replacement Products

I wish to use private interest theories of regulation to explain why regulation of NRPs in the US led to wide availability (GSALE) of these products, but to indications and instructions for use which were historically restrictive. To the interest groups listed above now I add the tobacco lobby and the anti-smoking lobby as also relevant. I also focus upon consumers and their perceptions of NRPs. Finally, the motives, and priorities of the FDA as a bureaucracy are considered.

The wide availability of NRPs is at least partly due to the fact that only two categories exist in the US. Thus, when NRPs had been shown (after a period PO) to be safe, they were moved to the GSALE category. However, the original licensing decision and the switch to GSALE were met with opposition and could have been delayed or refused by the FDA. The lobbying debate regarding NRPs in the US centred on what the indications and instructions for use accompanying the products would be. One relevant issue was consumer perceptions of nicotine as addictive, which prompted an ambivalent response from consumer to NRPs: welcoming of a product which would assist in quitting addictive smoking, but fearful that the product itself would become an addiction for many.

Tobacco Lobby and Pharmaceutical Industry

Turning first to the tobacco lobby,[64] initially it was the tobacco industry which developed NRPs, as early as the 1950s, however they avoided bringing them to market first fearing a regulatory response from the FDA. By the late 1970s Nicorette® had been developed in Sweden by pharmaceutical firm Leo AB. Once the products began to become licensed in various jurisdictions other pharmaceutical firms took an interest in developing and marketing these products for what looked to be a very large market of former smokers from the 1980s onwards. Their problem in getting these products licensed was that public perceptions of nicotine were tainted by association with cigarettes. To tackle consumer perceptions, USPI took two different approaches. The first was to present NRPs to the anti-smoking lobby and to consumers as a way to 'beat' addiction to cigarettes. The second was to present the FDA with expert medical evidence showing that NRPs had low dependence and harm potential.

Once NRPs began to become successful on the US market the tobacco lobby took interest again. Tobacco companies wished to develop their own products as a long-term replacement for cigarette sales. Their approach, unlike the pharmaceutical industry, was not to present the products to consumers as a way to 'beat' smoking, which would have been counterintuitive given the tobacco industry's perceived culpability for the harms caused by smoking. Instead, the tobacco lobby focused its efforts on lobbying the FDA for wide indication and instructions for use to be permitted on NRPs. Thus, whilst in the public eye of consumers, USPI and the tobacco lobby were opposed to each other on the issue of NRPs, behind closed doors in their lobbying efforts they were asking the FDA for the same thing – wide availability and wide indications. To convince the FDA, therefore, USPI and the tobacco lobby drew extensively

64 Apollonio, Dorie, and Stanton A. Glantz. "Tobacco industry research on nicotine replacement therapy:"If anyone is going to take away our business it should be us"." American journal of public health 107, no. 10 (2017): 1636-1642.

upon expert opinions and clinical studies which they sponsored themselves.[65] However, US consumers - as advocated for by the anti-smoking lobby - were not convinced by expert studies, particularly where these had often been funded by large companies, a situation which the reader will expect already based upon the characterisation of US consumers set out in Chapter Two.

Anti-Smoking Lobby and Consumers

The anti-smoking lobby was happy to ally itself with USPI in so far as getting NRPs licensed, perceiving the products to be anti-smoking and harmful to the tobacco industry.[66] It did, however, still perceive NRPs to be addictive because they contained nicotine. Its objective therefore was to make the products available but only restrictively. The restrictions reflect the core concerns of the public from which the anti-smoking lobby drew most of its support. The fear of most consumers relates or related to addiction. Thus, the restrictions which the anti-smoking lobby sought when lobbying the FDA regarding sale classification and indications of/for NRPs was to discourage long term use of the product. Hence what was lobbied for was a restricted time frame for using the products, of maximum six weeks. The indications and instructions for use listed in the previous section were thus adopted for NRPs and the products were (eventually) made very widely available on GSALE with instructions not to be used in the long term - lest addiction to NRPs occur.

The FDA

The FDA at the time was caught between undeniable expert evidence relating to harm and widespread consumer perception of these new products as harmful because they were addictive. Remember that the FDA has a strong reputation for public protection and as a gatekeeper against unsafe products. The FDA is thus very susceptible to direct consumer pressure in the US relative to the effectiveness of consumer pressure on the EMA and NAs in the EUMS. The FDA perhaps was convinced by the expert advice as to the safety and efficacy of NRPs and their suitability for wide indication and instructions for use. But because the FDA is particularly susceptible to consumer pressure, and because at the FDA science is politicised, it could not simply side with the experts just because they were experts. Hence the compromise was reached that the products would be licensed and widely available on GSALE after a lengthy review period of 34 months.[67] However, the indications and instructions for use would be restrictive as set out above.

Conclusions: NRPs

Private interest theory helps us to understand the pressures that were on the FDA at the time that it made its decisions regarding NRPs. Private interest (bureaucracy behaviour) analysis of the FDA further helps to understand why it drew a compromise between expert advice and consumer pressure rather than merely siding with expert evidence. Consumer perceptions

65 Basham, Patrick, and John C. Luik. "Prescription for Conflict: Why the Alliance between the Pharmaceutical Industry and the Anti-Tobacco Movement is Not in the Best Interests of Smokers." Economic Affairs 32, no. 2 (2012): 41-46.

66 Etter, Jean-François, and John Stapleton. "Citations to trials of nicotine replacement therapy were biased toward positive results and high-impact-factor journals." Journal of clinical epidemiology 62, no. 8 (2009): 831-837.

67 Achanta, Anand S., and Christopher T. Rhodes. "OTC Switch Case History Evaluation: Nicorette®." Clinical Research and Regulatory Affairs 20, no. 1 (2003): 15-26.

are a key informal social institution which have affected the regulation of sale classification of NRPs in the US.

Herbal Remedies

I deal first with efficacy claims: the lack of a registration or licensing procedure for herbal remedies in the US. Then I turn briefly to address safety warnings.

Efficacy Claims

This set of products has never had a strong, well organised, and commercially resourced interest group representing them. Instead, there has only been strong interest groups opposing the certification of these products as effective. Both USPI and the herbal remedies industry as interest groups are important here. So are consumers, and the informal social institution of perceptions of herbal remedies amongst consumers.

The Pharmaceutical Industry

USPI adopts a business model in which research and development to find a new chemical entity synthesised or extracted in a laboratory precedes the obtaining of a market access license. It is the blockbuster model, based on innovation, as set out above in Table 55. Most importantly, the license is accompanied by a patent and period of market exclusivity. The business model rests on large expenditures pre-licensing and large revenues post licensing. The pre licensing expenditures lead to the post licensing revenues by justifying the high prices charged to insurers and consumers. The business model rests in the case of any given product on the patent, lest free riders take the additional profits. The business model for the industry in general also relies upon the claims of efficacy they are permitted to make as a reward for being granted the market access license. It follows that competition from a range of products which do not require any costly research and development is not welcome. USPI has opposed any attempt made by firms marketing such products to gain certification as effective through the grant of a license or some sort of registration.[68] Also, importantly, USPI is not interested in developing this product range themselves, precisely because a patent is not available. The patent is the key to the high revenues and the whole business model. Non synthesised, natural products cannot be patented.

Herbal Remedies Industry

Any commercial undertaking which seeks to market herbal remedies is unlikely to be able to compete with synthesised pharmaceutical products for the same reason – the lack of a patent for herbal remedies makes them unprofitable. The result is that herbal remedies in the US have never had a strong interest group arguing in favour of a system of efficacy certification.

Consumers

As set out fully in Chapter Six, perceptions of herbal remedies amongst consumers in the US are different to those found in the EU. Herbal remedies have long been unable to appear on the market as 'medicinal' products. Due to the lack of availability and/or presentation as a separate class of products, consumer perceptions of the herbal remedies in the US is such

68 Skinner, William J. "Allowable Advertising Claims for Dietary Supplements." J. Pharmacy & L. 5 (1995): 309.

that they are not perceived to be effective. This perception is partly shaped by the fact that there is no separate licensing/registration system in the first place.

Safety Warnings

Regarding the lack of safety labelling: this is explicable by reference to private interest lobbying from USPI. Historically in the US, when herbal remedies were marketed as dietary supplements, the making of any safety warnings on the label could lead to the impression being given on the product label that the product was being marketed as medicine and thus may have been tantamount to an efficacy claim. USPI opposed this and the FDA - not receiving any strong representations from consumer groups or a herbal remedies industry on this issue – sided with USPI.

Conclusions: Herbal Remedies

Private interest analysis helps to understand why herbal remedies are not allowed to make efficacy claims in the US, and also why the labels on these products (when sold as dietary supplements) were not allowed to provide safety warnings.

4.4.2.2 Generic Substitution

Most relevant to a private interest analysis of generic substitution in the US are doctors, USPI, pharmacists (meaning here LRP), the generics industry, healthcare insurers (private and public) and consumers. In addition, in the case of generic substitution in the US, certain other pre-existing institutions are relevant including the Drug Price Competition and Patent Term Restoration Act 1984[69] (the 'Hatch-Waxman Act').

Origins and Development of the Regulation of Generic Substitution

After the practice emerged in the US in the early 20th century, anti-substitution laws were enacted in almost all States by 1959. These laws were lobbied for by USPI – which wished to restrict competition from generic competitors.[70] Doctors, too, supported the introduction of the anti-substitution laws in most states, which makes sense given the alliance between doctors and USPI in the mid-20th century. Doctors, too, had strong brand loyalty to originator drugs, and were happy with the system in which USPI, through pharmaceutical firm detailing, would seek their prescribing power in return for various kickbacks. At this point there were few calls in favour of allowing generic substitution coming from the generics industry, which was in its infancy.

Budget Pressures: Medicare and Medicaid at the Social Security Administration

The process of repealing the anti-substitution laws occurred between 1972 and 1984. During this period generic substitution regulation was mostly becoming permissive-express in the states where the laws were being repealed. This movement likely occurred in response to pressure on healthcare budgets. Medicaid and Medicare were added to the Social Security

69 Public Law 98-417.

70 Although the reasons given by USPI were that generic substitution would stifle innovation and that generics were not as safe as originators.

Act in 1965 at the time when anti-substitution laws were becoming ubiquitous, and the Social Security Administration administers both. Medicare provides social health insurance to people in the US over the age of 65.[71] Medicaid provides social health insurance to those on low incomes regardless of age. In both cases the Social Security Administration (or the State level agency) pays the health services provider directly. With States and the Federal Government bearing the financial brunt (hundreds of billions of USD in 2019 for Medicare) of a large portion of the nation's healthcare - a large portion of which in turn was due to the cost of prescription pharmaceutical products - scrutiny came to be placed on the prices of these. Whilst the bureaucracies charged with administering the programs were likely happy to have control over ever increasing budgets year on year, direct political pressure came through State and federal legislatures and indirect pressure from the treasury departments, to control expenditure on the programmes.

Pharmacists and Repeal of the Anti-Substitution Laws

In addition to this there came pressure from pharmacists to overturn the anti-substitution laws. Pharmacists had seen their occupational task roles restricted by these laws, much in the same way that the prescription labelling exemption to mandatory product labelling had done from 1944 onwards. Moreover, LRP stood to benefit from permissive regulation of generic substitution as it would be able to offer consumers a wider range of products at a wider range of prices which stood to increase revenues. These lobbying and budget pressures – particularly the latter – grew, and by 1984 all States had legalized generic substitution.

Growth of the Generics Industry as an Interest Group

Budget pressures would only increase between 1984 and 2020. Moreover, once generic substitution had been permitted and generic drugs had greater access to the market, the political strength of the generics industry also grew. Brand loyalty was not the only barrier to entry for generics, as prior to 1984 there was also the need to make a full successful NDA to the FDA to get a generic product licensed. This process often could not even begin during the market exclusivity period of the originator lest the research activities by the generics industry infringe the patent. The generics industry was able to make a strong case to Congress that reform was needed to incentivise generics entry on to the market. These calls naturally faced fierce opposition from USPI which produced originator products.

Over time, however, the generics industry became allied with those consumers and taxpayers who baulked at the cost of Medicare/Medicaid and blamed the pharmaceutical industry for perceived high prices. Private insurers, too, were lobbying Congress to act on high drug prices. At this stage, the US Congress and/or State legislatures could have turned once again to the regulation of generic substitution and adopted a northern European mandatory model, or even accepted implied consent on the part of the consumer. This was not the preferred solution, however, in the US. Instead, Congress decided to act to increase competition in the drug market, with the overall aim of lowering drug prices. However, in doing so Congress was mindful of the voices of the pharmaceutical sector and its arguments regarding innovation. This intervention was the Hatch Waxman Act of 1984.

71 Prior to 1965 only 60% of these had coverage, partly due to excessively high premiums for elderly patients (Wikipedia).

Hatch Waxman 1984

Hatch Waxman amended the FDCA 1938 to do several things. The first and most important was to incentivise and facilitate the entry of generics on to the market by creating a new process for the approval of generic products: the Abbreviated New Drug Application (ANDA)[72] which required generics manufacturers to show only 1) information on how it would manufacture the drug, 2) quality assurance and 3) bioequivalence.[73] This process provides a simple and quick way for generics to gain a market access license and prevents the FDA from asking for more from the generic manufacturer Secondly, it provided generics manufacturers with a safe harbour from intellectual property infringement lawsuits (the 'research exemption') during the time which it prepared its ANDA. Then to protect innovation it: 1) Extended the term of patents given to originator products to cover the period that the originator spent under regulatory review by the FDA before receiving a market access license; and 2) Gave an additional period of market exclusivity to originator drugs (5 years) where these were a new chemical entity (i.e., they represented genuine innovation).

Hatch Waxman was equally focused upon protecting the innovative efforts of USPI as it was to benefit the generics industry. The Act is viewed here as a market-oriented instrument because it aimed to reduce the overall regulatory burden on companies (particularly generic NDAs and potential lawsuits), whilst maintaining the dynamic efficiency effects which should result from the grant of a patent in the case of innovation. Also, of course, it had the overall aim of increasing competition in the drugs market and increasing the range of products available to consumers. From 1984 onwards Hatch Waxman was very successful in promoting generic entry into the market. In 1995 Grabowski and Vernon[74] undertook an analysis of 18 drugs first experiencing generic competition after 1983 and concluded that the typical product from within this sample lost about half the market share two years after generic entry. Due to the much lower prices of generics, the average prices of drugs in the US reduced between 1984 and 1995.

In being a market-oriented approach, it is like permissive-express generic substitution regulation, which aims to give both consumers and pharmacists a choice and enable first party ordering of preferences in the marketplace. Hatch Waxman and permissive-express generic substitution thus complement each other in ensuring allocative efficiency. The former increases the number of generic products on the market, and the latter seeks to ensure that generic products will be consumed by those who prefer generic products, and originator products will be consumer by those who prefer originator products.

Post Hatch-Waxman: The Affordable Care Act

From 1984 to date State and Federal healthcare budget pressures – and private insurance premiums - in the US have seen further inflation. By the late 2000s uninsured consumers in the US too – some 48 million people around 2014 – were putting political pressure on Congress to further decrease drugs prices. The political momentum in the late 2000s lay with the Democrats whose political support base included large numbers of uninsured. In 2010 the Affordable Care Act was introduced under the Obama administration. This provided

72 Section 505(j) of the Act, codified as 21 U.S.C. § 355(j).

73 Showing that the generic drug operates the same in humans as does the originator drug.

74 Grabowski, Henry G., and John M. Vernon. "Longer patents for increased generic competition: The Waxman-Hatch Act after one decade." (1995): 95-11.

additional (means tested) social healthcare insurance for those currently uninsured. The Act came into force in 2014 and by 2016 an additional 20-24 million US people were then covered by social healthcare insurance (as of 2019 37 out of 50 states had adopted Obamacare, notably not including Texas and Florida). This approximately halved the number of uninsured. As expected, the Act placed further pressure on healthcare budgets. In time this led to the adoption of mandatory generic substitution in some States, however, permissive-express generic substitution remains the general rule.

Conclusions: Generic Substitution

Hatch Waxman and permissive-express generic substitution regulation are market-oriented solutions which complement each other. The effect of these together was that the market was indeed split along allocatively efficient lines, with most Medicare/Medicaid[75] (and later, Obamacare) beneficiaries consuming lower priced generic products, and those on private insurance proportionally more often consuming more higher priced originator products.

Private interest analysis has assisted in understanding the development of the regulation of generic substitution in the US. The particularly strong US position of LRP may be significant in rolling back the anti-substitution laws, just as the strength of the pharmaceutical industry and doctors together helps explain their introduction.

In addition, the ability of the consumer to choose between generic and originator according to their preferences is heavily protected in the US system. Why do consumers in the US care which of these types of product they receive when experts would say that they are bioequivalent, and the FDA has certified them to be? The informal social institution of consumer perceptions (of pharmaceutical products) therefore matters for explaining the US regulation further.

4.4.3 European Union/EUMS

To recapitulate again, the EU has three categories for sale classification: PO, PSO, and GSALE. There is more switching between these categories and as such (relative to the US) there are fewer products in the PO category and in the GSALE category, with those being found instead in the PSO category. NRPs are found in all three categories but most often in the PSO category. Herbal remedies are permitted to be sold as medicinal products, providing they obtain a full license under the 2001 Directive, but also – and much more easily – if they have TUR under the 2004 Directive. These are sold only on GSALE or under PSO (i.e., off prescription). Generic substitution was regulated in EUMS late relative to the US. In SEUMS there has been more pharmacist discretion (permissive regulation) for longer than in NEUMS but also more often implied consumer consent suffices. Another key difference between the NEUMS and SEUMS

75 Medicare and Medicaid work based on reimbursements. The consumer/patient will pay the bill and then apply to the Social Security Administration (or State agency) for reimbursement. Reimbursement limits are in place meaning that often the programs will only reimburse the patient/consumer up to the cost of the generic version of the product. As such, the patient/consumer will have to pay a real sum to consume the originator. This is why the permissive-express system in the US remains market oriented, and the consumer/patient is revealing their willingness to pay in the consumption decision.

Clusters is that NEUMS more often have a GSALE category of sale classification in addition to PO and PSO.

4.4.3.1 Sale Classification

Sale Classification Generally

In the EU, the interest group of retail pharmacists in IP – strong relative to the US - has had a part to play in ensuring the existence of the third category of sale classification: PSO. The existence of PSO benefits IP because it ensures that the products placed in the PSO category can only be sold in retail premises where a pharmacist is present. In the SEUMS Cluster this normally means a small independent pharmacy owned and operated by a pharmacist.[76] Thanks to the restrictions on chain ownership of pharmacies in those countries oriented towards the SEUMS Cluster, the independent pharmacies and the pharmacists who own and operate them are also protected against competition from LRP. Revenues are not the only way in which IP pharmacists benefit from the PSO category. Importantly, also, the PSO category preserves the occupational task role of the pharmacist as an expert-advisor on - in addition to a seller of – pharmaceutical products.

Additional Existence of the GSALE Category

The existence of GSALE in some EUMS was lobbied for and lies to the benefit of LRP. This was explained above for the case of the US. This also explains the differences seen between the use of the GSALE v PSO category in EUMS oriented towards the NEUMS and SEUMS Clusters respectively. In the north, where in some EUMS LRP dominates retail pharmacy, a mixture of the GSALE category and the PSO category are adopted. In the south, where an historically strong IP interest group has prioritised safeguarding its independence, the PSO category is heavily used and the GSALE category often does not exist.

Switching

Pharmacists in IP will support switching out of PO category to PSO category whilst they may oppose the switching out of PSO category to GSALE, in the former case because their revenues and occupational role is enhanced, in the latter because it may be lost to LRP. In the meantime, doctors are likely to be opposed to switching out of PO status, as this cuts out the occupational role and diminishes the importance of the doctor. Thus, the overall higher level of switching out of PO status in the EU is likely a by-product of the availability of the PSO category. It may also be assisted by the relative weakness of doctors vis a vis pharmacists as an interest group in the EU when compared to the US. That is not to say that pharmacists are overall the stronger interest group in the EU, but to say that the gap between doctors (on top) and pharmacists (below) is narrower in the EU than it is in the US. The strength of these interest groups, their priorities and these other factors together help to explain why the EU has these three categories and why it has relatively more switch out of the PO category (in to

76 In these cases, therefore the pharmacist can exploit the surplus revenue made available to him by the sale classification regulation instead of this being taken by a large non pharmacy retailer such as a drugstore. It would otherwise be likely that the non-pharmacy retailer would be able to drive independent pharmacies out of business thanks to their superior purchasing power and economies of scale.

the PSO category) than does the US. The relative strength of pharmacists in IP v pharmacists in LRP in the south versus the north of Europe, respectively, helps to explain the differences in sale classification regulation between these clusters.

Nicotine Replacement Products

Generally, across the EUMS NRPs are available under GSALE or PSO. In the EUMS oriented towards the NEUMS Cluster NRPs are more often available on GSALE (where available) than in those oriented towards the SEUMS Cluster where NRPs are often available only PSO. Across the EU, and much earlier than in the US, NRPs were licensed with approved indications and instructions for use that allowed for types 2), 3) and 4) use including concurrent use and use for temporary cessation only.

Availability

The placing of the products in the PSO category by a majority of EUMS is enabled by the fact that the category exists however, this is not a full explanation because some EUMS including Germany, which have a GSALE category available do not put NRPs in that category. It is submitted that in some EUMS NRPs are a product for which pharmacists in IP have been successful in lobbying for regulation beneficial to themselves. In these EUMS those interest groups have been able to lobby the NAs to place the product in the PSO category, benefitting the revenues of IP and maintaining the expert-advisor role of pharmacists in IP. Consumer perceptions of synthetic pharmaceutical products across the EU may have assisted in this.

Consider Germany as an example: it has a GSALE category (as well as a PSO category) yet NRPs still lie in the PSO category. Retail undertakings in Germany includes powerful companies like Budnikowsky - large chain drugstores, unable to dispense PO products or sell PSO products – which, if NRPs were in the GSALE category would be able to sell and profit from these products. Yet these retail interests have not been able to persuade the German national agency (BfArM) to classify NRPs as GSALE despite their classification as such in the UK, Ireland etc. In the section discussing NRPs in the US above I identified that consumer pressure can come to bear on the licensing agency when making the licensing decision I have argued that this is more the case in the US with the FDA than it is in the EU with the EMA and the NAs. However, risk and benefit perceptions of pharmaceutical products can also affect those making the decision in licensing agencies – despite their access to expert advice and data - in the same way as these affect consumers making consumption choices.

It is argued in Chapter Six that consumers and decision makers in certain parts of the EU are prone to perceive synthetic (non-natural) things as inherently harmful or potentially harmful to human health. Synthetic NRPs might be subject to the same phenomenon of risk perception, and this may affect sale classification regulation for these vis a vis cigarettes and other 'natural' tobacco products. Thus, it is argued that where retail interests lobbied for a GSALE classification for NRPs, and pharmacists in IP argued for a PSO classification, those at the licensing agency – nudged by their own and perhaps by anticipated consumer perceptions of the products – opted for the PSO category in some EUMS.

Indications/Instructions for Use

In the EU/EUMS, it seems that tobacco smoking is not so widely vilified as it was in the US, and the anti-smoking lobby is not so strong. Recall that when a license was originally sought

for Nicorette® in Sweden, this was rejected due to lack of an available indication – the Swedish agency not seeing 'addiction' as an indication, but rather seeing smoking as a lifestyle choice. Across the EUMS, when NAs were granting licensing approval of NRPs they did not come under such public pressure from an anti-smoking lobby to protect against the risk of addiction. Indications were thus seen which extended beyond a strict 'quit and abstain' approach which was what was insisted upon in the US by the anti-smoking lobby.

Conclusions

On availability, what is key is the role of the strong interest groups of pharmacists in IP, particularly in the EUMS oriented towards the SEUMS Cluster. They sought to keep these profitable products available only from the pharmacies which they own and run. On indications/instructions for use, differences between US and EU consumer and decision maker perceptions of the products – an informal social institution - may matter most.

Herbal Remedies

Consumer Perceptions of Efficacy

Consumer perceptions also seem to matter in the case of herbal remedies. In the EU, particularly in Germany, herbal remedies have long been perceived as effective.[77] This perception amongst European peoples may have led to high demand for herbal remedies to persist even after the modern chemical and pharmaceutical industries began to develop in Europe, as they did in the late 19th and early 20th centuries. For example, in Germany in 1901 an Imperial decree was issued permitting botanical remedies to be sold outside of pharmacies.[78] This decree was issued because those interest groups which had been making revenue from selling botanical remedies in Germany around this time were quick to drop them when the more profitable synthetic medicines emerged and were made available by the new German pharmaceutical (back then, chemical) industry.[79] German pharmacists became allied then with the new chemical-pharmaceutical industry to provide a distribution system for the new products being developed.[80] This was to the mutual benefit of both interest groups from a commercial perspective. However, it left no room within the product range of pharmacies for the old botanical remedies. Apart from the commercial disincentive - the higher prices commended by the chemical products - stocking such botanical products would have involved administrative expense for those pharmacies in maintaining expertise in both product ranges.

The alliance which had grown between the chemical-pharmaceutical industry and pharmacists lent itself much better to the development of a class of elite pharmacists who were experts in chemistry and who sold only the new chemical products, providing expert

77 Welz, A.N., Emberger-Klein, A. & Menrad, K. Why people use herbal medicine: insights from a focus-group study in Germany. BMC Complement Altern Med 18, 92 (2018). https://doi.org/10.1186/s12906-018-2160-6

78 Anquez-Traxler, Christelle. "The legal and regulatory framework of herbal medicinal products in the European Union: a focus on the traditional herbal medicines category." Drug information journal 45, no. 1 (2011): 15-23.

79 Hüntelmann, Axel C. "Pharmaceutical Markets in the German Empire. Profits Between Risk, Altruism and Regulation." Historical Social Research/Historische Sozialforschung (2011): 182-201.

80 Daemmrich, A., & Bowden, M. E. (2005). Emergence of pharmaceutical science and industry: 1870–1930. Chem Eng News, 83.

advice on these to the customers.[81] Demand for herbal remedies was persistent, however, because a large portion of the German populace still viewed them as effective and arguably because that same portion was fearful of the synthetic products.[82] Yet at the time herbal remedies could not be sold elsewhere, due to regulation preventing the sale of any medicinal products outside of pharmacies. Thus, these elements of German society sought new (de)regulation permitting botanical remedies to be sold outside of pharmacies, and this was granted in 1901. That Imperial Decree ensured that botanical remedies did not have to compete in the same product ranges as synthetic pharmaceutical products in Germany up until the German Medicines Act of 1976. The decree thus prevented the products from disappearing, and preserved demand. It also meant that a new interest group developed based around the commercial sale of herbal remedies: the herbal remedies industry. By 1976 this was big business in Germany and so the West German government were lobbied by this interest group to make special provision for herbal remedies in the Medicines Act 1976. The same happened in 2004 when the EU Directive was enacted.

4.4.3.2 Generic Substitution

Two major interest groups are relevant in the regulation of generic substitution in the EU/EUMS: pharmacists (IP) and doctors. In addition, the pre-existing legal and social institutions of socialised medicine and direct price controls have impacted upon the form of the regulation.

Timing of Implementation US v EU/EUMS

It was direct price controls on drugs which reduced the need for EUMS to use generic substitution as a policy tool for healthcare budget control – and thus the appearance of regulation - until late relative to the US. In turn, price controls have been easier to implement across the EUMS than in the US because of the presence of strong systems of socialised medicine. These systems often make the state a monopsonist buyer of drugs and other pharmaceutical products. These systems in the EU also facilitated other means of encouraging the uptake of generics by patients and doctors which fell short of permitting or mandating generic substitution by pharmacist. These pre-existing institutions therefore help to explain the late appearance and regulation of generic substitution across the EU.

Mandatory v Permissive Generic Substitution: SEUMS/NEUMS Clusters

It must further be considered why mandatory generic substitution became prevalent in the EU particularly in those EUMS oriented towards the NEUMS Cluster. This process – the movement from permissive to mandatory regulation – seems to be ongoing in the EU, as it is in the US, and one expects that many EUMS which currently regulate it permissively will eventually impose mandatory generic substitution. However, the timing differential vis a vis the NEUMS and SEUMS Cluster warrants explanation. One reason is that those EUMS oriented

81 Barger, G. "Grundriss der Geschichte der deutschen Pharmazie." Nature 137, no. 3464 (1936): 474-475.
82 Timmermann, Carsten. "Rationalizing 'Folk Medicine'in Interwar Germany: Faith, Business, and Science at 'Dr. Madaus & Co.'." Social history of medicine 14, no. 3 (2001): 459-482.

towards the SEUMS Cluster have a greater problem with ageing populations than those oriented towards the NEUMS Cluster which would lead one to expect earlier imposition of mandatory generic substitution in the south rather than the north. In addition, I add the effect of the sovereign debt crises which followed the 2008 financial crisis, striking southern EUMS to a greater extent than the NEUMS. Indeed, this led to the imposition of mandatory generic substitution in Spain after 2010 – which is the year in which the analysis here is anchored. Italy, too, had adopted mandatory generic substitution earlier. France provides an interesting example. Here there seems to have been reluctance to make generic substitution fully mandatory upon the pharmacist, although measures such as reimbursement limits, and margin equalisation strongly incentivise the pharmacists to substitute. France's most recent measures have instead targeted doctors – limiting very strictly the basis upon which these may veto generic substitution[83] - and studies show that it is doctors who pose the major obstacle in France to generics uptake.

I believe the answer to the NEUMS/SEUMS divergence lies in the relative strength of pharmacists as an interest group in the NEUMS and SEUMS Clusters. In the SEUMS Cluster pharmacists are a strong interest group and comprised overwhelmingly of IP. This is different to the north where pharmacists are strong but LRP is also present. In EUMS oriented towards the SEUMS Cluster pharmacists as an interest group have prioritised their independence from LRP. In the NEUMS Cluster LRP – employing pharmacists – have accepted mandatory generic substitution, which even though it cuts down the range of products and prices which can be offered to consumers, is at least simple to implement in terms of administrative cost. In the SEUMS Cluster there has been greater resistance to government moves to interfere with the independence and expert role of pharmacists, possibly coupled with the concern about potential losses of revenue to this interest group. In particular, mandatory generic substitution diminishes the role of the pharmacist as an expert and adviser who informs the consumer which version of the product will suit the patient best. This may explain that the latest regulatory movements in France have been to limit the circumstances under which the doctor can veto substitution. It may be that doctors tied the hands of pharmacists too often and pharmacists objected. In the north, where pharmacists are to a greater extent employed by LRP, this professional role is less important and less protected by that interest group, and so objections to mandatory generic substitution were not strong.

83 Addressing the stubbornness of doctors making 'Not for Generic Substitution' mentions, in 2019 the French government introduced new limits on the right of physicians to veto generic substitution. Pursuant to Article 66 of the 2019 Social Security Financing Act, from 1 January 2020 substitution could only be excluded on prescriptions in the following situations: 1) where substitution would disrupt the stability of dispensation, 2) where the patient is under 6 years old and there is no generic product with a suitable dosage but the originator does have this and 3) where the patient has a formal contraindication which is demonstrated as a contraindication to an excipient with a known effect present in all available generic substitutes but the originator does not contain that excipient. One of these justifications 1)-3) must be indicated by the doctor on the prescription. This is a strong restriction on the ability of French doctors to veto substitution. See Dylst, Pieter, Arnold Vulto, and Steven Simoens. "Analysis of French generic medicines retail market: why the use of generic medicines is limited." Expert review of pharmacoeconomics & outcomes research 14, no. 6 (2014): 795-803. See Dylst, Pieter, Arnold Vulto, Brian Godman, and Steven Simoens. "Generic medicines: solutions for a sustainable drug market?." Applied health economics and health policy 11, no. 5 (2013): 437-443.

Pharmacists in the SEUMS

Implied consumer consent is more often accepted in those EUMS oriented towards the SEUMS Cluster than those oriented towards the NEUMS Cluster. This indicates that it is pharmacists in the SEUMS Cluster which stood in the way of mandatory generic substitution, not doctors or consumers. After all, the ability of doctors to veto substitution in France is now highly restricted, and in Spain consumers cannot obtain the higher priced originator product even where they are willing to pay the difference. This willingness to interfere with the autonomy of doctors and consumers but not (yet, in some SEUMS) with that of pharmacists, suggests that pharmacists are influencing the regulation in those EUMS.

Pharmacists in the NEUMS

Nevertheless, in the NEUMS Cluster the strength of pharmacists vis a vis pharmacists in the US has also had implications for the introduction of mandatory generic substitution. It has made it easier in those EUMS where LRP is not entirely dominant, such as in the UK where generic substitution - far from being mandatory - is forbidden still. Where pharmacists instead work in smaller chains which may be franchised, and thus part of a LRP business operation, they are able to maintain their role as experts and advisors on drugs better than in large chain drugstores/pharmacies which are found in the US. Here, then, the ability of the pharmacist to reassure the consumer on their use of the generic product (mandatorily substituted) makes the introduction of mandatory generic substitution easier. That this is lacking in relative terms in the US may partly explain why so few US States have yet opted for mandatory generic substitution.

Conclusions: Generic Substitution

Price regulation and socialised medicine have impacted upon the transatlantic timing differential. The differences in implementation of mandatory v permissive generic substitution between NEUMS and SEUMS may reflect differences in the relative strength and priorities of the pharmacists in each and struggles over their occupational task boundaries vis a vis doctors. Thus, for the comparatively long time, pharmacists in the south have retained their discretion.

4.4.4 Summary

Private interest theory helps to explain both transatlantic and intra-EU regulatory divergence in both sale classification and generic substitution to some extent, but not fully.

Sale Classification

The strength, composition and (consequently) the objectives of the interest group of pharmacists is key to the regulatory positions taken in the US and across the EU. There are two models. In the US pharmacists are mostly employed by LRP. In the SEUMS Cluster pharmacists work in IP. Pharmacists operating in IP maximise their occupational task boundaries as experts and advisers in addition to their income. Pharmacists employed by LRP

are a weaker interest group, and it is the objectives of LRP in maximising its revenues which have been successfully secured.

In the US in the mid twentieth century a strong USPI allied with strong doctors instituted the mandatory prescription system, and this was supported by business minded pharmacists who sought to maximise their revenues. This started the US off on a path towards pharmacists being largely employed by LRP, and that interest group becoming the strongest. This interest group - now allied with doctors and USPI - seeks to maintain the two-category sale classification system, and the current level of switching in the US. In the EU, despite the prescriptions system, pharmacists in IP dominate in the SEUMS Cluster and pharmacists are stronger in the NEUMS Cluster vis a vis LRP than their counterpart pharmacists in the US are against LRP there. Pharmacists in the SEUMS Cluster have lobbied to maintain the third sale classification category, PSO. This category preserves the role of the pharmacist as an expert and advisor guiding consumers on use of pharmaceutical products.

Even combined with the public interest analysis in the previous section, however, this does not furnish a full answer. It is still not understood fully why pharmacists in mid-20th Century US were more business minded than their European (particularly southern European) counterparts. Pharmacists in both polities were faced with a trade-off between maximising revenues/income and maintaining their independence and occupational task boundaries as experts and advisors. This is shown below in Table 58.

Table 58 Trade-Off for Pharmacists in the EU and US from Mid-20th Century Onwards

	Maximise	**Method**
US	Revenues and income	Adopt larger business structures Employ pharmacists in large RP Support mandatory prescriptions Sacrifice expert advisory role
EU ***(particularly SEUMS)***	Occupational task boundary as experts and advisors	Retain ban on chain pharmacies Retain independent pharmacy Resist mandatory generic substitution Sacrifice revenues and income

Why did one interest group seek to maximise their income/revenues and the other seek to maintain their occupational task boundaries as experts and advisors? This is a question which is explored further in Chapter Six.

Sale Classification: Nicotine Replacement Products

In those EUMS oriented towards the SEUMS Cluster, the objectives of pharmacists are seen too in the case of NRPs albeit that their lobbying for PSO status also stood to benefit their income and revenues. In this case they may have been assisted in those EUMS by consumer and decision maker perceptions regarding the benefits and risks of NRPs as synthetic

products. In the US, lobbying by a strong LRP ensured wide availability on GSALE. Narrow indications and instructions for use were adopted due to different consumer perceptions of nicotine (as addictive) and a reputation protecting bureaucracy in the FDA, which was susceptible to consumer pressure, obliged, despite petition from a strong pharmaceutical industry and tobacco lobby based on expert medical views.

Again, this does not provide a full explanation, even with the addition of the public interest analysis. Consumers and decision makers in the US and the EU perceived these products very differently. The question – for which an answer is sought in Chapter Six – is why?

Sale Classification: Herbal Remedies

Here consumer perceptions matter too. Perceptions of herbal remedies as effective led to demand which was fostered by the creation of legal institutions such as the Imperial Decree of 1901 and the German Medicines Act of 1976. The objectives of pharmacists in Germany in the early 20th century – business minded as well as determined to cultivate a role as experts in the new chemical pharmaceutical products led to a unique turn of events where the market was split between natural and synthetic products through the Imperial Decree. This facilitated the growth of a herbal remedies industry which could hold its weight with the pharmaceutical industry. The products remained available thanks to the regulatory institutions and ultimately the 2004 Directive was enacted providing for TUR: limited efficacy claims plus safety warnings. In the US herbal remedies were not seen as effective and so when synthetic products emerged the former were outcompeted. As such no strong herbal remedies industry grew and the strong pharmaceutical industry opposed any attempt to make efficacy claims or even provide label safety warnings.

It is clear how formal legal institutions led to path dependence in this matter. What is not yet fully understood is why consumer perceptions of natural vs synthetic products differed so much at the time that chemical pharmaceutical products first emerged. That is what I focus upon in Chapter Six.

Generic Substitution

The introduction of limited socialised medicine in the US in the latter half of the 20th Century led to healthcare budget pressures which brought about the repeal of State anti-substitution laws. Key to this also were the lobbying efforts of LRP keen to offer consumers a greater range of products at a greater range of prices. Hence permissive-express generic substitution became the standard across US States. Yet ever increasing budget pressures, and the effects of the Affordable Care Act have not been enough to move many US states past the permissive-express stage. Perhaps this is due to the lobbying efforts of LRP and/or perhaps due to consumer resistance to interference with the express consumer consent requirement. The option preferred to mandatory substitution has been supply side reforms – Hatch Waxman – which taken together with permissive-express substitution has ensured a strongly market oriented system in the US. Late emergence of the practice and its regulation in the EU was due to price regulation in turn facilitated by strong socialised medicine systems. Yet mandatory substitution has been slow reach the SEUMS Cluster despite a higher willingness there to accept implied consumer consent. A strong pharmacists interest group, maintaining its role as experts and advisors against incursion by the government and seeing to protect this occupational task boundary has resisted mandatory generic substitution. In the NEUMS

Cluster where pharmacists have different priorities, mandatory generic substitution has been accepted but consumer consent must generally be express.

Both jurisdictions/clusters have faced the same budget pressures but have responded differently. The US chooses market-oriented measures and protects consumer choice (express consent) whilst across all EUMS there is less concern for this. Meanwhile when faced with a trade-off, in the US LRP seeks to maximise revenues, but in the SEUMS Cluster IP has protected its independence and occupational task boundaries. Further explanation is needed for these different choices.

4.4.5 Relevant Institutions

Analysis of the interest groups has assisted in understanding the form of the regulation. The same goes for the organisations. Of the interest groups, it is EU and US pharmacists which have had the greatest impact upon sale classification and generic substitution regulation, and these interest groups receive the most attention in Chapter Six where culture is applied. The relevant institutions are both formal legal institutions and informal social institutions. The formal legal institutions include: Socialised medicine which has affected the ability of both polities to implement generic substitution in its various forms, and Price regulation which has affected the need for both polities to implement generic substitution in its various forms. Finally, there are important **informal social institutions** which appear to have impacted upon the regulation of generic substitution and sale classification in both polities. These are: Consumer (and decision maker) risk perceptions concerning NRPs: in particular whether the product is perceived as 'harmful' because it poses a risk to human health (the expert medical view), and/or whether it is perceived as risky simply due to being addictive. Consumer perception of generic products versus originator products, which amounts to public perception of the value of brands, revealed by willingness to pay for a branded product when making a consumption choice. Consumer (and decision maker) risk perceptions of herbal remedies, in particular whether they are perceived as 'effective' only by virtue of 1) expert scientific testing (in randomised controlled clinical trials), 2) synthetic processing, or 3) a longstanding history of use within a community over time. The most important of these organisations, groups and institutions are considered in Chapter Six.

4.4.6 Final Note on the NEUMS and SEUMS Clusters

In Chapter Six I argue that the NEUMS and SEUMS Clusters are culturally distinct. To be able to make this argument I must first substantiate that the within-Cluster differences in the areas I have considered is smaller than the between-Cluster differences. In other words, I need to establish that these are indeed Clusters. In Table 36 above I made an initial placement based only on geography and two initial aspects of the regulation. Now that the analysis is concluded I can expand that Table. This is done in Table 59 below.

In Table 59 I include the following aspects considered in this Chapter:

1. Whether the EUMS had a GSALE category in 2009:

   (no = SEUMS/yes = NEUMS)

2. Whether NRPs were available on GSALE in 2019:

   (no = SEUMS/yes = NEUMS)

3. Whether nicotine patches were available on prescription only in 2004:

   (yes = SEUMS/no = NEUMS)

4. Whether the pharmacist had discretion in generic substitution in 2010:

   (yes = SEUMS/no – NEUMS)

5. Whether implied consumer consent was accepted in generic substitution in 2010:

   (yes = SEUMS/no = NEUMS)

6. Whether chain ownership of more than four pharmacies was permitted in 2017:

   (no = SEUMS yes = NEUMS)

7. Number of pharmacists per 100,000 population:

   (above 100 = SEUMS/below 100 = NEUMS)

8. Number of pharmacies per 100,000 population:

   (above 25 = SEUMS/below 25 = NEUMS)

Table 59 NEUMS Cluster and SEUMS Cluster Final Placement

	GSALE[1]	NRPs GSALE[2]	NRPs PO[3]	PDisc GSub[4]	CCsent GSub[5]	Chain Pharma[6]	Phmcicts[7]	Phmcies[8]
NEUMS Cluster	**YES**	**YES**	**NO**	**NO**	**NO**	**YES**	**-100**	**-25**
Sweden	YES	YES	NO	NO	NO	YES	-100	-25
UK	YES	YES	NO	NO	N/A	YES	-100	-25
Netherlands	YES	NO	NO	YES	NO	YES	-100	-25
Germany	YES	NO	NO	NO	NO	NO	-100	-25
Denmark	YES	NO	NO	NO	NO	NO	-100	-25
Finland	YES	YES	NO	NO	NO	NO	-	-
Ireland	YES	YES	NO	NO	N/A	YES	+100	+25
Austria	YES	NO	NO	NO	N/A	NO	-100	-25
Belgium	NO	NO	NO	NO	N/A	YES	+100	+25
Italy	NO	NO	NO	NO	NO	NO	+100	+25
Greece	NO	NO	YES	YES	NO	NO	-	-
Portugal	NO	NO	YES	YES	NO	NO	-100	+25
Spain	NO	NO	NO	YES	YES	NO	+100	+25
France	NO	NO	YES	YES	YES	NO	+100	+25
SEUMS Cluster	**NO**	**NO**	**YES**	**YES**	**YES**	**NO**	**+100**	**+25**

There is a clustering observable which is correlated with geography. France, Spain, Greece, and Portugal have a great deal in common between them and so do Sweden, the UK, the Netherlands, Germany, and Denmark. But between the two clusters there are wide differences.

1 Whether the EUMS had a GSALE category in 2009 no = SEUMS yes = NEUMS
2 Whether NRPs were available on GSALE in 2019 no = SEUMS yes = NEUMS
3 Whether nicotine patches were available on prescription only in 2004 yes = SEUMS no = NEUMS
4 Whether the pharmacist had discretion in generic substitution in 2010 yes = SEUMS no - NEUMS
5 Whether implied consumer consent accepted in generic substitution in 2010 yes = SEUMS no = NEUMS
6 Whether chain ownership of more than four pharmacies permitted in 2017: no = SEUMS yes = NEUMS
7 Number of pharmacists per 100,000 population: above 100 = SEUMS below 100 = NEUMS
8 Number of pharmacies per 100,000 population: above 25 = SEUMS below 25 = NEUMS

4.5 Conclusions

In this Chapter I have introduced sale classification and generic substitution as well the case studies of NRPs and herbal remedies. I have set out the regulation in the US and the EU as well as between the NEUMS and SEUMS Clusters. I have then evaluated these regulatory positions against public interest theory and found that further explanation was needed. Not only did the regulatory approaches in the jurisdictions/clusters differ from each other but they differed also from a public interest approach which would be adopted if an 'expert' medical view were also adopted. This was found, for example, to be the case for NRPs as shown below again in Table 60.

Table 60 Puzzling Regulation of Sale Classification NRPs US and EU

	Availability	**Use**
Expert View/Public Interest	**Wide**	**Wide**
United States	Wide	Restricted
European Union	Restricted	Wide

I then turned to private interest theory and institutional analysis to find some explanation. I identified that certain interest groups had been responsible for bringing the regulation in to creation and/or maintaining it in both polities and clusters. The most important of these was pharmacists: operating either as IP or within LRP. These groups, and their lobbying efforts, had interacted with organisations such as the FDA, the EMA and the NAs to bring about the regulation as it stood in both places. They had also been responsible for the creation of certain formal legal institutions which either constrained or widened the regulatory choices available. In addition, the efforts of these groups were aided or impeded by informal social institutions which persisted in each polity: consumer and decision maker product risk and benefit perceptions. Taken together, the public interest analysis and the private interest and institutional analysis assisted me in understanding how the regulatory positions came to be adopted in each polity/cluster.

There is room, however, for much further explanation. Consider again the case study of NRPs. The puzzle remained unsolved because I am left unsure why the FDA chose to protect against the potential 'harm' posed by these products through restrictive indications/instructions for use (whilst allowing wide availability) whilst on the other hand some NAs in the EU chose to protect against the 'harm' by restricting availability (whilst allowing broader indications/instructions for use). That puzzle, and the others raised here, are the final issues addressed in Chapter Six of this work, where culture is applied. For now, the problem is defined, in the case of sale classification and generic substitution.

Chapter Five: Cultural Theories

5.1 Introduction

In Chapters One through Four I identified six transatlantic regulatory divergences in the pharmaceutical sector. These were shown, in each case, to result from a combination of 1) private interest lobbying by interest groups and the behaviour of bureaucrats in agencies; 2) the effects of jurisdiction-wide institutions which constrain or widen the choices available to regulators and the efforts of those interest groups; and 3) the demands of the 'public interest' which lie in the background and may be pushed for directly by consumers (as an interest group) and/or their democratic representatives.[1] As such, I am left with a list of jurisdictions, organisations, (sub)groups, and institutions which I have identified to be proximate to the development of the regulatory divergences across all six cases. These are shown in Table 61 below.

My research question asks whether cultural theory can add further explanation to the extant theories already considered in the case of these regulatory divergence. I will consider the answer to that question to be yes, if it emerges that a within-jurisdiction consistent cultural orientation is shown for all the items in Table 61. In that case, underlying culture will have been shown to have an effect through the private interest mechanisms (the behaviour of the interest groups and organisations) and because of the culturally distinct jurisdiction-wide institutions. This will have been in addition to the public interest explanations for the regulatory positions adopted which, as noted, may themselves have been informed by shared group preferences (or culture) in each case. Therefore, in Chapter Six, I culturally analyse all items in Table 61.

1 Bearing in mind the observation made on several occasions by this stage, that what consumers demand as 'in the public interest' may well depend upon their collective (shared) preferences.

Table 61 Jurisdictions, Organisations, (Sub)Groups, and Institutions Proximate to the Divergences

JURISDICTIONS	
United States	European Union *NEUMS Cluster* *SEUMS Cluster*
ORGANISATIONS	
FDA	EMA
	NAs
GROUPS	
US Doctors	EU Doctors
US Consumers	EU Consumers
US Pharmaceutical Industry	EU Pharmaceutical Industry
US Lawyers	EU Lawyers
US Pharmacists (dominated by LRP)	EU Pharmacists (more IP)
INSTITUTIONS	
US Free Speech Protections	EU Free Speech Protections
Private Healthcare	Socialised Healthcare
US Common Law	EU Legal System
No Price Regulation	Price Regulation
Norm of Litigiousness	Norm against Litigiousness
US Product Perceptions	EU Product Perceptions

To be able to do this, first I need to adopt an approach to culture which is pragmatic for this task. In this Chapter I turn to theories of culture. I begin by adopting a basic definition of culture as the values and norms shared within a group, and by clarifying some key concepts. Next, drawing on literature from economics and institutional theory, I set out my approach to culture in this work, which is based around institutions. Having settled upon this approach, next I seek some contents for the values and norms of culture: a workable typology or set of dimensions which I can use to analyse the items in Table 61. Having selected the Cultural Theory of Risk and the Group-Grid typology, I continue by operationalising both this, and the institutional approach to culture, for my purposes in Chapter Six.

5.2 Definitions and Clarifications

Definition of Culture

In this Chapter, and therefore in this work as a whole, I define 'culture' as the values and norms shared within a group. Thus, in neither this Chapter nor the next do I look specifically at the cultural orientation of *individuals* in *isolation from each other*. The 'shared' element is crucial because it distinguishes theories of culture from the approach taken by methodological individualism. Martin[2] considered 12 different definitions of organisational culture. He concluded that what all had in common was that they encompassed some 'shared' element and were *"distinctive"* to a particular context. This mirrors the view taken by major cultural theories outside of the (strictly) organisational context, including the Cultural Theory of Risk/Grid-Group (CT-GG) and Hofstede's Dimensions of National Culture (DNC). My approach here in applying culture supplements the approach of methodological individualism, the latter which is the preferred approach within the social sciences.[3] One advantage of this is that cultural theories can provide an endogenous account of preference formation. They can provide an account of why individuals' preferences fall the way that they do, and how this interacts with the shared element of culture.[4] In that sense I could speculate as to individual preferences based upon the cultural orientations of the groups in which individuals interact, however, I reiterate that in this work I do not seek to measure 'cultural biases' at the individual level. Instead, I consider the cultural orientation of groups, through cultural analysis of the institutions which bind together those groups.

Groups, Institutions, Norms/Values and Behaviours/Practices

Because I define culture this way, my analysis in the next Chapter must be focused on groups. However, as set out below, what I analyse culturally in Chapter Six is institutions. Thus, I need to clarify the relationship which I posit between groups and institutions. Moreover, I define culture as shared values and norms, but as Schein notes,[5] it is difficult to identify, empirically, what the values and norms of a group are, and organisational theories of culture therefore sometimes refer to 'practices' (within an organisation) instead of norms and values. A second thing that I

2 Martin, J. 2002. Organizational culture. London: Sage Publications.

3 Methodological individualism has been employed in the previous chapters when applying public and private interest theories of regulation.

4 Methodological individualism, a strict rational-actor approach, treats preferences as endogenous and given.

5 Edgar Schein. believes that organisational culture is difficult to measure because much of it cannot be observed. He defines it as, *"a pattern of shared basic assumptions… stable and difficult to change"*. Thus, a second common aspect between definitions of organisational culture, and definitions of culture at other levels, is that culture is, to some extent, considered to be "stable" however, because cultural change clearly does occur in the longer run, any theory of culture must be able to account for cultural change. Schein, Edgar H. "Career theory and research: Some issues for the future." *Work, Family, and the Career: S* (1980): 357-365. Schein, Edgar H. Organizational culture and leadership. Vol. 2. John Wiley & Sons, 2010.

need to clarify, then, is the relationship between 'values and norms', on one hand, and 'practices' on the other.

These conceptual problems are solved by adopting an 'institutional approach' to culture, which I explain fully below. The core insight is that all groups, of any size, are bound together by institutions, which guide individual group member in how they should interact with other individual members of the same group. Considering first the concept of a group: these can range from the entirety of the human population, to just two individuals. In Table 62 below I set out some examples of groups and subgroups which I consider in this work.

Table 62 Examples of Groups for Cultural Analysis

Groups
Subgroups (e.g. professions, industries)
Organisations (e.g. regulatory agencies)
Nations
Jurisdictions

Throughout this work I have spoken in terms of 'groups, organisations and institutions.' Where I refer to organisations, I am referring to just one type of group. Where I refer to institutions, I am referring to institutions which guide the interaction of members in any of the groups listed above, *or* between those groups. Thus, whenever I culturally analyse an institution, I am always doing so in order to analyse the cultural orientation of the group abiding by that institution. In the case of jurisdiction-wide institutions, I am analysing these to ascertain the cultural orientation of the group which is the whole jurisdiction.

What makes a group? In my view a group exists where there is any human interaction. It is more likely that we will call a series of human interactions a 'group' where those interactions are repeated over a relatively long-lasting time. The core argument made below is that all human interactions are governed by institutions. Thus, it is likely that where there is an identified number of individuals interacting on a regular basis with each other (so as to be recognised as a 'group'), then that group will have its own institutions governing intra-group interactions between members. Groups, therefore, I say, are given form and boundaries by their institutions. Therefore, in the next chapter, I look to work out what these institutions are, by considering the *behaviour* of the group, before analysing the cultural orientation of the institution, and thus the group.

As to the potential confusion between 'norms/values' on one hand and 'practices' on the other. This, too, is resolved by adopting the institutional approach to culture. The key to this is looking at group behaviour – i.e., its practices. By looking at the practices and behaviour of the members of the group in their intra-group interactions, I can deduce the institutions (the 'rules') governing and guiding those interactions. Once I have identified an institution, I can analyse that culturally and ask which of the abstract norms and values (tendered by the theories of culture set out below) that institution reflects. Moreover because, as noted above, groups are given form by

their institutions, I can ascertain the cultural orientation of a group by considering its practices and behaviours.[6]

In the sections which follow I seek first an *approach* to culture. That approach should be able to account for (the observable fact of) cultural change, whilst not denying the possibility that differences between jurisdictional cultures can and do manifest in a relatively stable way, which makes cultural comparison between two jurisdictions possible over the course of the 100-300 year time period considered in all aspects of this work. That approach should also be capable of giving some account of where cultural diversity comes from in the first place. In addition, that approach to culture should permit me to consider groups and subgroups of all sizes, through consideration of institutions. In the next section I set out how the institutional approach to culture, found mainly in the economic literature on culture, satisfies all of these criteria.

I then seek some *contents* for culture. My adopted approach to culture does not on its own tell me about the content of the shared values and norms. I need to find typologies or dimensions of culture which will provide me with this, enabling the cultural analysis of groups, organisations, and institutions in Chapter Six. In seeking this, I have several criteria, which are set out at the beginning of that section. A meta-criterion is that the theory adopted to provide some contents for culture should be compatible with the institutional approach to culture adopted in the first section. Thus, for example, the theory selected for the content of culture must be compatible with the account given for cultural change in the institutional approach, and thus necessarily must not assume internal cultural coherence within a group.

6 I also – in the case of the jurisdictions (which are also groups) – consider formal legal institutions which apply to the whole jurisdiction. In addition, I consider informal institutions such as social customs, but these, too, amount to behaviours and practice.

5.3 An Institutional Approach to Culture

In this Section first, I explain in more detail what institutions are and my approach taken here that culture is the basic institution (or the 'institutional logic') within any group. Then, I elaborate upon the relationship between groups and the institutions created within and by groups. I argue that it is the existence of specific formal/informal institutions which demarcate the boundaries of smaller groups, and the existence of the basic institution of culture which demarcates the boundary of the wider group within which the smaller group operates. After this, I consider how economists have presented the relationship between institutions, culture, and economic outcomes, including the account given of 'where' culture 'comes from'. Finally, I apply work taken from institutional theory to provide an account of how culture (and other institutions) change over time.

5.3.1 Definitions of 'Institution'

North[1] defines institutions as, *"the humanly devised constraints that structure human interactions"* and he says they include both, *"formal constraints (rules, laws, constitutions), (and) informal constraints (norms of behaviour, convention, and self-imposed codes of conduct)"* and their enforcement characteristics.[2] What is common to all of these is that they in some way guide individuals in their interactions with other individuals within a group. Some examples of formal and informal institutions are given in Table 63 **Examples of Formal and Informal Institutions (2)**below. Under other definitions there are institutions even less formal than North's informal institutions, including 'institutional frames of reference'[3] and 'institutional logics.'[4] The latter have been described as follows,[5] *"collections of interrelated rules and routines that define appropriate actions in terms of relations between roles and situations. The process involves determining what the situation is, and what role is being fulfilled, and what the obligation of that role in that situation is."*

1 See North, Douglass C. "A transaction cost theory of politics." Journal of theoretical politics 2, no. 4 (1990): 355-367. And Milgrom, Paul R., Douglass C. North, and Barry R. Weingast. "The role of institutions in the revival of trade: The law merchant, private judges, and the champagne fairs." Economics & Politics 2, no. 1 (1990): 1-23.

2 North's definition is set out in Alesina, Alberto, and Paola Giuliano. "Culture and institutions." Journal of Economic Literature 53, no. 4 (2015): 898-944.

3 Jordan, Andrew, and Tim O'Riordan. Social institutions and climate change: applying cultural theory to practice. Centre for Social and Economic Research on the Global Environment, 1997.

4 Thornton, Patricia H., and William Ocasio. "Institutional logics." The Sage handbook of organizational institutionalism 840, no. 2008 (2008): 99-128. See also Thornton, Patricia H., and William Ocasio. "Institutional logics and the historical contingency of power in organizations: Executive succession in the higher education publishing industry, 1958–1990." American journal of Sociology 105, no. 3 (1999): 801-843.

5 March, James G., and Johan P. Olsen. "The logic of appropriateness." In The Oxford handbook of political science. 2004.

Table 63 Examples of Formal and Informal Institutions (2)

Type of Institution	Example
Formal Legal Institutions	Constitutional free speech protections Strict liability for defective products Specific regulations (e.g. banning DTCA)
Informal Social Custom/Practice	Hierarchical doctor-consumer relationship Practice of giving public apologies Shared heuristic of perception e.g. 'natural-is-better'

All groups are bound together by institutions. Organisations, for example, may be established through formal legal institutions. And, because organisations are groups - in which individuals interact (necessarily) according to shared basic values and norms - organisations have a cultural orientation of their own. That culture may be reflected in the formal institutions governing the organisation itself (e.g., its mission statement or charter). This is the focus of much of the work on institutional logics, which have found application in the management sciences. This work on institutional logics also suggests that organisations will abide by institutional logics which enable them to better interact with other entities in a wider group such as a jurisdiction. Institutional logics come from institutional theory, which began with Selznick[6] and Parson.[7] The idea was that any given organisation needed some way to fit in to the wider social context in which it operated – including other organisations within a jurisdiction. These interactions are governed by rules of some kind, and the institutional theorists called the rules which govern the interaction between organisations 'institutions.' I have already adopted a definition of institutions here broad enough to cover interactions between organisations, other groups, and individuals. In the view of Parson, institutions, *"function to integrate organisations with other organisations in society, through universalistic rules, contracts and authority"*.[8]

The argument of this Section is that culture itself is the *basic* institution (or 'institutional logic') in a group, and all other institutions within a group are derived from the basic institution of culture. I have defined culture here as shared values and norms within a group. Arguably, this could render culture itself an 'informal institution' on a par with those discussed by North.[9]

6 Selznick, Philip. "Foundations of the theory of organization." American sociological review 13, no. 1 (1948): 25-35. Selznick, Philip. "TVA and the Grass Roots." (1949). Selznick, Phillip. 1957. Leadership in Administration. Berkeley: University of California Press.

7 Parsons, Talcott. "Suggestions for a Sociological Approach to the Theory of Organizations-I." Administrative science quarterly (1956): 63-85. Parsons, Talcott. "Suggestions for a Sociological Approach to the Theory of Organizations. II." Administrative Science Quarterly (1956): 225-239.

8 This is the basis upon which I say there is likely to be a link between jurisdictional culture and the culture of subgroups within a jurisdiction such as organisations, regions, or professions. By abiding by the same fundamental values and norms, these subgroups can interact with each other within the wider group which is the whole jurisdiction.

9 In their 2015 work, Alesina and Giuliano decline to include culture itself within their definition of institutions, for pragmatic reasons. Alesina and Giuliano (2015).

For North, the informal institutions he refers to, *"are a part of… culture."*[10] However, I consider that some of the informal constraints listed by North can cover rules too specific to be the basic institution of culture. The conventions which North refers to can be very specific.[11] Culture, on the other hand, is more abstract: it relates to the most basic values and norms which orientate the more concrete rules.[12]

5.3.2 Institutional Logics: Culture as the Basic Institution

Culture as an institution is the most abstract guide to human behaviour in a group. The pyramid in Figure 16 below represents the group in question and encompasses all the institutions guiding the behaviour of individuals in the group in their interaction with other individuals in the group. At the bottom of the pyramid sits the basic institution of culture. From that, informal institutions are derived, and normally formal institutions will be created in accordance with the basic and the informal institutions. The pyramid may represent any group or subgroup. If the group is a subgroup, then that subgroup can interact with other subgroups within a larger group by sharing the basic institution (the culture) of the wider group, even if its informal and formal institutions differ from the wider group to some extent.

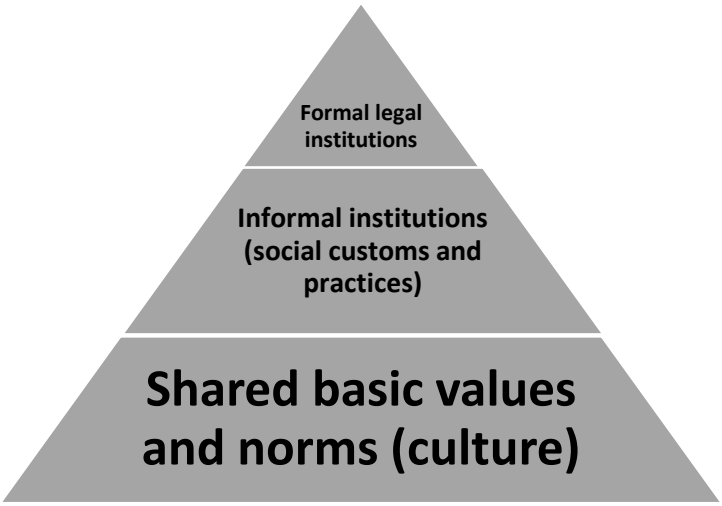

Figure 16 **Culture as the Basic Institution in a Group or Subgroup**

One question posed in the literature relates to whether institutions are exogenous to human behaviour or endogenous to it.[13] Alesina and Giuliano say that North treats institutions as

10 North (1990)

11 They range from constitutional conventions which set out very specific procedures such as that the British monarch will not refuse royal asset to a Bill passed by both houses of Parliament, to less grand but still rather specific conventions such as the requirement to remove one's hat inside a church. These are specific guides to behaviour, they are specific *"rules of the game"* (North, 1990) even if they are not written laws.

12 Hence, I say, all these informal institutions identified by North, because they are *informed* by values and basic norms, are related to culture and thus the rules – the institutions, formal or informal – can be classified or placed on that cultural matrix.

13 Alesina and Giuliano (2015).

exogenous to human behaviour: *"the rules of the game are separate from the way the game is played"* but that is because for the purposes of his research he did not need to answer the question of where the institutions came from, or how they are linked to culture – he was studying human behaviour in the shadow of given institutions. Grief, on the other hand believed, *"institutions represent equilibria of a game rather that the rules of the game."*[14] That is to say, institutions were not decided first, from which behaviour followed, but rather that the institutions are a *description* of human behaviour within a given group. This is closer to my approach here. Below, I set out the argument that the basic institution of culture, and the other institutions, are mutually co-produced and thus mutually reinforcing. As such, institutions are endogenous to human behaviour.[15]

Culture – as I have described it here – is therefore very similar to what are called 'institutional logics' in institutional theory. Institutional logics help to explain how human behaviour is related to formal and informal institutions.[16] The concept ties together human behaviour and institutions because it considers how broad belief systems (institutional logics) affect individual cognition and individual behaviour. Institutional logics emerged as a part of the development of institutional theory, around the time of the 1970s. Thornton and Ocasio describe it as *"both a metatheory and a method of analysis."* They[17] define institutional logics in the following way, *"the socially constructed, historical patterns of material practices, assumptions, values, beliefs and rules by which individuals produce and reproduce their material subsistence, organise time and space, and provide meaning to their social reality."*[18] Friedland and Alford said that they were, *"a central logic – a set of material practices and symbolic constructions – which constitute (the orders of western societies') organising principles and which (are) available to organisations and individuals to elaborate."* Meyer and Rowan[19] and Zucker[20] first emphasised how culture and cognition matter in analysing institutions, and this is where the concept of institutional logics comes from.

Cultural diversity will lead to contested meanings. The cognition of given things - success, efficiency, responsibility etc. - by individuals, and thus by whole organisations, will be

14 Grief, Avner. "Institutions and the Path to the Modern Economy: Lessons from Medieval Trade" Cambridge University Press. Cambridge UK (2006).

15 This argument is important to the account I give here (taken from the economic literature) for the origins of cultural diversity. It is also important to understanding how culture may change over time, in that it permits of the possibility of formal (and informal) institutional change leading to a change in underlying culture and thus human behaviour; but, it implies that the basic institution of culture will change the most slowly, even where reforms have been made to formal legal institutions. It is because the basic institutions of culture change only very slowly in response to a reciprocal feedback relationship with the other institutions further up the pyramid, that a change in formal legal institutions will not immediately effect a change in human behaviour and therefore, say, economic outcomes.

16 Thornton and Ocasio (2008). See also Thornton and Ocasio (1999)

17 Thornton and Ocasio (1999)

18 Thornton, Patricia H., William Ocasio, and Michael Lounsbury. The institutional logics perspective: A new approach to culture, structure, and process. Oxford University Press on Demand, 2012.

19 Meyer, John W., and Brian Rowan. "Institutionalized organizations: Formal structure as myth and ceremony." *American journal of sociology* 83, no. 2 (1977): 340-363.

20 Zucker, Lynne G. "The role of institutionalization in cultural persistence." *American sociological review* (1977): 726-743. See also DiMaggio, Paul J., and Walter W. Powell. "The iron cage revisited: Institutional isomorphism and collective rationality in organizational fields." *American sociological review* (1983): 147-160. And DiMaggio, P. J., & Powell, W. W. (1991). Introduction. In W. W. Powell & P. J. DiMaggio (Eds.), The new institutionalism in organizational analysis (pp. 1-38). Chicago: University of Chicago Press

dependent upon the basic institution or the institutional logic which is culture. I.e., upon the basic shared norms and values which give everything else meaning. Hence, I place this basic institution at the bottom of the pyramid in Figure 16. Without these highly abstract values and norms being determined first as the foundation, the more specific and concrete institutions found above them in the pyramid will end up being the subject of contested meanings. Friedland and Alford's[21] theoretical contributions, alongside empirical work by Thornton and Ocasio and others[22] *"posited institutional logics as defining the content and meaning of institutions."* This is a departure from methodological individualism because *"institutional logics shape rational mindful behaviour"*[23] hence they tell individuals (in this theoretical context, within organisations – but we can also just say groups) how to act rationally.[24] Moreover, the institutional logic scholars recognised that individual behaviour can also shape institutional logics: the two-way interaction between institutions (governing social relations) and culture which is described below: Thornton says, *"individual and organisational actors have some hand in shaping and changing institutional logic."*[25]

5.3.3 Groups, Subgroups, Institutions, and Cultural Diversity

A 'group' may be identified by the relative intensity of interactions between individuals in any given setting. The interactions within groups are governed by institutions which were created by group members to govern those interactions. Hence, institutions demarcate the boundaries of the group. All groups are composed of subgroups: i.e., a group can be the entire human population (interacting even only in subgroups of nation states through war with each

21 Friedland and Alford (1991)

22 Haveman, Heather A., and Hayagreeva Rao. "Structuring a theory of moral sentiments: Institutional and organizational coevolution in the early thrift industry." *American journal of sociology* 102, no. 6 (1997): 1606-1651. See also Thornton and Ocasio (1999) and Scott, W. Richard, Martin Ruef, Peter J. Mendel, and Carol A. Caronna. *Institutional change and healthcare organizations: From professional dominance to managed care*. University of Chicago Press, 2000.

23 Thornton, Patricia H. Markets from culture: Institutional logics and organizational decisions in higher education publishing. Stanford University Press, 2004.

24 Thus, my discussion, up to this point, of 'public interest approaches' to regulatory questions takes on an entirely new meaning (albeit heavily hinted at up to this point in this work). What lies in the public interest will depend on the shared values and norms of the consumer (public) being regulated. Therefore it is perhaps better to consider public interest approaches to regulation as a form of private interest approaches to regulation, whereby consumers are viewed as a specific interest group with aims and objectives dictated by their own institutions. Given that such an interest group is the broadest possible within a jurisdiction, however, the institutional logic or cultural orientation of the interest group of consumers is highly likely to be congruent with the institutional logic or culture of the jurisdiction as a whole.

25 The question of the relationship between institutional logics (and thus, in my approach, between cultures) has also been addressed within the institutional logics literature. Thornton, Jones and Kury, building on the work of Bourdieu take a *"pluralistic approach… focusing on multiple competing logics and contestation of meaning"* and on how *"multiple logics can create diversity in practice by enabling variety in cognitive orientation and contestation over which practices are appropriate. As a result, such multiplicity can create enormous ambiguity, leading to logic blendings, the creation of new logics and the continued emergence of new practice variants".* Thornton, Patricia H., Candace Jones, and Kenneth Kury. "Institutional logics and institutional change in organizations: Transformation in accounting, architecture, and publishing." In Transformation in cultural industries. Emerald Group Publishing Limited, 2005. See also Bourdieu, Pierre. Structures and the habitus. 1977.

other) or just two individuals together conversing. There will be a hierarchy of institutions governing the interactions between all groups and subgroups on the planet. Thus, the whole of human civilisation may be said to share some fundamental value or norm: say, perhaps, that interactions between human beings are valued.[26] However, as one moves from the whole of human society to smaller subgroups within it: say jurisdictions like the EU or the US, then those basic cultural norms will become more specific but still compatible to some extent with the global fundamental value or norm. For example, in one jurisdiction human interaction will be valued, but the form of interaction more greatly valued is that done on an individual one-to-one basis. Whereas, in another jurisdictional culture human interaction is valued relatively more when done on a group basis. This is where cultural diversity starts to manifest. There will also be further diversity in the formal and informal institutions found in these jurisdictions, and that diversity will mirror the relative differences in the basic cultural institution. This is how groups form: individuals within groups interact relatively more with each other within the group than they do with others outside of the group, thus they construct institutions to govern those interactions, and those institutions will reflect the underlying culture of the distinct (sub)group.[27]

Having noted that groups create institutions, and that group boundaries are defined by the institutions, I further note that institutions take time to develop,[28] and once developed, are relatively stable in form, even though they are constantly 'renegotiated'[29] by individuals or subgroups from within the group. Thus, institutions can and do *change* over time, but only relatively slowly. This is due in part to the fact that the cultural outlook of individuals within a group are likely to be shaped *by* the institutions of the group. In the words of Giddens,[30] individuals *"create society at the same time as we are created by it."* Moreover (adopting what has been called the approach of 'sociological institutionalism') when entirely new institutions are created in a group, these develop in the context of the pre-existing institutions which surround them. Thus, in the development process, the form of the new institutions is likely to be affected by the form of the old institutions, and the ex-ante cultural 'orientation' of the group reflected ex-post. Due to the potentially circular relationship between institutions and culture, the construction of institutions acts as a way of entrenching culture in the group - despite the passage of time and the addition and/or subtraction of members. Aaron Wildavsky explained the process in his paper: *'Choosing Preferences by Constructing Institutions: A Cultural Theory of Preference Formation.'*[31] He argues that individuals construct institutions together according to their aligned preferences, which are determined by their culture. The formation of individual preferences in that group are then affected by the form of the institutions which individuals encounter when living in groups, and through which they perform social interactions. Because institutions are constructed to provide guidance to

26 An assumption in the Cultural Theory/Grid-Group matrix, which is instead designed to look at smaller groups and individuals.

27 This account does not yet elaborate on why a given group may adhere to a *specific* culture (content of culture) and thus (or at the same time) create institutions of a specific type, but an account of that is given below.

28 Berger, Peter L., and Thomas Luckmann. *The social construction of reality: A treatise in the sociology of knowledge*. No. 10. Penguin Uk, 1991.

29 Jordan and O'Riordan (1997)

30 Giddens, Anthony. *The constitution of society: Outline of the theory of structuration*. Univ of California Press, 1984.

31 Wildavsky, Aaron. "Choosing preferences by constructing institutions: A cultural theory of preference formation." *American political science review* 81, no. 1 (1987): 3-21.

human beings in their interactions with each other, the institutions of a group guide the social relations of individuals within a group. As such, preference formation (and culture) can be said to be endogenous to groups through their creation of institutions.

5.3.4 Culture, Institutions and Economic Outcomes

Economic approaches to culture generally do not propose a classification of cultural 'types' but instead seek to measure culture (using a given cultural classification) and the effects of culture on economic outcomes, often through the mediating effects of institutions. Before concrete attempts were made to measure culture and its effects, first the literature identified that culture was having *some* effect on economic outcomes beyond the effect caused by institutional differences between groups in different regions. The link between institutions and economic development has long been recognised, for example by North, Acemoglu, Johnson and Robinson.[32] However, it has also been observed that institutional changes (or 'shocks') do not seem to change economic outcomes. In the words of Tabellini and Harari, *"economic and policy outcomes are often much more persistent than the institutions which are supposed to shape them and institutions which are rapidly changed (institutional shock) may lead to no change in economic development."* [33] In addition, sometimes where political institutions have been stable for centuries, within some countries there can be wide variation across regions in economic outcomes as is the case for example in the north and south of Italy.[34] Tabellini and Harari suggest that the north-south divide in Italy is evidence that institutions alone cannot explain economic outcomes, and that a *"legacy of history"* leads to the difference in economic outcomes and the functioning of institutions between the two regions.[35] They concluded that shared values and norms must be relevant - in addition to institutional explanations - to explaining economic outcomes.

In 2008 Tabellini proposed[36] a formal model which ties together 'inherited norms of good conduct' with what the methodological individualist would call 'rational preferences.' The former are internalised by individuals in childhood. He found that the equilibrium was one in which there were *"complementarities"* between these instilled values and behaviour in the world which *"reinforce(s)"* changed external conditions. As such, because internalised norms and values evolve gradually over time, attempts at institutional change may be ineffective to change economic outcomes where (for example) the *"quality of legal enforcement is chosen under majority rule".* In a paper from 2010 Tabellini further argued that culture has a causal

32 North, Douglass Cecil. *Structure and change in economic history*. Norton, 1981. Acemoglu, Daron, Simon Johnson, and James A. Robinson. "The colonial origins of comparative development: An empirical investigation." *American economic review* 91, no. 5 (2001): 1369-1401.

33 Tabellini, Guido, and Mariaflavia Harari. "The effect of culture on the functioning of institutions: Evidence from European regions." CESifo DICE Report 7, no. 1 (2009): 13-19.

34 Alesina and Giuliano (2015).

35 Tabellini and Harari (2009). This, they say, implies something more is needed to explain why *"rational voters keep voting for corrupt politicians"* and why it is possible to overcome the collective action problem in some situations but not in others.

36 Tabellini, Guido. "The scope of cooperation: Values and incentives." *The Quarterly Journal of Economics* 123, no. 3 (2008): 905-950.

effect on macroeconomic development.[37] He found that culture – measured by *"indicators of individual values and beliefs such as trust and respect for others, and confidence in individual self determination"* – was strongly correlated with the 2010 economic development of the European regions.[38] In that paper, Tabellini sought to isolate only the exogenous component of culture, i.e., he did not consider specifically how institutions may shape culture within a group.

Alesina et al.[39] considered a specific pathway through which culture may affect institutions, and subsequently economic outcomes. They found that groups with shared norms that value strong family ties were more likely to choose strong labour market regulation, such that the mobility of workers (away from the family) was not so necessary. This stronger labour market regulation was, in turn, linked to lower wages and higher unemployment in these regions.[40] Alesina and Giuliano's 2011 work[41] confirms a further link between the strength of family ties on one hand and generalised trust and political participation on the other: the latter two are lower when the former is higher. Generalised trust and political participation in turn affect economic outcomes. They say, *"the more individuals rely on the family as a provider of services, insurance and transfer of resources, the lower is civic engagement and political participation."*[42] In *'Institutions and Culture'*[43] Tabellini provides evidence for a link between *"individual values and convictions"* in this case *"about the scope of application of norms of good conduct"* and the functioning of current institutions. He found that individually held values which were consistent with generalised morality (i.e. good conduct towards all) were prevalent in societies where, historically, governance had been non-despotic.[44] Whilst these earlier papers did not draw out a specific relationship between culture on one hand and institutions on the other (and how both interact to shape economic outcomes), much more recently, Torsten and Tabellini[45] provide empirical and theoretical support for a *"dynamic interaction"* between cultures and institutions.

37 Tabellini, Guido. "Culture and institutions: economic development in the regions of Europe." *Journal of the European Economic association* 8, no. 4 (2010): 677-716.

38 In doing so he ensured that only the exogeneous component of culture was captured by reliance upon the instrumental variables of literacy rate and political institutions, taken from history. This work on the predictive power of culture for economic development indicated a causal relationship between culture and macroeconomic outcomes, which may of course occur through the medium of institutions (reflecting underlying culture) which support economic development. Tabellini (2010).

39 Alesina, Alberto, Yann Algan, Pierre Cahuc, and Paola Giuliano. "Family values and the regulation of labor." *Journal of the European Economic Association* 13, no. 4 (2015): 599-630.

40 Specifically, they found a positive association between rigid labour market regulation at the beginning of the 21st Century, and family values before World War Two, and family structures in the Middle Ages.

41 Alesina, Alberto, and Paola Giuliano. "Family ties and political participation." *Journal of the European Economic Association* 9, no. 5 (2011): 817-839.

42 Alesina and Guiliano later proposed a more subtle two-way relationship between culture and institutions, suggesting they are mutually co-produced, a view which I adopt in my theoretical framework going forwards here. Alesina and Giuliano (2015).

43 Tabellini, Guido. "Institutions and culture." Journal of the European Economic association 6, no. 2-3 (2008): 255-294.

44 The form of governance being an institution.

45 Persson, Torsten, and Guido Tabellini. "Culture, institutions, and policy." In The Handbook of Historical Economics, pp. 463-489. Academic Press, 2021.

5.3.4.1 A Two-Way Relationship Between Culture and (Other) Institutions

Alesina and Guiliano[46] proposed a more subtle two-way relationship between culture and (other) institutions, suggesting they are mutually co-produced. This is a view which I have already implicitly adopted, and which I now expressly adopt for this work. They emphasise *"a feedback effect between the two – given this interdependence, both institutions and culture co-evolve, which can generate multiple stable equilibria with different sets of self-enforcing institutions and cultural norms."* Various scholars have investigated the impact of culture upon institutions (for example Fischer[47] and Todd[48]) and this work - in addition to the work of Alesina[49] and Tabellini[50] - seems to confirm the work of Banfield on the link between prevailing morality and the functioning of institutions.[51] The implication of the sum of this work is that a lack of social capital - which reflects values of only specific and not general morality (and may have its genesis in a history of despotic governance) - leads: to low civic participation, to weak institutions for civic participation and trust, and subsequently to poor macroeconomic outcomes particularly in certain regions of Europe. This work posed only a unidirectional account: one which goes from an observation of underlying culture (values and norms) working towards institutional and macroeconomic outcomes. The conclusions reached there leave open the suggestion that a change to institutions (a shock to institutions, for example the introduction of a new civil code) would lead to changes for macroeconomic outcomes. The same line of literature is clear that this is not the case – culture continues to have an effect even when institutions change. It showed that institutional shocks often do not change macroeconomic outcomes, precisely because values and norms remain relatively fixed.

The question then arises whether *institutional* changes can lead to changes in underlying *culture*: does the relationship work the other way around? The literature suggests that this does not happen quickly. The fall of communism in Eastern and Central Europe was investigated by Roland[52] who found that the transition from authoritarian institutions to democratic institutions did not affect the view and endorsement of the populace of authoritarian forms of governance. Glaeser et al[53] and Guiso, Sapienza and Zingales[54] together argue that the values and norms held by individuals form part of their human capital, that the shared element of these within (groups) amounts to social or civic capital, and that a precondition for democratic institutions to function properly is a social or civic capital which

46 Alesina and Giuliano (2015).

47 Fischer, David Hackett. *Albion's seed: Four British folkways in America*. Vol. 1. America: A Cultural History, 1989.

48 Todd, Emmanuel. *The explanation of ideology: Family structures and social systems*. Oxford [Oxfordshire]; New York, NY, USA: B. Blackwell, 1985.

49 Alesina et al. (2015)

50 Tabellini (2010). Tabellini (2008).

51 Banfield, E.C. 1958. The moral basis of a backward society. New York: Free Press

52 Roland, Gérard. "Understanding institutional change: Fast-moving and slow-moving institutions." *Studies in comparative international development* 38, no. 4 (2004): 109-131. See also: Shiller, Robert J., Maxim Boycko, Vladimir Korobov, Sidney G. Winter, and Thomas Schelling. "Hunting for Homo Sovieticus: situational versus attitudinal factors in economic behavior." *Brookings Papers on Economic Activity* 1992, no. 1 (1992): 127-194.

53 Glaeser, Edward L., Giacomo AM Ponzetto, and Andrei Shleifer. "Why does democracy need education?." *Journal of economic growth* 12, no. 2 (2007): 77-99.

54 Guiso, Luigi, Paola Sapienza, and Luigi Zingales. "Does culture affect economic outcomes?." *Journal of Economic perspectives* 20, no. 2 (2006): 23-48.

will support them. The view of Roland[55] is that *"long-run history"* shapes the evolution of institutions in any given region. This observation fits with the findings elsewhere in the literature, suggesting that underlying culture shapes the form of current institutions and the creation of new institutions. A new institution may look democratic, but due to the effect of culture (civic or social capital), the form of that institution in practice may instead be authoritarian and macroeconomic outcomes will follow accordingly. On the other hand, experimental evidence shows that institutional environments do affect norms and values – i.e. that the 'causal effect' can be argued to go the other way. Work by Gneezy, Liebbrandt and List,[56] and by Herrmann et al.[57] show that differences in institutional environments (which, for example, affect the expected payoffs available from cooperation) can affect the *"prevalence"*[58] of certain norms and values. This is supported by empirical work from Bardhan,[59] Levine and Tyson,[60] and Black and Lynch[61] which shows that where institutions are democratic, this is likely to affect the norms governing cooperation within the group where those institutions exist. This in turn supports the view that there is a bi-directional relationship between institutions and underlying culture.

Having considered all of this literature, Alesina and Giuliano[62] argue that, *"the most promising approach, both theoretically and empirically, to studying the interaction between culture and institutions recognises and embraces a two-way effect to explain economic development and other types of economic outcomes, rather than stressing causality in one direction of the other".* They point to contributions from, for example, Tabellini[63] which look at *"the coevolution of culture and institutions, leading to multiple equilibria characterised by a combination of some types of culture and some types of formal institutions".* This is the approach I adopt here in this work. They say, *"the general idea underlying this approach is that a country (or a region or an ethnic group, for example) shares certain cultural values, which leads to the choice of certain institutions. In turn, certain institutions lead to the survival (and transmission across generations) of certain cultural values."* This perspective fits very well with what Wildavsky says about preference formation being related to the institutions through which individuals interact in groups, and also to my framing of 'groups' and 'subgroups' as being demarcated in their boundaries by the institutions which govern interactions within them. What the economic literature surveyed here adds to this, is a tighter explanation for how the basic institution of culture can become entrenched in a group such that it (culture) is relatively slow to change. That is because, in order to change the underlying

55 Roland (2004)

56 Gneezy, Uri, Andreas Leibbrandt, and John A. List. "Ode to the sea: Workplace organizations and norms of cooperation." *The Economic Journal* 126, no. 595 (2016): 1856-1883. Leibbrandt, Andreas, Uri Gneezy, and John A. List. "Rise and fall of competitiveness in individualistic and collectivistic societies." *Proceedings of the National Academy of Sciences* 110, no. 23 (2013): 9305-9308.

57 Herrmann, Benedikt, Christian Thöni, and Simon Gächter. "Antisocial punishment across societies." *Science* 319, no. 5868 (2008): 1362-1367.

58 Alesina and Giuliano (2015).

59 Bardhan, Pranab. "Irrigation and cooperation: An empirical analysis of 48 irrigation communities in South India." *Economic Development and cultural change* 48, no. 4 (2000): 847-865.

60 Levine, D. I., & Tyson, L. D. 1990. Participation, productivity, and the firm's environment. In A. S. Blinder (Ed.), Paying for productivity: A look at the evidence: 183-243. Washington, DC: Brookings Institution

61 Black, Sandra E., and Lisa M. Lynch. "What's driving the new economy?: The benefits of workplace innovation." *The Economic Journal* 114, no. 493 (2004): F97-F116.

62 Alesina and Giuliano (2015).

63 Tabellini (2008)

cultural institution, it is necessary to first change many of the formal and informal institutions, since the latter two and the first are mutually co-produced and mutually reinforcing. This approach does, however, leave open the possibility that changes in institutions (institutional shocks) will lead to changes in underlying culture. I.e., that a group can move from one of the multiple equilibria to another, however, it implies – because institutions and culture are mutually reinforcing – that this will only happen *slowly*. This analysis has also allowed economists to provide an account of where culture 'comes from' in the first place.

5.3.4.2 Multiple Equilibria and Path Dependence: Where Culture 'Comes From'

Due to the economic approach focusing upon measurement and outcomes it often treats, as did Tabellini in his 2010 paper,[64] the shared values and norms comprising culture, as exogeneous and 'given'. However, in a publication from 2011[65] Alesina, Giuliano and Nunn demonstrated, through ethnographic evidence, that societies which had historically adopted the plough for agriculture had lower levels of fertility in the 21st Century. This – they argued – was because where plough agriculture was used, women and children were *"relatively less useful in the field"* and this brought about a preference in these societies for fewer children. Alesina and Giuliano have argued[66] that multiple equilibria exist whereby there are a discrete number of combinations of mutually reinforcing 1) values and norms (culture) on one hand; and 2) institutions, on the other. Combining both insights, this points to an economic account of where culture comes from. Small initial differences in the conditions faced by historical groups - such as whether the land on which they lived was fit for plough agriculture – may lead the group through history towards one of these multiple equilibria. Once a group has started its historical development along one path, the mutually reinforcing (mutually co-producing) nature of culture and institutions leads to path dependency and settlement upon one equilibrium from which change is difficult: it is possible in the long term only.

This is an account both for where culture comes from – historical accident – and for cultural diversity: differences in culture between groups in different places at different times.[67] Going

64 Tabellini (2010)

65 Alesina, Alberto, Paola Giuliano, and Nathan Nunn. "Fertility and the Plough." American Economic Review 101, no. 3 (2011): 499-503.

66 Alesina and Giuliano (2015).

67 By way of example, applying this approach to the issues considered in this work: in Chapters Two and Six I analyse the group of doctors in the United States (US). I say that in the 16th-17th Century the initial conditions for this group were such that the group lacked any internal stratification, and neither did it have strong external boundaries. This was because there were very few or no 'noble' European doctors on the ships to the new world at this time. This historical, accidental, difference in initial starting conditions for this group may account for the development of this group over history, and may help to explain why US doctors today share different values and norms to other groups such as doctors in the European Union(EU)/EU Member States (EUMS). In particular, the fact that in 1700 there were only few barriers to entry to the profession and little stratification within the group led to a preference for free market competition between individual doctors for patients, as well as to a preference for independence from hospitals and agencies. In addition to competing internally, the group chose to cooperate with each other when dealing with external entities such as hospitals and agencies (against whom they maintained their independence), and with other entities – such as the US pharmaceutical industry (USPI) – which they chose to cooperate with on a more flexible basis, at all times maintaining their independence and autonomy. That, too,

back to Tabellini's 2010 work on economic development in the European regions: whilst he controlled to capture only the exogenous component of culture, that exogenous component will have some historical reason for its existence. Thus, it might be that the current levels of economic development in the European regions is causally related to historic initial conditions which, through a long process of mutual feedback between institutions (and creation of institutions) with culture itself, leads to the long-run phenomenon which is observed as the 'effects of culture'.[68]

5.3.5 Explaining Cultural Change using Institutional Theory

From the review and analysis so far, it is clear that (in the institutional approach to culture) cultural change is possible, but that due to path dependency towards discrete but multiple equilibria it will be gradual only. This view is well supported by the literature from institutional theory discussing institutional change, which stresses that this is a gradual process only. I say that culture, too, as the basic institution, changes only gradually. Furthermore, *because* it is the basic institution in a group, it will be the slowest institution to change. Streeck and Thelen[69] offer some analytic tools for institutional change which focus upon the gradual nature of that change, extrapolating from observations about the liberalisation of markets which occurred in many countries in the 1980s onwards.[70] This is an approach in concordance with my view of culture as the basic underlying institution, and the bi-directional causation and/or mutual coproduction of institutions and culture endorsed by Alesina and Giuliano.[71]

Streeck and Thelen lament the tendency in the literature to dismiss signs of small, gradual institutional change as mere reproduction of the status quo, whilst it focuses solely upon institutional shocks, repeatedly concluding that institutional shocks do not affect real change. What is understudied, they believe, is gradual change. As new institutions are created (liberalising markets) old institutions (for example those created under socialist institutions) push back. Bringing in culture as the basic institution and tying this to the work of Giuliano and Alesina, I add that this basic institution of culture also pushes back. The effect is gradual, not sudden change, in economic (and other) outcomes. The slowest institution to change is the basic institution of culture (values and norms) whereas the fastest institutions to change

has had implications for how US doctors entered into relationships with consumers (e.g., the preference for patient centred medicine) and for the objectives of US doctors when lobbying on issues of pharmaceutical regulation.

68 Institutional 'shock' (say, for example, the adoption of a new civil code) can hurry the process along to some extent, but not in an immediate way. Alesina, Tabellini and Trebbi produced work in 2017 showing that between 1980 and 2008 extensive economic integration in Europe (amongst the EUMS) had not been accompanied by institutional or cultural convergence. Again, this suggests that the effects of culture, both being shaped by and shaping institutions, develops and changes over the long term, rather than from the setting of immediate (rational actor) economic incentives. Alesina, Alberto, Guido Tabellini, and Francesco Trebbi. *Is Europe an optimal political area?*. No. w23325. National Bureau of Economic Research, 2017.

69 Streeck, Wolfgang, and Kathleen Thelen. Introduction: Institutional change in advanced political economies. Univ. Press, 2005.

70 See also Offe, Claus. "Disorganized capitalism: Contemporary transformations of work and politics." (1985) and Lash, Scott, and John Urry. The end of organized capitalism. Univ of Wisconsin Press, 1987.

71 Alesina and Giuliano (2015).

are – for example – formal legal institutions like regulations. Streeck and Thelen provide their own analytical framework for gradual institutional change.[72]

They propose five different types of gradual institutional change: displacement, layering, drift, conversion, and exhaustion. Displacement is the *"slowly rising salience of subordinate relative to dominant institutions;"* layering is where *"new elements attached to existing institutions gradually change their status and structure;"* drift is the *"neglect of institutional maintenance in spite of external change resulting in slippage in institutional practice on the ground;"* conversion the *"redeployment of old institutions to new purposes; new purposes attached to old structures;"* and, exhaustion is the *"gradual breakdown (withering away) of institutions over time"*. Hall and Thelen[73] have applied this gradual approach to institutional change in the case of 'varieties of capitalism' (the liberalisation of markets) positing a basic analysis based on institutional stability, and arguing that, in addition to the *"aggregate welfare effects"* of those institutions and whether they are pareto optimal, what also matters is the distributive effects of these institutions and a *"continuous (process) of mobilisation through which the actors test the limits of the existing institutions"*. Donahue and O'Leary[74] have investigated institutional change within organisations – particularly within the US National Aeronautics and Space Administration finding that shocks to the institutions there – institutional changes following from three major disasters – did not change the organisations because, *"there were barriers embedded in the fabric of the agency that are likely to thwart change".*

5.3.6 Summary: The Institutional Approach to Culture

This institutional approach to culture provides an account of what the shared values and norms comprising culture are: the basic institution, or the 'institutional logic' within a group. Thus, it also illuminates what a 'group' is - a collection of individuals bound together in their interactions by shared institutions. It differentiates between culture and other institutions, thus helping to understand why institutional change will be slow to effect cultural change (and economic and other outcomes) whilst leaving open the possibility for culture to change *gradually* within a jurisdiction. It further explains how subgroups within a wider group (such as a jurisdiction) may integrate into the jurisdiction whilst there remains horizontal cultural diversity as between subgroups within the jurisdiction. It provides a tentative account of how culture develops: this is the mutual coproduction of mutually reinforcing culture on one hand and other institutions on the other, which tend – through a historical process of path dependency – towards one of only a few discrete stable potential equilibria, each of which represent compatible combinations of culture and other institutions. Finally, it provides an account of where culture might 'come from' i.e., that small changes in initial conditions faced by a group may have caused it to create institutions of a certain type, leading to the path

72 Streeck, Wolfgang, and Kathleen Thelen. Introduction: Institutional change in advanced political economies. Univ. Press, 2005.

73 Hall, Peter A., and Kathleen Thelen. "Institutional change in varieties of capitalism." Socio-economic review 7, no. 1 (2009): 7-34.

74 Donahue, Amy K., and Rosemary O'Leary. "Do shocks change organizations? The case of NASA." Journal of Public Administration Research and Theory 22, no. 3 (2011): 395-425.

dependence, which thus leads to observable differences between groups in the cultural orientation of their institutions, including the group culture.[75]

The institutional approach to culture, set out in this Section provides an account for all aspects of culture necessary for this research project, save for its contents. Nothing has been said, definitively, about 'types' of cultures. The observation made regarding multiple (discrete) potential equilibria does suggest that there may be a limited number of cultural 'types' which can exist.

5.4 The Contents of Culture: Typologies and Dimensions

In this Section I first set out some criteria for selecting a theory which provides a typology or dimensions of culture, and I list some potential candidate theories. Then I analyse Geert Hofstede's Dimensions of National Culture (DNC) considering its major criticisms, and defences. After this I turn to the Cultural Theory of Risk and the Grid-Group typology of Culture (CT-GG) again considering its strengths and weaknesses. I then provide reasons for selecting CT-GG as the theory of culture adopted for the analysis in Chapter Six, and I finish by setting out the affinity between CT-GG (as a theory providing the contents of culture) and the institutional approach to culture adopted already above.

5.4.1 Criteria and Candidates

There are many theories of culture found in several different disciplines. To culturally analyse the transatlantic regulation of the pharmaceutical sector, I need to select the most appropriate theory. Here, I briefly survey the field of cultural theories, and then I place my

75 This approach places institutions at the centre of the cultural analysis. By considering jurisdiction-wide institutions (in Chapter Six) and their cultural orientation, I am likely to be able to deduce the culture of the jurisdiction (the group) itself. Then, when considering smaller subgroups such as regulatory agencies (organisations) and/or the professions, I can consider the institutions governing the behaviour of those interacting within the organisation or group, whilst also bearing in mind that the culture of that organisation or group will necessarily be compatible (and thus close) to some extent with the cultural orientation of the wider group – the jurisdiction. It permits me to consider the cultural orientation of a jurisdiction (or two) over a relatively long period of time, such as the 100-300 years covered in all aspects of this work. It also reminds me of the importance of looking beyond merely just regulations to consider the cultural orientation of a whole jurisdiction. As the pyramid in Figure 16 shows, the regulations are the first things that can be changed and are the quickest and easiest things to change. To understand how the regulations have resulted from and/or reflect underlying jurisdictional culture, however, I need to look beyond just the regulations, also to other formal (and informal) institutions. Private interest theories of regulation tell me I must also consider subgroups and organisations and their motivations and behaviour. The institutional approach to culture here tells me that by looking at their behaviour (which is governed by the institutions created in the subgroup) I can deduce the cultural orientation of the subgroup. In doing so I must bear in mind that this is likely to be compatible with (to match, to some extent) the basic cultural institution of the jurisdiction in which they operate.

focus upon two cultural theories which I consider to be potentially useful: DNC[76] and CT-GG.[77] I need to take a pragmatic approach. For this reason, I reject emic[78] theories of culture, in favour of etic[79] theories which are easier to use for the purposes of evaluating differences between separate cultures. To explain further: there are paradigm differences to be found across the cultural literature. On one hand, Clifford Geertz favours an 'interpretive' theory of culture.[80] For him, the job of the cultural researcher is one of 'thick description'. The researcher gets inside the culture and understands it from the internal perspective, which is an emic approach. In this case, culture has an 'emergent' aspect and cannot be reduced to fixed typologies as functionalist theories like DNC and CT-GG seek to do. The focus of emic theories is upon internal consistency and coherence. At the other end of the spectrum is the functionalist paradigm.[81] The cultural theories of Hofstede (DNC),[82] Trompenaar,[83] Schwartz[84] and Douglas and Wildavsky (CT-GG)[85] all take an etic approach and enable comparison between cultures.[86]

I also draw a distinction at this stage between 'attitudinal' and 'inclusive' approaches to theories of culture.[87] The attitudinal approach looks at what individuals think, and culture is built by adding these together, without considering how those individuals interact with each other in society, or any account of how society shapes their thoughts. The inclusive approach sees individuals in social context. In other words, the thoughts, and attitudes (or values) of individuals are shaped (at least in part) by the society in which they sit. Both CT-GG and (to a lesser extent) DNC fit within the 'inclusive' camp. The inclusive approach lends itself much better to the institutional approach to culture adopted already here. The inclusive approach leads to, *"an institutional theory of multiple equilibria"*[88] as described and explained in the

76 Hofstede, Geert. Culture's consequences: International differences in work-related values. Vol. 5. Sage, 1984.

77 Douglas, Mary, and Aaron Wildavsky. Risk and culture: An essay on the selection of technological and environmental dangers. Univ of California Press, 1983.

78 *"Relating to or denoting an approach to the study or description of a particular language or culture in terms of its internal elements and their functioning rather than in terms of any existing external scheme".* (Oxford Dictionaries).

79 *"Relating to or denoting an approach to the study or description of a particular language or culture that is general, non-structural, and objective in its perspective"* (Oxford Dictionaries).

80 Geertz, Clifford. "Thick description: Toward an interpretive theory of culture." In The cultural geography reader, pp. 41-51. Routledge, 2008.

81 See e.g. Morgan, Gareth. "Paradigm diversity in organizational research." *The theory and philosophy of organizations: Critical issues and new perspectives* 13 (1990): 29.

82 Hofstede (1984)

83 See e.g. Trompenaars, Fons. "Resolving international conflict: Culture and business strategy." *Business strategy review* 7, no. 3 (1996): 51-68.

84 See e.g. Schwartz, Shalom H. "Beyond individualism/collectivism: New cultural dimensions of values." (1994).

85 Douglas and Wildavsky (1983)

86 It is stressed that neither one nor the other of these approaches need be considered 'correct', and neither is a theory of culture only to be considered worthy if it is 'complete'. Culture as a concept is the elephant standing behind the locked doors: see Patterson (2014), *"Anthropologists, sociologists, psychologists and even political scientists look through the keyholes and each sees a different part. None can claim that they have grasped the concept fully, but neither is what they have seen a lie."* It makes sense, therefore, that the researcher would adopt a framework - for considering the phenomenon of culture -which practically enables the research design. Patterson, Orlando. "Making sense of culture." *Annual Review of Sociology* 40 (2014): 1-30.

87 Hoppe, Robert. "Applied Cultural Theory: Tool for Policy Analysis." Handbook of public policy analysis (2006): 289.

88 Hoppe (2006). Grendstad, Gunnar, and Per Selle. "The formation and transformation of preferences. Cultural theory and postmaterialism compared." *Cultural theory as political science* (1999): 43-58 at 46.

Section above. Moreover, the inclusive approach fits with my initial definition of culture as the values and norms shared in a group and later explained to be the basic institution of the group. The inclusive approach – taken together with the institutional approach and the definition of culture adopted here – allow me to focus on whole groups (and their institutions) rather than upon individuals.

Finally, even accepting that a cultural theory is inclusive, etic, and functionalist, still then the theory must present me with a workable and limited number of cultural 'types' which will permit me to draw comparisons between the jurisdictions discussed in Chapter Six.

Table 64 Criteria for Shortlisting Theories of Culture

Criteria
Inclusive approach
Etic approach
Functionalist approach
Practically workable (parsimonious)
Applicable to institutions and groups of all sizes

Within the functionalist paradigm, there are four major candidates: 1) DNC; 2) CT-GG; 3) Schwartz' cultural values framework ('CVF');[89] and 4) the Global Leadership and Organisational Behaviour Effectiveness Project ('GLOBE project') framework.[90] DNC, Schwartz' CVF and the GLOBE project all adopt dimensions of culture, whilst CT-GG uses the Grid-Group matrix.

Schwartz' CVF is very similar in many respects to Hofstede's DNC. Schwartz claimed that his values were more comprehensive than those adopted by Hofstede and included Hofstede's dimensions within them.[91] In almost all other respects the approach of Hofstede and Schwartz are close together[92] including the methodology which they use to reach their dimensions and/or values. Schwartz' approach has the advantage of having been devised at both the individual level and the group level. The 'cultural level' values (which were fewer and different from the individual level values) were:[93] 1) embeddedness v autonomy; 2) hierarchy v egalitarianism; and. 3) mastery v harmony. These followed from his seven culture level value types: 1) conservativism, 2) intellectual autonomy, 3) affective autonomy, 4) hierarchy, 5) mastery, 6) egalitarian commitment, and 7) harmony. With some similarity, but simpler overall, the most important of Hofstede's dimensions were: 1) Individualism v collectivism; 2) Power distance; 3) Uncertainty avoidance; 4) Masculinity v femininity. Hofstede's dimensions

89 Schwartz (1994).

90 See House, Robert J., Paul J. Hanges, Mansour Javidan, Peter W. Dorfman, and Vipin Gupta, eds. *Culture, leadership, and organizations: The GLOBE study of 62 societies*. Sage publications, 2004.

91 Schwartz (1994).

92 Imm Ng, Siew, Julie Anne Lee, and Geoffrey N. Soutar. "Are Hofstede's and Schwartz's value frameworks congruent?." International marketing review 24, no. 2 (2007): 164-180.

93 Schwartz, Shalom H. "A theory of cultural values and some implications for work." *Applied psychology* 48, no. 1 (1999): 23-47.

are also very closely related to the theory adopted by the GLOBE project.[94] That theory sought to account for both organisational culture and national culture, whereas Hofstede's dimensions are specifically dimensions of national culture. The GLOBE project, like Hofstede and Schwartz, began by gauging culture at the individual level and aggregating towards a national (or organisational) culture. Hofstede and his compatriots were of the view that in seeking to identify organisational culture one should pay attention to individual practices, but in seeking national culture it is individual values which matter. The GLOBE project used values *and* practices to measure both national culture and organisational culture. CT-GG is also functionalist. CT-GG and DNC are both more parsimonious (and thus more practically workable) than either CVF or the GLOBE project, without the latter offering advantages which are particularly relevant for the task at hand here. As such, of the functionalist theories considered here it is DNC and CT-GG which are progressed, below for consideration.

5.4.2 Hofstede's Dimensions of National Culture

The most important of Hofstede's DNC are: 1) individualism v collectivism; 2) power distance; 3) uncertainty avoidance; and, 4) masculinity v femininity. The central claim of DNC is to have identified culture at the national level – although Hofstede's research was undertaken via surveys given to individuals.[95] Based on the results of these surveys, Hofstede aggregated to arrive at 'scores' for nations along each dimension. For this reason, McSweeney[96] (criticising), claimed that Hofstede's conception of culture is grounded in psychology. Hofstede himself described it as *"a collective programming of the mind"*[97] although he later clarified that *"culture presupposes a collective"*; thus, whilst the values themselves may be identified in individuals, those survey responses are merely a proxy for 'shared values' which are national culture. Empirical evidence does seem to provide support for the predictive power of the DNC national culture scores in relation to organisational outcomes. For example, a meta study undertaken in 2010[98] which used data from over 200,000 individuals analysed the relationship between Hofstede's original four dimensions and organisationally relevant outcomes. It found that individual cultural values could predict those outcomes equally well or better than other variables such as personality traits.

94 See House et. Al. (2004).

95 Employees of the multinational company IBM.

96 McSweeney, Brendan. "Constitutive contexts: The myth of common cultural values." Handbook of institutional approaches to international business (2012): 142-172 at 156-158.

97 Hofstede, Geert. "Culture and organizations." International Studies of Management & Organization 10, no. 4 (1980): 15-41.

98 Taras, Vas, Bradley L. Kirkman, and Piers Steel. "Examining the impact of culture's consequences: A three-decade, multilevel, meta-analytic review of Hofstede's cultural value dimensions." Journal of applied psychology 95, no. 3 (2010): 405.

5.4.2.1 Major Criticisms and Defences of DNC

Criticisms

Major criticisms of Hofstede's theory include: that it assumes internal cultural coherence (and in doing so may commit the 'ecological fallacy'); denies agency to individuals; does not account for change; ignores the influence of other factors than culture; inappropriately uses countries as a unit of analysis; adds nothing to theories of organisational culture; is only capable of being a relative and not an absolute measure of culture; suffers from measurement problems - particularly in the use of survey data; has an inbuilt western bias; and, employs a fifth cultural bias[99] which is flawed.[100]

Brendan McSweeney has been critical of DNC. An influential paper from 2002 made the overall claim that it was implausible for national cultures to be systematically causal of individual behaviour.[101] He criticised Hofstede's implicit assertion that culture is internally coherent, and thus contains no internally contradictory elements.[102] He also attacked Hofstede's methodology by challenging some *"crucial methodological assumptions".* These included: 1) That there were three distinct components to culture: the 'organisational', the 'occupational' and the 'national', which did not interact with each other and were not affected by each other. McSweeney considered this to be unlikely.[103] 2) That the national was identifiable in the micro-local. I.e. that either: Hofstede has assumed national culture to be present in all individuals within a nation and uniform across all individuals –which would be excessively deterministic and would deny agency to individuals; or, Hofstede claims that the 'central tendency' of cultural scores measured at the individual level represented the national culture. McSweeney countered that the average scores of the sample (of IBM employees) may not necessarily represent the national average due to differences between the IBM sample and the national population. 3) That national culture *caused* the responses to the IBM survey.

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99 Added later, by Hofstede: long term v short term orientation.

100 McSweeney, Brendan. "Hofstede's model of national cultural differences and their consequences: A triumph of faith-a failure of analysis." Human relations 55, no. 1 (2002): 89-118. McSweeney, Brendan. "Dynamic diversity: Variety and variation within countries." Organization Studies 30, no. 9 (2009): 933-957. McSweeney (2012): McSweeney, Brendan. "Fashion founded on a flaw: The ecological mono-deterministic fallacy of Hofstede, GLOBE, and followers." International Marketing Review 30, no. 5 (2013): 483-504. Flory, Marja, Juup Essers, and Giorgio Touburg. "National habitus: an antidote to the resilience of Hofstede's "national culture"?." Journal of Organizational Change Management (2016). Gerhart, Barry, and Meiyu Fang. "National culture and human resource management: assumptions and evidence." The International Journal of Human Resource Management 16, no. 6 (2005): 971-986. Gerhart, Barry. "How much does national culture constrain organizational culture?." Management and Organization Review 5, no. 2 (2009): 241-259. Ailon, Galit. "Mirror, mirror on the wall: Culture's consequences in a value test of its own design." Academy of management review 33, no. 4 (2008): 885-904. Taras, Steel and Kirkman (2016). Fang, Tony. "A critique of Hofstede's fifth national culture dimension." International journal of cross cultural management 3, no. 3 (2003): 347-368.

101 McSweeney (2002).

102 He also attacked Hofstede on the basis that the concept of 'national' cultures presented, implied that they were: *"implicit, core, systematically causal, territorially unique and shared"*. None of these claims, in McSweeney's view, were warranted. McSweeney (2002).

103 Ibid.

McSweeney said that this requires that the individuals surveyed were 'cultural 'dopes'[104] – *"mere relays of national culture"*.[105] 4) That the survey responses would have been the same in any circumstances within a nation. This assumption, McSweeney argued, is necessary to make the claim that the aggregation of the survey responses in this study represents 'national culture' rather than merely (say) the organisational culture of IBM.[106]

McSweeney rejected the notion of a *"mono-causal link between national cultures and actions within borders".* He points to non-cultural causation, to the influences of other cultures, and to within-country differences in culture. Others have criticised Hofstede on related grounds. Almost all have taken aim at his choice of using countries as the unit of analysis. McSweeney warns against the temptation to equate country with culture, emphasizing the inappropriateness of a geographical or territorial approach, and pointing to examples such as Poland, where the boundaries of the state have grown, diminished, or disappeared on multiple occasions over the centuries. Taras, Steel and Kirkman[107] make a subtler point, asking what proportion of cultural variation is found between countries rather than within countries. They found that 80% of cultural difference resided within countries. Surveying populations using Hofstede's dimensions but grouping by professions and socio-economic class, they found that these may be more appropriate units of analysis than the country, given less variation within the class and greater variation between classes. Importantly, their results suggested that country averages could not act as proxies for the cultural values of small groups or of individuals but would only be appropriate if the study itself were done at the national level, such as examining GDP per capita.[108]

Gerhart and Fang echo this,[109] in a study which also found within-country differences to be greater than between-country differences. The criticism of Hofstede here has two aspects. The first is that Hofstede's survey sample was too small to say anything meaningful about the national average ('central tendency') itself. The second, and more powerful objection, is that adherents of Hofstede risk committing the 'ecological fallacy', believing that a country level average would be able to predict the cultural value of a smaller unit, including an individual. McSweeney gives some examples[110] when commenting upon Brewer and Venaik's review[111] of Hofstede's work and of the GLOBE project's work which, like the work of Gerhart and Fang, found that only a very small part of differences in individual values was explained by national differences. One example of the ecological fallacy would be to say that, *"any Japanese person is collectivist because Japan, it is supposed, is a collectivist country"*.[112] Schwartz[113] refers to

104 Garfinkel, H. Studies in ethnomethodology. Englewood Cliffs, NJ: Prentice Hall, 1967
105 McSweeney (2002)
106 Ibid.
107 Taras, Steel and Kirkman (2016)
108 McSweeney (2013)
109 Gerhart and Fang (2005)
110 McSweeney (2013).
111 Brewer, P. and Venaik, S. (2012), "On the misuse of national culture dimensions", International Marketing Review, Vol. 29 No. 6, pp. 673-683.
112 Another example given is that *"the USA is a 'masculine' country and therefore industrial relations in that country is characterized by aggression"*. McSweeney (2013).
113 Schwartz, Shalom H. "Universals in the content and structure of values: Theoretical advances and empirical tests in 20 countries." In *Advances in experimental social psychology*, vol. 25, pp. 1-65. Academic Press, 1992

the example of a difference between a hung jury at two levels. The jury is undecided, but no individual jury member is undecided. McSweeney says Hofstede has committed the *"ecological mono-deterministic fallacy",* in so far as he has tried to claim that national culture is *causing* differences at the lower level of organisations, individuals etc. This must mean that individuals act the way that they do because they are 'programmed'[114] to do so. That goes further than saying that an attribute or quality measured as a national average will be found in an individual – which is merely a (mistaken) statistical assertion. National culture, says McSweeney, cannot have ontological causal power. More importantly, this denies agency to individuals.

Moving to the (related) objection, that national culture adds nothing to organisational culture: Gerhart[115] asks to what extent will national culture affect or constrain organisational culture. As national culture clearly exists (i.e. between country differences do exist and are observed) how much will that tell us about the culture of an organisation located in any given country? He found that most differences in organisation cultures were not explained by country. National culture does not constrain organisational culture to any great extent, and therefore it would be wrong to predict organisational behaviour based upon national culture. Finally, Ailon[116] argues that Hofstede's work itself discloses an inbuilt western bias. She concludes this by assessing Hofstede's work against his own dimensions. She says, for example, that Hofstede's surveys sought to ascertain the level of power distance (hierarchy v egalitarianism) in its respondents, yet the surveys themselves were hierarchical in nature. The surveys were standardised and distributed worldwide *"implying a neutral equality of treatment"* yet by sending the same questionnaire to everyone, the survey exercise sought to limit the range of responses which could be given, to those considered relevant by the western researchers who devised them. Moreover, the surveys purported to gauge the wants and needs of respondents, but served the concerns of the researchers. In other words, the surveys themselves reflected a large power distance value, a hierarchical approach.

Defences

Hofstede responded to many of the criticisms. In relation to the complaints made about the ecological fallacy, he stressed that his dimensions were only suitable at the nation level of analysis and accepted that to draw direct comparisons between nations, the samples drawn from each would have to be precisely matched.[117] He also points out that despite discrepancies between within-country and between-country cultural differences, the latter do exist. Therefore, national culture exists. It is merely a question of whether it is appropriate, in any given case, to use national cultural differences to explain variation. In response to Ailon, he says she uses *"an old debater's trick… building a straw man and then burning it"*,[118] arguing

114 Geertz (2008).
115 Gerhart (2009).
116 Ailon (2008).
117 Hofstede, Geert, Cheryl A. Van Deusen, Carolyn B. Mueller, and Thomas A. Charles. "What goals do business leaders pursue? A study in fifteen countries." *Journal of International Business Studies* 33, no. 4 (2002): 785-803. Hofstede, Geert. "The pitfalls of cross-national survey research: a reply to the article by Spector et al. on the psychometric properties of the Hofstede Values Survey Module 1994." (2002). Hofstede, Geert. "What did GLOBE really measure? Researchers' minds versus respondents' minds." *Journal of international business studies* 37, no. 6 (2006): 882-896.
118 Hofstede, Geert. "Who is the fairest of them all? Galit Ailon's mirror." Academy of Management Review 34, no. 3 (2009): 570-571.

that she had presented, as his, statements about national culture which could not have been inferred from what he had written.

In a 2002 reply to McSweeney, Hofstede sought to respond to criticisms made generally of his work from all quarters.[119] He accepted that surveys should not be the only way of measuring culture. In relation to his choice of countries as the unit of analysis, he says that these are usually the only units available for comparison, and that *"they are better than nothing".* In response to the criticism that the IBM study could not provide sufficient information to inform on national cultures, he stressed that what he was studying was the differences *between* national cultures. His scores are a relative measure, not an absolute one. Turning to the accusation of ecological mono-deterministic fallacy he says, *"this rigidity (between national culture and individual action) is in the eye of the beholder".* He reminds McSweeney that what he observed are actions, not mental programs. From actions, the presence of mental programs is inferred. Values and dimensions do not really exist, according to Hofstede, but are mere constructs which are useful because they can help to explain and predict behaviour. As such his theory does not rely on individuals having been mentally programmed by national culture. It is merely that the central tendency of actions of individuals from the same country seem to be different from the central tendency of actions of individuals from another country, and as such we use the construct of 'cultural values' to better communicate this fact.

McSweeney, says Hofstede, has misunderstood the reference to organisational culture within the latter's work. Hofstede does not claim that organisational culture is an entirely separate thing from national culture, but he has noted (in other work) that between (same country) organisation differences in values were small relative to differences in what he called 'practices' and which he suggest are pivotal to understanding organisational culture. Importantly, nationally held cultural values are much less susceptible to change than organisation level practices. The criticisms made of Hofstede's use of survey data are defunct when one considers that central tendencies are a perfectly valid (and eminently useful) statistical measure within the social sciences and bearing in mind: a) the need to use matched samples when making between-country comparisons; and b) that Hofstede's comparisons based on culture only seek to be a relative, and not an absolute measure.

Hofstede is not the only person to defend Hofstede. Dermot Williamson suggests that between Hofstede and McSweeney there is a conflict of paradigms.[120] Hofstede's theory fits within the functionalist paradigm because it relies upon data collected from large samples and analyses these data using accepted statistical techniques. He arrives at etic dimensions of national culture which are universally applicable. McSweeney's critique overall comes from the interpretive paradigm, whilst also rejecting Hofstede's methodology from within the functionalist paradigm. Williamson implies that it is unfair to criticise a man both for his choice of paradigms and for methodological choices made which were a result of the constraints put in place by the paradigm choice. The first assumption attacked by McSweeney was that there exist three distinct cultures (the occupational, the organisational and the national) which do not interact with each other. Thus, says McSweeney, Hofstede was not controlling for

119 Hofstede, Geert. "Dimensions do not exist: A reply to Brendan McSweeney." Human relations 55, no. 11 (2002): 1355-1361.

120 But asserts that McSweeney's critique of Hofstede discloses mixed paradigms itself and thus is not forceful, see: Williamson, Dermot. "Forward from a critique of Hofstede's model of national culture." Human relations 55, no. 11 (2002): 1373-1395.

organisational culture and his findings reflect combinations of national culture with organisational (or occupational) culture. Williamson points out that this criticism is negated by evidence from others[121] who have tested Hofstede's dimensions controlling for factors such as gender and occupation.

McSweeney's criticism of assumption two - that national culture is identifiable at the micro level of IBM samples - is also attacked by Williamson. The first version of this assumption essentially says that Hofstede was claiming that every individual in the same country has the same culture, and that this is inconsistent with observed within-country variation in cultural values held by individuals and by organisations. Williamson points out that Hofstede was aware of this and of also of the dangers of the ecological fallacy. For a start, organisational culture may be subject to different dimensions than national culture, in that whilst two organisations in one country have different organisational cultures (e.g. one may exercise tight control, the other loose control), this does not necessarily mean that they differ to a great extent in Hofstede's dimensions, such as uncertainty avoidance.[122] Responding to the ontological causation and (therefore) 'cultural dopes' argument, Williamson points out that what Hofstede meant is that the central tendency of the survey responses represented national culture, not that the responses themselves were uniform within nations - which was clearly not true. Hofstede recognises the within-country variation, and it is therefore clear that he attributes the within-country variation in responses to non-cultural factors, including *"institutional influences, social structures and economic conditions".*

5.4.2.2 Overall Evaluation of DNC

I need to decide whether Hofstede's DNC is an appropriate theory of culture to be applied in this research project. Upon considering the defences of Hofstede some, at least, of the concerns raised in the literature are addressed. Hofstede's paradigm – the functionalist approach – is the right one for the task at hand. This makes some of McSweeney's criticisms of the theory irrelevant for my purposes here. As to mono-determinism, ontological causation, and denial of agency; I agree with Hofstede that these criticisms are weak. I accept the view that Hofstede's national cultural scores are merely the central tendency of the survey responses by nation. There is, in substance, no problem with this approach. It is also relevant that his scores are necessarily relative in nature and not absolute. Relative scores are adequate for my task here, given that the research question is not to 'discover' an absolute measure of the culture of either the United States (US) or the European Union (EU), but rather

121 Trompenaars, Fons, and Charles Hampden-Turner. *Managing people across cultures*. Chichester: Capstone, 2004. Hampden-Turner, Charles, and Fons Trompenaars. "Response to Geert Hofstede." *International Journal of Intercultural Relations* 21, no. 1 (1997): 149-159. Hofstede, Geert. "Riding the waves: A rejoinder." *International Journal of Intercultural Relations* 21, no. 2 (1997): 287-290.

122 Matching Hofstede's reply to the criticism of the second version of this assumption, which states that the IBM average represented the national average: and differences between the IBM sample and the nation may be sufficiently large to make extrapolation to the national level impossible: Williamson points out that what was being measured was not culture itself, which is a construct and cannot be measured. In addition, Hofstede's theory is a relative one, not an absolute one. He was measuring differences between nations using the proxy of the survey responses. What matters, therefore, is whether the differences between survey responses were reflecting differences in the underlying target variable – culture - rather than something else. See Williamson (2002).

to compare them. This can be done using relative measures. Having dropped the deterministic assumption that Hofstede's theory requires complete cultural uniformity, then the claim that he denies agency to individuals must also be dropped. As to mono-determinism: clearly, once it is accepted that there are within-country difference in culture and accepted that this does not fatally flaw the theory, then there is room for non-cultural factors to explain within-country variation. In relation to ontological causation, I do not see the need to establish linear causation between culture and the divergence because I adopt the institutional approach outlined above.

However, turning to the problems which remain, Hofstede is not entitled to assume internal coherence of national culture. No strong defence seems to have been raised by Hofstede or others to this accusation. The selected cultural theory needs to recognise that within nations, groups and individuals of very different cultural outlooks contradict each other. Neither has Hofstede expressly accounted for cultural change. He seems to be clear that the core of national culture remains the same indefinitely. This latter position does not fit with the institutional approach to culture adopted above, which permits the possibility of cultural change. What is lacking from the institutional approach is a better account of how cultural change may happen over times (with reference to specific dimensions or typologies of culture). I argue below that CT-GG is better able to provide this than DNC. DNC, in seeming to assert that national culture does not change, clearly also does not offer an account of how national culture might change by reference to the specific dimensions. Finally**,** there is a problem with the units of analysis which DNC may be applied to. I need a cultural theory which can be applied to institutions, and thus to groups and subgroups of all sizes. It is unclear whether Hofstede's dimensions can be employed for anything other than nations. Below, I argue that CT-GG provides this, and provides an account of internal cultural incoherence, thus adding everything that is currently missing from the institutional approach, whilst also ticking the other boxes from the criteria in Table 64 **Criteria for Shortlisting Theories of Culture**above.

5.4.3 The Cultural Theory of Risk and Grid-Group

The Grid-Group typology of culture devised by Mary Douglas, Aaron Wildavsky and others is embedded within the 'Cultural Theory of Risk'.[123] The central assertion of CT-GG is that *"the meanings of risk, their ontological qualities and moral implications are said to be socially and culturally constructed by means of collectively shared representations"*. As was the case with Hofstede, therefore, there is a departure from the stance of methodological individualism, and CT-GG asserts that there *is "no single rationality with regard to knowledge of risks and the ways in which they should be managed"*.[124] I say 'departure' but really the grid-group typology adds further texture to the approach of methodological individualism. According to Wildavsky it can be seen as an expansion of the rational choice paradigm (or, as an alternative

123 Tansey, James, and Tim O'riordan. "Cultural theory and risk: a review." Health, risk & society 1, no. 1 (1999): 71-90.

124 Boholm, Åsa. "The cultural nature of risk: Can there be an anthropology of uncertainty?." Ethnos 68, no. 2 (2003): 159-178.

to it). In this work I view the typology as an expansion of that paradigm, in my focus upon the ability of cultural theory to add further explanation to the extant theories of public interest and private interest, both of which are rooted in rational choice methodological individualism. To explain further, CT-GG confirms that individuals do act rationally, but asserts,[125] *"that rationality is plural and several types of rationality can be established."* As Kahan points out[126] *"self interested individuals need to figure out which activities, courses of action, and states of affairs promote their interest."* Regulation, therefore, cannot be explained only by asking what individuals will do to maximise utility – largely because their utility function will depend upon their preferences and the extant theories have no endogenous explanation for preference formation.

One benefit of CT-GG, which it shares with Hofstede's DNC and the other functionalist theories of 'national' culture, is that culture is not presented as endlessly relative or subjective. CT-GG, like the dimensions of Hofstede, Schwartz and Trompenaars, reduces culture to a workable typology, in this case consisting of four *"basic sociological forms"*:[127] hierarchism, fatalism, individualism and egalitarianism. CT-GG incorporates some widely used theories in the social sciences, for example the two modes of organising: into hierarchies and markets[128] and Ouchi's typology of organisations: as 'markets' (individualism), 'hierarchies' (hierarchism) and 'clans' (egalitarianism).

Before explaining the theory in more detail, some background is provided to CT-GG. It was formulated by Mary Douglas, a British anthropologist, in response to the lack of a cultural theory which could be applied across anthropology.[129] It began with her insight that human beings, living together in societies, perceive events as good or bad and attach blame to these events in a subjective way. This is not completely comprised of an assessment of risk as it is understood by economists today. There is no 'rational' assessment of harm coupled with an inquiry into proximate scientific causation of the event in question. As such, the result is not to regulate activities identified to have caused the event in a proportionate way so that the marginal costs of regulation would be equal to the marginal benefits of regulation. Instead, throughout history (including today) the allocation of blame is *"a normal strategy for protecting a particular set of values belonging to a particular way of life".* This, she called the 'forensic model of danger'.[130]

That same model can be applied to modern regulation of risk, despite the abundance of 'experts' available to assess 'risk', society still responds in the same way: attributing blame and regulating an activity as a way of protecting a particular set of values belonging to a particular way of life.[131] In 'Purity and Danger'[132] Douglas wrote that *"laws of nature… are*

125 Mamadouh, Virginie. "Grid-group cultural theory: an introduction." *GeoJournal* 47, no. 3 (1999): 395-409 at 395

126 Kahan, Dan M., and Donald Braman. "Cultural cognition and public policy." *Yale L. & Pol'y Rev.* 24 (2006): 149 at 154

127 Ibid.

128 Lindblom, C. (1977) Politics and Markets. New York: Basic Books

129 Douglas, Mary. Risk and blame. Routledge, 2013. Douglas, Mary. Essays on the Sociology of Perception. Routledge, 2013.

130 Douglas and Wildavsky (1983).

131 This insight was like that of Ulrich Beck in her book: Beck, Ulrich, Scott Lash, and Brian Wynne. *Risk society: Towards a new modernity*. Vol. 17. sage, 1992.

132 Douglas, Mary. *Purity and danger: An analysis of concepts of pollution and taboo*. Routledge, 2003.

dragged in to sanctions of the moral code" thus *"adultery, incest, the confusion of sexual functions and roles, various acts of political disloyalty or disrespect for authority – all are viewed not merely as impious but as dangerous. They naturally spawn the outbreak of contagious disease within the community at large, the occurrence of devastating natural disasters, the dampening of human fertility, and the like."*[133] Even in modern societies it is that which contravenes societies' rules for ordered social relations which provoke feelings of revulsion and disgust, and which are viewed as dangerous. As Kahan puts it, *"sensibilities and perceptions of danger are artifacts of our commitment to distinctive cultural orderings."*[134] In Douglas' view, longstanding taboos, and the risks of today are separated only by a question of degree, and both could simply be called 'dangers'. Together with Aaron Wildavsky, Douglas applied the forensic model of danger to the history of the US.[135] They argued that there had always been a tension in the US between the 'center' which favoured the market and hierarchy, and the 'border'. The border arose in the 1960s and 1970s following the weakening of the center which followed the great depression, and the border favoured egalitarianism. It was from out of this work that the Grid-Group typology arose.[136]

5.4.3.1 The Grid-Group Typology

CT-GG started out just as Grid-Group[137] which Mamadouh describes as *"a theoretical framework, a heuristic device, a classification scheme*" short of a *"full explanatory theory"* and which was developed by Douglas *"as a tool to deal with cultural diversity."*[138] The attraction of Grid-Group for my purposes here is just this – it represents a parsimonious way to represent cultural diversity. Originally presented in 'Cultural Bias' by Douglas[139] it was then developed by her in a series of essays, 'Risk and Blame',[140] 'How Institutions Think'[141] as well as in 'Risk and Culture' with Aaron Wildavsky in 1982. Other scholars who have contributed to the field include: Steve Rayner,[142] Michael Thompson,[143] Richard Ellis[144] and Michiel Schwarz.[145] Many of those helped to develop Grid-Group into the full blown Cultural Theory of Risk. According

133 Kahan and Braman (2006) at 149
134 Ibid at 150
135 Douglas and Wildavsky (1983).
136 Tansey, James, and Tim O'riordan. "Cultural theory and risk: a review." *Health, risk & society* 1, no. 1 (1999): 71-90.
137 Douglas, Mary. *Cultural bias*. No. 35. London: Royal Anthropological Institute, 1978.
138 Mamadouh (1999) at 395
139 Douglas (1978).
140 Douglas, Mary. *Risk and blame*. Routledge, 2013.
141 Douglas, Mary. *How institutions think*. Syracuse University Press, 1986.
142 Gross, Jonathan L., and Steve Rayner. *Measuring culture: A paradigm for the analysis of social organization*. Columbia Univ Press, 1985. Rayner, Steve, and Elizabeth Malone. "The challenge of climate change to the social sciences." (1998).
143 Grendstad, Gunnar, Per Selle, and Michael Thompson, eds. *Cultural theory as political science*. Routledge, 2003.Thompson, Michael, Richard Ellis, and Aaron Wildavsky. *Cultural theory*. Routledge, 1990.
144 Coyle, Dennis J., and Richard J. Ellis. *Politics, policy, and culture*. Routledge, 2019. Ellis, R., and Michael Thompson. "Culture matters." *New York* (1997).
145 Schwarz, Michiel, and Michael Thompson. *Divided we stand: Redefining politics, technology, and social choice*. University of Pennsylvania Press, 1990.

to Mamadouh (referring to both together)[146] *"The main claim of grid-group cultural theory is that culture matters. Preferences and justifications shape the world of social relations. Everything human beings do or want is culturally biased"* and that *"it is possible to distinguish a limited number of cultural types"* by construction of typologies of culture which include "*viable combinations of patterns of social relations and patterns of cultural biases"* called 'cultural orientations.'[147] To put this another way, Mamadouh writes,[148] *"combinations are viable when social relations and cultural biases reinforce each other, that is: the cultural bias justifies the social relations which confirm the expectations raised by the cultural bias"* and as such, any group will belong within one of the four quadrants and have a specific cultural orientation.

Finally, Grid-Group claims that this typology is universal and can be applied to anything at any time[149] because the two dimensions of sociality which are used *"grasp the fundamental nature of the social being"*[150] and as such, when applied to individuals it says these derive *"preferences, perceptions, opinions, values and norms"*[151] from their cultural orientation. As such, the importance of institutions, through which our social interactions take place, is obviously key, and study of institutions and their cultural orientation will tell us where the cultural orientation of the relevant group is likely to be placed on the matrix. As Douglas observes, *"institutions do the thinking for us"*.[152] This also works the other way around. From the typology, dimensions and worldviews/cosmologies, analysts *can "deduce preferences, attitudes and behaviours regarding all kind of topics for each ideal type"*.[153] Grid-Group is thus both etic and functionalist, it lies in the 'inclusive' camp, and works well with the institutional approach to culture adopted above. Having only four (maximum five) cultural orientations, it is also sufficiently parsimonious to be practically workable here.

5.4.3.2 The Cultural Theory of Risk

Moving away from Grid-Group, towards the full Cultural Theory of Risk, this was a development of Mary Douglas' Grid-Group approach by Ellis, Wildavsky and Thompson.[154] They assert 1) the *"compatibility condition"*[155] which *"asserts that social relations (patterns of interpersonal relations) and cultural bias (shared value and beliefs) cannot be combined contrary to each other: they must be mutually supportive"*[156] which means that biases and social relations *"reinforce each other"* such that for one group (within which social interactions take place) they must match each other in the cultural orientation which they reflect.

146 Mamadouh (1999) at 395
147 Sometimes also called 'cosmologies', 'ways of life', or 'worldviews'.
148 Mamadouh (1999) at 395
149 Ibid
150 Ibid
151 Mamadouh (1999) at 396
152 Douglas (1986)
153 Mamadouh (1999) at 396
154 Thompson, Ellis and Wildavsky (1990)
155 Thompson, Ellis and Wildavsky (1990) at pg. 2
156 Mamadouh (1999) at 396

Wildavsky[157] also asserts 2) the impossibility theorem[158] which tells us that there are maximum five cultural orientations (including the fifth way: 'hermit') which *"are viable combinations of biases and social relations"*.[159] Finally, in 'Cultural Theory' it is argued that the cultural orientations, *"need each other to be viable"*,[160] called 3) the 'variety condition'[161] because if adhered to universally in isolation, then *"each cultural bias leads to catastrophe"* unless it is *"corrected"* by the others[162] and, moreover, each bias is defined by the other biases. This leads to *"interdependence"* between the worldviews/biases[163] because, as

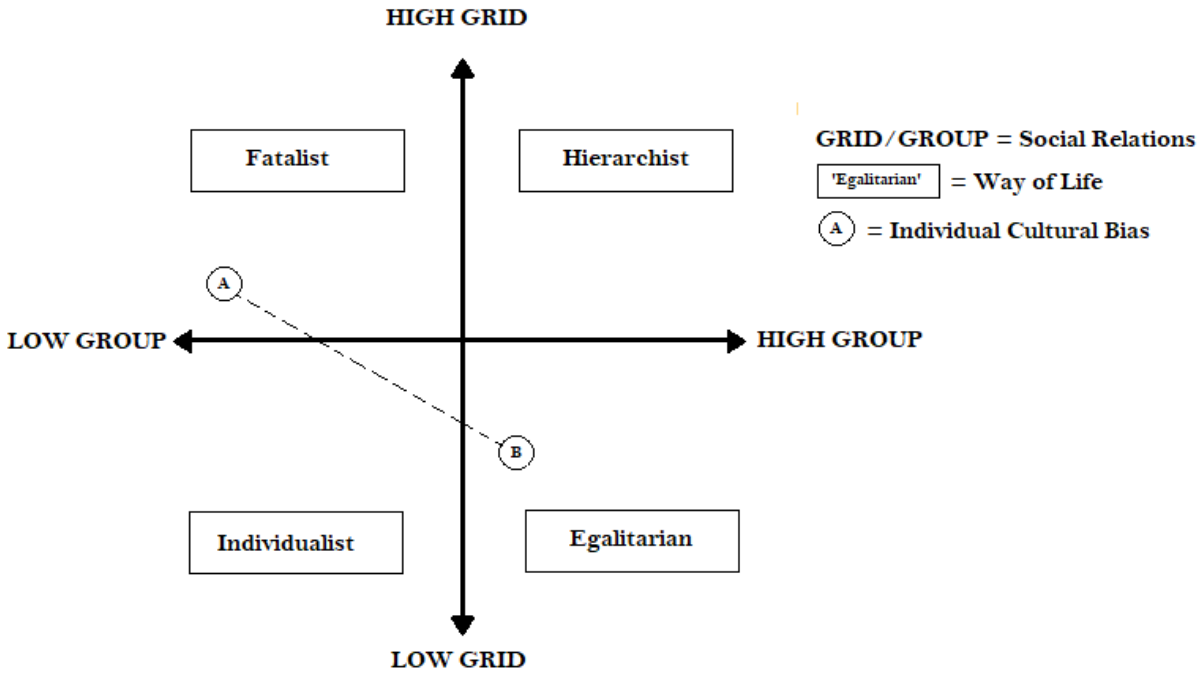

Figure 17 **Group-Grid Typology – Three Components of Culture in Cultural Theory**

Adapted From Mary Douglas' 'Natural Symbols' (1973)

Wildavsky says, *"conflict among cultures is a precondition of cultural identity."*[164]

Already, therefore, CT-GG begins to provide an account of internal cultural incoherence, which Hofstede's DNC could not, and thus it is seen to work well with the institutional approach to culture to provide an account of (long term, gradual) cultural change in large groups such as jurisdictions.

157 Wildavsky (1987) at pg. 5
158 Thompson, Ellis and Wildavsky (1990) at pg. 3
159 Mamadouh (1999) at 396
160 Ibid.
161 Thompson, Ellis and Wildavsky (1990) at pg. 4
162 Mamadouh (1999) at 396
163 Ibid.
164 Wildavsky (1987) at pg. 7

The Grid-Group typology is shown on the matrix in Figure 17[165] above, where the three components of the term 'culture',[166] which are inherent in Cultural Theory, can be seen. These are 1) the cultural biases: which refers to the values held by individuals, and which are described in detail below. In Figure 17 this (for any given individual) will be represented by a point plotted somewhere on the two axes, such as the circles labelled A and B. The second component of culture is, 2) social relations: defined as patterns of interpersonal relations. These are represented by the axes themselves. The term 3) 'way of life' is the third component of culture in CT.[167] I refer to this going forward as 'cultural orientation' instead. When speaking about cultural orientations, these are represented by four quadrants labelled: hierarchical, fatalist, egalitarian and individualistic. Because I do not include it in this project (it has no use here) I have not shown the fifth cultural orientation from CT-GG: the autonomous hermit. However, the fifth type would be present in the exact centre of the grid.[168]

To explain further: social relations and cultural biases interact with each other. Individuals justify their social relations by reference to their cultural biases and their cultural biases provide them with a set of instructions to go about doing their social relations. In the words of Jackson they are *"reciprocal, interacting and mutually reinforcing, the so-called 'compatibility condition' where social relations and biases must complement one another"*.[169] It is because of this that it is possible to represent social relations as a pair of axes (two dimensions) upon which cultural biases can be plotted for individuals. It can be seen from the matrix in Figure 17, that one cannot be high on the 'grid' axis for one's social relations, but then still fall within the lower two quadrants, that is regardless of one's place on the group axis. Once one is high grid, one must necessarily be either fatalist or hierarchical. To put that more simply: one cannot be high grid and low grid at once, this is impossible. Because social relations are plotted on the axes, all individuals must fall within one of the four quadrants.

The four quadrants represent the only viable combinations of cultural bias and social relations. These are the four cultural orientations ('ways of life'). Wildavsky puts it another way,[170] he says that an impossibility theorem lies at the heart of Grid-Group. Thus, whilst there are a potentially infinite number of cultures that an individual can adhere to, only the four cultural orientations can be manifest.[171] Note that whilst this has been applied to individuals here, because the focus is upon individuals in their social relations with each other, and taking into account the fact that social relations are by definition governed by institutions, then the term 'cultural orientation' can be applied to individuals, groups (of all sizes) and the institutions themselves. Echoing the above: the basic institution of the group (and thus most individuals within it) will be one of the four cultural orientations. More specific formal and informal institutions which govern the interactions between individuals (their social relations) will be informed by that basic institution and thus those formal and informal institutions (higher up in the pyramid in Figure 16) will also reflect the underlying basic institution which is the cultural orientation of the group. The four cultural orientations, therefore (in terms of

165 Douglas, M., 1973. *Natural symbols*. Routledge.
166 Jackson, Stephen, and George Philip. "Organizational culture and the management of technological change: A theoretical perspective." ECIS 2005 Proceedings (2005): 149.
167 Thompson, Ellis and Wildavsky (1990) at pg. 4
168 I explain the fifth type below.
169 Jackson and Philip (2005)
170 Wildavsky (1987)
171 Ibid.

the institutional approach to culture) are the most abstract versions of the values and norms of that group.

Backtracking slightly: the possible social relations, put forward by Douglas, were based on *"the minimum forms of commitment to life in a society postulated by political theory"*.[172] That can be defined in terms of the level of one's attachment or allegiance to a group: who does one interact with?[173] On the other hand, Douglas considered the level of regulation within or outside of the group: how does one interact? The two questions are posed differently by different exponents of CT-GG: another variant of the theory claims, in simpler terms, that the individual asks of herself two questions:[174] The first: who am I? The second: what shall I do? Where the individual answers the first question: 'my ties to others are weak, and my choices bind only myself',[175] their social relations are 'low (or weak) group' and lie on the left of the horizontal axis. When they answer: 'my ties to others are strong, I form part of a collective and the decisions of the collective are binding on me' their social relations are 'high (or strong) group' and lie to the right of the horizontal axis. The answer to the second question may be either: 'I am subject to many external prescriptions, my choices are tightly constrained,'[176] or 'I am subject to few external prescriptions and I am a free spirit'. The former answers are given by those who are, 'high (or strong) grid' and are plotted towards the top of the vertical axis. The latter are given by 'low (or weak) grid' persons and are plotted in the lower half of the vertical axis in Figure 17.

I explain the dimensions and the quadrants in detail in the next section when setting out how I operationalise CT-GG for use in Chapter Six. First, I consider whether, and if so how, CT-GG can furnish me with a theory of the contents of culture which fits better with the institutional approach to culture than DNC does. This, I say, comes down to the ability of CT-GG to be applied to institutions and thus groups. The major criticisms of CT-GG have focused upon the poor predictive power of CT-GG in the context of individuals' cultural orientations, and this comes down to some conceptual difficulties with CT-GG in the stability (or mobility) of individual cultural biases. I avoid this problem precisely because I do not look at individuals, but instead adopt the institutional approach to culture which enables me to place the focus on institutions and groups.

Secondly – setting individuals and their internal cultural (in)coherence to one side - CT-GG has the advantage over DNC that it is able to accommodate the possibility of internal cultural incoherence of groups. It can do so because it is recognised that larger groups are made up of building blocks of smaller subgroups, with differing cultural orientations to the wider group, and in which individual and (sub)group strategic behaviour may take place to disrupt the established social relations which are enabled by the culture of the wider group.[177] In fact, CT-GG *requires* internal cultural incoherence within groups because of the 'interdependence' and 'viability' conditions described above, and as such within a given group the four cultural orientations are likely to be in a constant state of disequilibrium. Thus, CT-GG also provides

172 Tansey and O'Riordan (1999).
173 Ostrander, David. "One-and two-dimensional models of the distribution of beliefs." *Essays in the Sociology of Perception* (1982): 14-30.
174 Ibid.
175 Wildavsky (1987)
176 Ibid.
177 Mamadouh (1999) at 396

an account of cultural change which also fits well with the institutional approach. The constant state of disequilibrium (over time) may lead to cultural change. However, because – as the institutional approach illustrates – culture and other institutions are mutually reinforcing and mutually co-produced, that change is likely to be gradual only. As such, comparison between jurisdictions over a time frame of 100-300 years remains possible.

5.4.3.3 Stability, Mobility, Cultural (In)Coherence, Cultural Change and Units of Analysis

Stability v Mobility Hypotheses and Individual Cultural Biases

Mary Douglas originally argued that individual cultural orientations (which she called 'cultural biases') were a *"permanent characteristic"*[178] of a person. By this she meant that whilst an individual's cultural biases may change over the course of his life, it was nevertheless *"hegemonic"*[179] in that the cultural bias was consistent in all that individual's areas of life. Rayner[180] labelled this the 'stability hypothesis'. However, the stability hypothesis is not borne out by attempts made to gauge individual cultural biases through surveys.[181] On the other hand, Michael Thompson and Aaron Wildavsky later argued that it is possible for individuals to adhere to different biases in different contexts.[182] This is the 'mobility hypothesis.' Mamadouh points out that adherence to the stability hypothesis makes it possible and meaningful to consider individual cultural orientations but then the explanatory power of the theory is weakened because we do not know or understand where the original 'hegemonic' bias came from. On the other hand, the mobility hypothesis makes *"the cultural bias of individuals so volatile that it does not make sense to map it".*[183] Attempts have been made to verify either the stability or mobility hypothesis. Olli[184] has investigated – empirically – the veracity of the mobility and stability hypotheses. Unfortunately, his work simply found that some individuals abide by one cultural bias and reject others, some others abide by one and are open to others, and some others abide by two simultaneously.[185] According to Johnson and Swedlow, individuals do not normally 'flit'[186] between the cultural biases in different contexts, *"CT expects a "strain to consistency" in individuals but recognizes that different cultural biases may also dominate different parts of people's lives."* It seems, therefore, that the reality in the case of individual cultural orientations lies somewhere in between the

178 Mamadouh (1999) at 403

179 Ibid.

180 Johnson, Branden B., and Brendon Swedlow. "Cultural theory's contributions to risk analysis: A thematic review with directions and resources for further research." *Risk analysis* 41, no. 3 (2021): 429-455

181 Johnson and Swedlow (2021): 429-455. at 422. See also Grendstad, Gunnar. "Comparing political orientations: Grid-group theory versus the left-right dimension in the five Nordic countries." *European Journal of Political Research* 42, no. 1 (2003): 1-21. And Kiss, S. J., E. Montpetit, and E. Lachapelle. "Measuring grid and group in the Canadian context." In *annual meeting for the Midwest Political Science Association, Chicago, April*, pp. 7-10. 2016.

182 Mamadouh (1999) at 403

183 Ibid

184 Olli, Eero. "Cultural Theory Specified-The Coherent, Sequential and Synthetic Individual Approaches." *University of Bergen* (1995). Olli, Eero. "Rejection of cultural biases and effects on party preference." *Cultural theory as political science* (1999): 59-74. Olli, Eero. "Rejected cultural biases shape our political views: a migrant household study and two large-scale surveys." (2012).

185 Mamadouh (1999) at 403

186 Rayner, Steve. "Cultural theory and risk analysis." (1992).

stability and mobility hypotheses, and thus mapping individual cultural orientations is problematic.

Indeed, problems which have come about because of attempts to map individual cultural orientations are the main weakness of CT-GG. Scholars have developed survey measures to assess individual cultural orientations. This includes those devised by Dake[187] and Grendstad.[188] These have often focused on risk analysis and risk perception and environmental issues.[189] At the level of the individual and his or her cultural orientation these have been shown to have only modest predictive power[190] with various criticisms made of the usefulness of surveys for assessing this and a lack of proper application of the theory.[191] CT-GG has, however, been much more successful in anthropology and political science.[192] Here, it has been very apt for identifying *"competing arguments and conflicting strategies."*[193] I do not focus on individuals in this work. Instead, my focus in on groups and the institutions which bind these groups together. My approach is closer to the approach taken by CT-GG theorists within political science, and avoids the problems associated with individual measurement of cultural orientations.

Cultural (In)Coherence and Change

The major problem with DNC was that it assumed cultural coherence in nations, and thus did not permit of the possibility of cultural change. It was thus incompatible with the institutional approach to culture. On the other hand, if culture in groups is internally incoherent (i.e., in conflict) and changes very rapidly, my practical task in this research project – which requires me to compare two jurisdictions over a 100-300 year period - becomes impossible. The institutional approach to culture set out above suggests that cultural change would take place

187 Dake, Karl. "Orienting dispositions in the perception of risk: An analysis of contemporary worldviews and cultural biases." *Journal of cross-cultural psychology* 22, no. 1 (1991): 61-82. Dake, Karl, and Aaron Wildavsky. "Individual differences in risk perception and risk-taking preferences." In *The analysis, communication, and perception of risk*, pp. 15-24. Springer, Boston, MA, 1991. Dake, Karl Manning. "Technology on trial: Orienting dispositions toward environmental and health hazards." PhD diss., University of California, Berkeley, 1990. Dake, Karl. "Myths of nature: Culture and the social construction of risk." *Journal of Social issues* 48, no. 4 (1992): 21-37. Dake, Karl, and Michael Thompson. "The meanings of sustainable development: household strategies for managing needs and resources." *Human ecology: crossing boundaries* (1993): 421-436.

188 Grendstad, Gunnar. "Europe by cultures: An exploration in grid/group analysis." PhD diss., Verlag nicht ermittelbar, 1990. Grendstad, Gunnar. "Party followership and leadership in Norway: A political culture approach." *Party Politics* 1, no. 2 (1995): 221-243.; Grendstad, Gunnar, and Per Selle. "Cultural myths of human and physical nature: Integrated or separated?." *Risk Analysis* 20, no. 1 (2000): 27-40. Grendstad, Gunnar, and Per Selle. "Cultural theory and the new institutionalism." *Journal of theoretical politics* 7, no. 1 (1995): 5-27.

189 Ellis, Richard J., and Fred Thompson. "Culture and the environment in the Pacific Northwest." *American political science review* 91, no. 4 (1997): 885-897. Coughlin, Richard M., and Charles Lockhart. "Grid-group theory and political ideology: A consideration of their relative strengths and weaknesses for explaining the structure of mass belief systems." *Journal of Theoretical Politics* 10, no. 1 (1998): 33-58. Marris, Claire, Ian H. Langford, and Timothy O'riordan. "A quantitative test of the cultural theory of risk perceptions: Comparison with the psychometric paradigm." *Risk analysis* 18, no. 5 (1998): 635-647.

190 Boholm, Åsa. "Risk perception and social anthropology: Critique of cultural theory." *Ethnos* 61, no. 1-2 (1996): 64-84. Milton, Kay. "Ecologies: anthropology, culture and the environment." *International Social Science Journal* 49, no. 154 (1997): 477-495. Sjoberg, Lennart. "World views, political attitudes and risk perception." Risk 9 (1998): 137. Tansey and O'Riordan, 1999

191 Boholm (1996)

192 Mamadouh (1999) at 403

193 Ibid

within large groups such as jurisdictions only slowly: making possible the comparison which I set out to make. I argue here that by adopting the typology of CT-GG within the institutional approach to culture, I avoid the stability v mobility problem, and I provide an account of cultural incoherence and cultural change which fits well with the institutional approach, and which makes my research task practically possible.

CT envisages a continuously evolving dynamic relationship between the four cultural orientations. Each of the cultural orientations is constantly in competition with each other and corrects each other.[194] Any given group will contain a mixture of all four cultural orientations (present, for example, in the subgroups) and will combine them in different proportions.[195] Wildavsky argued for the variety condition: implying that each of the four (five) cultural orientations requires each of the others – interdependence between them**.** Douglas and Ney argue[196] that the cultural ways of life are inherently adversarial and that it is not possible to merge them. However, Mamadouh says that *"cultural plurality is an asset"* thus, because each of the ways of life individuals can be 'surprised' a society (or other group) in which all of the ways of life are present is less likely to be surprised. Mamadouh argues that this makes CT-GG in its *"strongest form"* a "*normative theory".* In 'Cultural Theory' Ellis, Wildavsky and Thompson explain cultural change by *"the theory of surprise"*.[197] They say that the ways of life *"are resistant to change"*[198] and thus the combination of cultural biases and social relations remain relatively stable in the cosmology which they reflect. However over time, gradually, the cumulative effect of large or small surprises – outcomes which do not fit the expectations *"raised by a way of life"*[199] and are normally *"explained away"* - can eventually result in a *"change in paradigm"* i.e. a whole society (such as a jurisdiction) can change its paradigm from one quadrant to another. In my view, therefore, once one takes the focus away from individuals and their cultural orientation, one finds an account of cultural incoherence and cultural change which fits very well with the approach of institutional theory to institutional change: of *gradual* change over time, for example, Streeck and Thelen's[200] displacement, layering, drift, conversion, and exhaustion.

Considering the institutional approach adopted here, the stability v mobility problem is not troubling. It is only problematic if my research project depends upon analysing individual cultural biases. Moreover, the mobility hypothesis can be synthesised with the institutional approach. CT-GG, where it uses the individual as a unit of analysis, looks at the *"socialised being"*[201] and the socialised being is *"necessarily embedded in institutions"*. However, this need not be a *"culturally monolithic institutions"* and is highly unlikely to be, given the arguments made in the CT-GG literature that every group is comprised of subgroups which will have (slightly) different cultural orientations. In a recent review Johnson and Swedlow

194 Jackson and Philip (2005).

195 Hendriks, F (1994). Cars and cultures in Birmingham and Munich. In Coyle, D. Ellis, R (eds) Politics, Policy and Culture. Edwards Elgar. Hendriks, F (1999). Political Institutions and Public Policy: A Tale of Two cities. Edwards Elgar. Adler, Paul S. "Market, hierarchy, and trust: The knowledge economy and the future of capitalism." Organization science 12, no. 2 (2001): 215-234

196 Douglas, Mary, and Steven Ney. Missing persons: A critique of the personhood in the social sciences. Vol. 1. Univ of California Press, 1998. Pgs 104-106

197 Thompson, Ellis and Wildavsky (1990) at pg. 69-81

198 Mamadouh (1999) at 397

199 Ibid

200 Streeck and Thelen (2005).

201 Johnson and Swedlow (2021) at 422.

believe[202] it is more likely that individuals are socialised in culturally pluralised institutions[203] and the question is whether their individual cultural biases then reflect the pluralisation[204] or, instead, they hold to one cultural bias.

Units of Analysis

That CT-GG can be applied to a wide range of units of analysis (a wide range of groups and subgroups) is already implied by this stage. In addition to cultural orientations being present (but difficult to identify) in individuals, it is possible to discern the cultural orientation of groups large and small. This can be done by considering the institutions binding those groups, and this is easier than using surveys to gauge individual cultural biases. From relatively small groups such as professions, or clusters of EU Member States (EUMS), one can also extrapolate to larger groups such as whole jurisdictions. Rayner describes[205] the institutional and organisational units to which cultural theory may be applied as the 'building blocks' for larger entities such as nation states. In terms of what specific units (groups and subgroups) to analyse, Mamadouh argues that ultimately *"delimitation depends… on the research agenda"*.[206] She says that CT-GG has been *"applied at very different scales"* and the grid group typology *"can be applied to any system: with elements much larger or smaller than human beings."* It can be applied to one individual in all the different roles that he plays, or it can be applied to whole states and how they interact with each other in an international system.[207] She says, *"the typology is applicable to a much broader range of phenomena than the theory itself"*. Thompson argues that the worldviews can be *"operationalised"*[208] at any unit of analysis from the individual to a village to the whole world.[209] Thus I can apply CT-GG to analyse groups and subgroups of any size and any nature.

According to Grenstad, Selle and Thompson, cultural theory embodies political science.[210] They say that the grid-group typology *"allows us to go 'inside' any of the social units (nations, firms, churches and so on) that are conventionally characterised in terms of their distinctive cultures"* because cultural theory focuses upon how we bind ourselves to each other, our *"social solidarities"* (or, as named elsewhere, 'social relations'). These social solidarities are universal. Thus, if one looks closer at the unit of analysis (group of any size) under discussion, one will be able to note the social solidarities exhibited therein and CT-GG allows us to assign them (relative to each other from all under discussion) to a quadrant of the GG matrix. This approach, taken by Grenstad, Selle and Thompson, is precisely what I seek to do in Chapter Six, save that I refer to institutions rather than social solidarities. These appear to mean the same thing.

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202 Ibid

203 Johnson and Swedlow (2021) at 423

204 Earle, Timothy C., and George Cvetkovich. "Culture, cosmopolitanism, and risk management." *Risk Analysis* 17, no. 1 (1997): 55-65.

205 Rayner (1992)

206 Mamadouh (1999) at 402

207 Ibid.

208 Ibid.

209 Thompson, Michael. "Security and solidarity: an anti-reductionist framework for thinking about the relationship between us and the rest of nature." *Geographical Journal* (1997): 141-149.

210 Grendstad, Gunnar, Per Selle, and Michael Thompson, eds. *Cultural theory as political science*. Routledge, 2003. At pg 1.

Douglas believed that to work out the culture of a (group) one should look what individuals do in their social environments.[211] This is why I have looked at the behaviour and practices of the various groups and organisations in Chapters One to Four, and why this then enables me to analyse the groups culturally in Chapter Six: the behaviours and practices disclose institutions, which in turn disclose a cultural orientation. Mamadouh speaks of looking at both interpersonal relations and at behavioural strategies.[212] I say that both will reflect institutions: interpersonal relations are conducted through institutions of social interaction, and behavioural strategies are effectively rules (institutions) governing behaviour. I submit, therefore, that because I am not looking at individual cultural biases but rather at the institutions binding together groups and subgroups, and that I look at two jurisdictions, the differences between the stability and mobility hypothesis need not stand in the way of my research project. Moreover, CT-GG has provided me with an account of cultural incoherence and cultural change which fits well with the institutional approach to culture.

5.4.4 CT-GG Selected

In summary, CT-GG Is preferred here, to DNC, for the purposes of this research project and the question of what typologies or dimensions will be employed for analysing the contents of culture. CT-GG fitted all the initial criteria adopted for selecting a theory for the contents of culture (set out in Table 64 above). In addition, CT-GG fits better with the institutional approach to culture than did DNC, because: CT-GG acknowledges that culture may be internally incoherent (within groups and subgroups); CT-GG permits that cultural change can happen in any group, but that it is likely to be a gradual process only (thus enabling the 100-300 year time period comparison in Chapter Six); and, CT-GG can be used to analyse institutions directly which enables cultural analysis of groups of any size. CT-GG is thus selected as the theory of culture applied to provide the contents of culture in Chapter Six. Below, I operationalise CT-GG for this task by unpacking what the dimensions and the quadrants (cultural orientations) of CT-GG represent – what they would predict of institutions (and thus groups) which adhere to them.

211 Mamadouh (1999) at 402
212 Mamadouh (1999) at 400

5.5 Operationalising CT-GG for Analysis of Groups, Organisations, and Institutions

In this section I unpack what is meant by the grid and group dimensions, and by the four cultural orientations in CT-GG. I use insights from the CT-GG literature to develop a set of pairs of predicates for the hierarchism-individualism 'diagonal'. I later use these in Chapter Six to analyse the groups, organisations and institutions which are proximate to the regulatory divergences in each of the cases examined in Chapters Two through Four.

5.5.1 The Dimensions of Grid and Group and What These Represent

What do the dimensions really mean? Wildavsky puts it most simply. He says the two dimensions are the response of individuals to two fundamental questions: 1) who am I? (group axis) and 2) how should I behave? (grid axis).[213] Mamadouh says the group axis applies to social *"incorporation or boundedness."*[214] Of the group dimension, Grenstad, Selle and Thompson (paraphrasing Douglas) say this *"taps the extent to which the individual's life is absorbed in and sustained by group membership."*[215] According to Mamadouh the grid axis applies to *"regulation or prescription"*.[216] The grid axis represents *"the cross-hatch of rules to which individuals are subject in the course of their interaction."*[217] Grenstad, Selle and Thompson say the grid axis is *"much the same as Durkheim's notion of regulation."*[218]

I now reason deductively – and also set out how others have reasoned deductively - to consider what institutions governing social relations (identified through behaviours) one would expect based upon the dimensions (high or low) and the cultural orientations. Before I turn to the cultural orientations, I consider first the dimensions.

5.5.1.1 The Group Dimension

Many[219] see the poles of these dimensions as relating to several different aspects of behaviour, no one of which is essential to qualify for that pole. For the group dimension, Mamadouh says The group axis is strong or high group where *"the individual is a member of one corporate group"*, and weak, or low group, *"when individuals do not belong to such a*

213 Wildavsky (1987) at pg. 6
214 Mamadouh (1999) at 396
215 Grendstad, Selle, and Thompson (2003) at pg 4.
216 Mamadouh (1999) at 396
217 Douglas (1978) at pg. 8
218 Grendstad, Selle, and Thompson (2003) at pg. 4. See also Durkheim, Emile. "Sociologie et philosophie." (1951) at Chpt. 5
219 Douglas (1978) at pg. 15. Gross, Jonathan L., and Steve Rayner. *Measuring culture: A paradigm for the analysis of social organization*. Columbia Univ Press, 1985 at Chpt. 4. Mamadouh (1999) at 397.

group".[220] Mars employs *"frequency of interaction, mutuality, scope of activities, and group boundary"*[221] Grenstad Selle and Thompson say, *"a lower group score would be given to an individual who 'spends the morning in one group, the evening in another, appears on Sunday in a third, gets his livelihood in a fourth'"*[222] and higher to *"a person (an Amish, say) who joins with others in 'common residence, shared work, shared resources and recreation'"* Gross and Rayner include:[223] *"proximity (closeness of members to each other), transivity (of relations), frequency (proportion of the allocable time of members during which they interact with other members of the unit, scope (activities with members as a proportion of all activities inside and outside the relevant social unit), and impermeability (which measures how easily eligible non members who want to join actually join the unit."*

Table 65 The Group Dimension: High/Strong and Low/Weak

(own table containing quotes from cited literature)

High/Strong Group	Low/Weak Group
Groups are strong	*Groups are weak*
High group loyalty	*Low group loyalty*
The individual is a member of one corporate group	*The individual does not belong to one group*
High frequency of interactions	*Low frequency of interactions*
More mutuality	*Less mutuality*
'My ties to others are weak, and my choices bind only myself'	*'My ties to others are strong, I form part of a collective and the decisions of the collective are binding on me'*
Wide scope of group activities	*Narrow scope of group activities*
Group boundary is strong	*Group boundary is weak*
Individuals interact in one group for most or all purposes	*Individuals interact in many groups for many different purposes*
Group members are close to each other	*Group members are distant from each other*
Group members spend a lot of their time interacting with each other	*Group members spend little of their time interacting with each other*
More of all the activities undertaken within a wider social unit by the individual are undertaken within one group	*Relatively few of all the activities undertaken within a wider social unit by the individual are undertaken within one group*
Impermeable group boundaries: it is difficult to join the group even if you are eligible	*Permeable group boundary: it is easier to join the group if you are eligible*

220 Mamadouh (1999) at 396.
221 Mars G., 1982: Cheats at Work, an Anthropology of Workplace Crime. George Allen and Unwin, London at pp. 24-28
222 Douglas M. (ed.), 1982b: Essays in the Sociology of Perception. Routledge and Kegan Paul, London at pg. 202
223 Gross and Rayner (1985) at pg. 72

Thompson considers just "unfettered competition" (low group) and "fettered competition" (high group) for the group axis.[224] Webber and Wildavsky keep it simple with just 'group strength' (high/low) for the group axis. Verweij goes for 'preferred amount of group loyalty' (high/low) for the group axis. I set these out in Table 65 above.

To these observations, taken from the literature, I add my own thoughts. First, being 'low-group' does not mean that the individual does not interact with others in society. The two dimension both relate to 'social relations' which are inevitable for most human beings. It may well be that there are differences between an extreme example of the 'low group' individual and of the 'high group' individual whereby the former spends more time alone, not interacting, and the former more time with others, interacting.[225] The main question for the group axis instead is: within the social unit (the wider group) what do the *groups* look like, and how do the *groups* behave? In a low group jurisdiction there will be many, less tightly bounded subgroups. In a high group jurisdiction there will be fewer, more tightly bounded subgroups. This follows from the observations about allocable time spent interacting within groups, and scope of activities undertaken within groups. It also follows from the permeability of group boundaries. Within a high group society, if the lion's share of one's time is spent interacting with one group and the lion's share of one's day to day activities take place within the group, then the individual has neither the time nor the need to belong to many groups. Moreover, if it is difficult to leave one group and join another group then one better stay put in one's group. In low group societies, I say, group membership is either highly flexible (being only loosely bound) in the individualist case or is found only in the smallest possible units (the fatalist case).

What can one expect the behaviour within any given group in a high group, and a low group culture, respectively, to be? Again, avoiding extreme examples: in a high group society one's interactions with others in a group are premised upon the assumption of one's continued membership of the group. Whereas, in a low group culture this is not assumed, or the opposite is assumed. As such, in a high group culture it can be expected that there will be less intra-group competition, and that the extent of intra-group cooperation will not be strongly limited by the benefits available to individual 'members' from their cooperation within the group in the short to medium term. The converse will be true for low group cultures. I said in Chapter Three, and I continue in Chapter Six, that lawyers in the US cooperate in several different groups, and I make the claim in Chapter Six that US lawyers are relatively individualistic as a group. They are lawyers and cooperate with all other lawyers. But they are also (e.g.) claimant-side lawyers, and so they also cooperate within the larger group of lawyers in the subgroup of claimant sided lawyers. Most of all they are just individuals with individual interests. So which group or subgroup do they cooperate with most? The group or subgroup through cooperation with which their individual (say, financial) interests are most likely to benefit. Thus, they are only loosely tied to 'all lawyers' as a professional interest group, but more tightly bound to their group of 'claimant sided lawyers' with whom they share tactics, and

224 Thompson M., 1997a: Cultural theory and integrated assessment. Environmental Modeling and Assesment, 2: 139–150 at pg. 142

225 However, it is only the fifth type (see below) the autonomous 'hermit' who seeks to keep to himself. Instead, the group dimension is all about groups within the relevant social unit. That is – as I have said above, any number of individuals interacting with each other. A nation is a group, a jurisdiction is a group. A family is a group. Importantly, even two individuals interacting at a single point in time is a group.

strategies, and with whom they team up together to lobby for legal changes which benefit claimants, and thus benefit themselves. Most of all, they are individuals, so where the requirements of cooperation in the subgroup stand in the way of individual success, then the individual interest comes first. They interact in society, they are members of groups, they can (unlike fatalists) be trusted, (so long as cooperation stands to benefit them), but they are not true team players. They will not 'take a hit for the team', unless an offsetting (and greater, subjectively valued) benefit is presented to them in the future, and (as they can do) they trust that this will materialise.

This perhaps clarifies the one aspect from Table 65 above which might at first appear confusing: Thompson's decision to employ 'fettered' v 'unfettered' competition to mean high, and low, group, respectively. At first glance we might think this fits better within the grid dimension. However, group membership, where it is assumed to be relatively permanent and stable, fetters within-group competition. If group membership is assumed to be stable, then there is no need for anyone to move around within the group. Competition is an attempt to change one's place within a group, to rearrange it until the structure of the group settles upon a new 'equilibrium' position which may change again when circumstances change. The wider group, and all subgroups, will expand and contract at various times. Individuals, competing to obtain some goal, leave and join as to do so furthers their competitive interests. New groups develop, and disappear, over time. No group is very stable over time, because of competition, which is 'unfettered' by group membership. This is, at least, the case for the individualist. The fatalist (the non-extreme example) belongs only to the smallest possible group at any one time.[226]

In Chapters Two and Four, and later in Chapter Six, I talk about certain professions, and I talk about integration. I also talk about 'stratification' and 'division of labour'. Below, in this chapter, I will set out that CT-GG scholars say that division of labour is a characteristic of hierarchical groups. Here, where they say division of labour, they mean stratification – rules which divide labour rigidly and fix these divisions in place. Individuals are assigned a role in society and they stay there. Once, through stratification (external rules) occupational and/or social roles are fixed, there is little mobility within the hierarchical group. The subgroup undertaking that role cannot grow, and take on other roles (e.g., take on the role of 'sale' in addition to 'advice' for pharmacists). But neither can it split and become two new subgroups, one of which focuses on 'sale' and the other on 'advice', a process which might occur in an individualistic group and a process which is also a 'division of labour', but one that is brought about by market forces and is efficient, unlike the rigid division of labour found in hierarchical groups.[227] A lack of stratification similarly facilitates integration – the ability for two groups to join together (where it was efficient to do so) hence the retail druggists in the US became vertically integrated with large retail pharmacy (LRP) in the latter half of the 20th century. In addition, though, where the new group forms, following 'division of labour' (a group split) or

226 In a society which is high grid in addition to being high group, one would not only not compete within groups, but the group will be subject to rules which restrict competition – barriers to entry to professions, for example taxes which redistribute the rewards of competition on a progressive basis.

227 Thus, the Southern EUMS (SEUMS) pharmacists, once society had assigned them the role of 'advice', stayed that way. There was no schism. For a time, US (and Northern EUMS (NEUMS)) pharmacists took on both roles, then - because relatively little stratification existed to prevent them from doing so – they split into retailers (chemists in the UK) and advisers (general practitioners in the UK). The ability to split this way was presented by the lack of stratification in the original group.

'integration' it need not have rigid boundaries, where the wider group has a relatively low group culture. Hence my use of 'partial vertical integration' (or 'capture') to describe the relationship between US doctors and the US pharmaceutical industry (USPI) (at its height) at the middle of the 20th century. US doctors did not become employed by the pharmaceutical industry but cooperated closely with pharmaceutical industry whilst maintaining their independence.

In low group cultures, the size of the various subgroups varies over time and the intensity of the intra-group interactions vary over time. The subgroups may divide, or they may integrate.[228] Doctors and pharmacists are good examples of this.

5.5.1.2 The Grid Dimension

For the grid dimension, in 'Cultural Bias'[229] Mary Douglas suggests *"insulation, autonomy, control and competition"* and Gerald Mars, in his work,[230] substitutes reciprocity for control. Gross and Rayner, who presented a mathematical model for Grid-Group[231] adopt four grid predicates, *"specialisation (operationalised as the proportion of all possible roles that a member assumes, asymmetry (lack of symmetry in role exchange), entitlement… (the proportion of all roles that are ascribed to certain categories of persons as opposed to roles open to all that can be attained by achievement, and accountability (operationalised as the proportion of all roles that are accountability interactions, which are interactions in which there is one dominant role and one subordinate role, and the former can put sanctions on the latter."*[232] Mamadouh says, the grid axis represents *"the cross-hatch of rules to which individuals are subject in the course of their interaction"*[233] and it is high grid where these are many and low grid where these are few. Grenstad Selle and Thompson say, *"a high grid (that is, a highly regulated) social context is characterised by 'an explicit set of institutionalised classifications that keeps individuals apart and regulates their interactions.'"*[234] Thus, *"in such a setting, 'male does not compete in female spheres, and sons do not define their relations with fathers.'"*[235] They say, *"as one moves down-grid, individuals are increasingly expected to* negotiate their own relationships with others." Webber and Wildavsky use 'number and variety of prescriptions' (high and varied/low and unvaried) for the grid axis.[236] Thompson considers 'symmetrical transactions' (low grid) and 'asymmetrical transactions' (high grid) for the grid axis.[237] Verweij goes for 'preferred amount of prescriptions' (high/low) for the grid axis.[238] I set these out in Table 66 below.

228 And, where the culture is additionally low-grid, they are free to do so because no, or few, external rules rigidly fix the group in its current size and its current behaviour.
229 Douglas (1978) at pg. 16
230 Mars (1982) at pgs. 24-28
231 Gross and Rayner (1985)
232 Mamadouh (1999) at 398
233 Douglas (1978) at pg. 8
234 Grendstad, Selle, and Thompson (2003) at pg 4.
235 Douglas M. (ed.), 1982b: Essays in the Sociology of Perception. Routledge and Kegan Paul, London at pg. 192
236 Webber and Wildavsky (1986) at pg. 25
237 Thompson (1997a) at pg. 142
238 Verweij M., 1995: Cultural theory and the study of International relations. Millenium, 24(1): 87–111 at pg. 92

Table 66 The Grid Dimension: High and Low

(own table containing quotes from cited literature)

High/Strong Grid	Low/Weak Grid
High number of varied prescriptions	*Low number and unvaried prescriptions*
Individuals subject to many rules in the course of their interactions	*Individuals subject to few rules in the course of their interactions*
Highly regulated social context	*Less regulated social context*
Restrictions upon competition	*Free competition*
Insulation (from change)	*No/little insulation (from change)*
Control over behaviour/transacting	*Little/no control over behaviour/transacting*
Little individual autonomy	*More individual autonomy*
Little reciprocity in transacting	*More reciprocity in transacting*
Rigid specialisation (occupational roles)	*Flexible specialisation (occupational roles)*
Asymmetry in role exchange/transactions	*Symmetry in role exchange/transactions*
Fixed entitlement to social roles (low social mobility)	*Social roles open to competition (high social mob.)*
Accountability (to a superior transacting party)	*Absence of accountability (to the same)*
An explicit set of institutionalised classifications that keeps individuals apart: e.g. male does not compete in female spheres	*Few or no institutionalised classifications keeping individuals apart*
Rules govern relationships: e.g. sons do not define their relations with fathers.	*Individuals are expected to negotiate their own relationships with others*
'I am subject to many external prescriptions, my choices are tightly constrained'	*'I am subject to few external prescriptions and I am a free spirit'*

It will be clear already how Thompson's group predicates of fettered and unfettered competition are linked to some of the grid predicates here. Express restrictions upon competition can be found (in the form of rules) in high grid contexts, supplementing (in a high grid, high group context) the high-group predicate of competition being fettered due to the stable existence of groups and stable group membership over time. Indeed, these rules which restrict competition, and other rules, will insulate social units from the effects of change, keeping the group and any subgroups relatively fixed as they are without the possibility of splitting, or integrating. These restrictions on competition are not just written rules, norms, or conventions, but also come from 'entitlement'. Things are fixed the way they are, or at least they are seen that way, and there is no social mobility. Thus, fatalists will always be in the smallest possible groups and fending for themselves/their families whilst in hierarchies the hierarchical structure will 'always' remain the same. Linking specialisation to what was said previously, here the specialisation is rigid in nature. There may be little occupation flexibility

(indeed little labour market flexibility) and this contributes to an overall lack of social mobility, in a group with a high grid culture.

Accountability requires explanation here. The hallmark of accountability in a high-grid context is the asymmetry of roles. The superior transacting party will always be able to sanction the inferior transacting party. Accountability has been a major theme in this work thus far, and this concept is developed further in Chapter Six. There is a difference between accountability to the group as a whole, and accountability to a specified superior occupying an asymmetric (superior) role. Below, it is noted that egalitarian societies are marked by 'symmetry and accountability'[239] and in these cases the only actor which can hold an individual accountable is the whole group. Thus, there is accountability, but because of the requirement of symmetry, it cannot be 'to a superior'. In hierarchies these are characterised by asymmetry and accountability. Here, the accountability is to a specified superior (and always the superior). In individualistic societies there is 'symmetry and the absence of accountability.' In the egalitarian society where the whole group sanctions the individual he is expelled (because egalitarianism is high group) but not so in individualistic societies. Here, transactions are symmetrical (anyone can do business with anyone, as equals) and no one can hold anyone to account: neither of the parties to the transaction, nor the group as a whole, and due to the nature of individualism as low group, group expulsion is not the logical option.

What this means is that individualistic societies will work on the basis of reciprocity in transacting. That is, in the absence of accountability of any kind, parties transacting symmetrically will co-operate based on the 'tit-for-tat' strategy: co-operation until defection, then defection in retaliation, until memory fades and cooperation resumes.[240] Reputation thus become key for doing business (or any form of transacting), in an individualistic society. Where one builds a reputation as a good co-operator, everyone will want to transact. But, where one builds a reputation as a bad co-operator, no one will wish to do so. Whereas in a hierarchical society, reputation will matter relatively less because trust in the non-defection of the co-operative partner is ensured by their accountability status (as superior or subordinate). Of course, the corollary of this is that for individualistic groups to become market economies, a mechanism to ensure trust, and thus ongoing cooperation, is vital. Thus, individualists cherish the existence of contract law – the possibility of enforcing contracts – in the shadow of which they bid and bargain, as much as they cherish 'freedom of contract' which permits them to bid, bargain and renegotiate everything they choose.[241]

Applying these insights on accountability to the work done so far: 'double', and 'treble' 'insulation' at the European Medicines Agecy (EMA) and EU Member States (EUMS) national agencies (NAs) refers to insulation of ministers from accountability to consumers (the whole group) whereas 'direct-to-consumer accountability' refers to the practices of the US Food and Drug Administration (FDA) being responsive to the whole group (of consumers) relatively more than to a specified superior such as the President, or industry leaders. In (what I say is) the relatively individualistic US, the FDA is very focused upon its reputation, and its reputation in the eyes of the broad group of consumers rather than to a specified superior. This is the

239 Grendstad, Selle, and Thompson (2003) at pgs. 10-11.

240 See Axelrod, Robert, and William Donald Hamilton. "The evolution of cooperation." *science* 211, no. 4489 (1981): 1390-1396.

241 Contractual enforcement is undoubtedly a high grid institution. Thus, this is one example of how the four cultural orientations rely upon each other for their viability.

approach one would expect in an individualistic society. Whilst the use of the word, 'accountability' is confusing here remember that accountability in this context (grid dimension) refers to the ability to sanction. Consumers cannot sanction the FDA. They cannot shut it down. Nevertheless, the FDA cares very much about its reputation in the eyes of these consumers.

Finally, in Chapters Two, Three and Four I discuss the professional interest groups of doctors, lawyers, and pharmacists, respectively. In Chapter Six I develop these points further using this cultural theory. I say there in all cases that in a relatively hierarchical (including high grid) jurisdiction these professionals are more likely to maximise social status and the social esteem bestowed thereby, than they are to maximise monetary income. I also suggest that one way to obtain social status and esteem in an individualistic jurisdiction is by maximising income and/or amassing wealth. This, too, follows from some of the predicates of the grid dimension set out above inTable 66. Social mobility is low in high grid jurisdictions because there is rigid specialisation (of occupational roles) and there is a fixed entitlement to social roles.

Of the group and grid predicates I pick four that are key for Chapter Six. Of these, the most important is competition – which I call competition/economic freedom – the freedom to enter and compete on markets. Later, I incorporate these predicates into the predicates for the quadrants.

Table 67 Key Group/Grid Dimension Predicates

Own table based upon insights set out above

Individualistic	**GRID AND GROUP**	**Hierarchical**
Free/Unfettered	Competition/Economic Freedom	*Restricted/fettered*
Reputation instead	Accountability	*To specified superior*
Low	**GROUP**	**High**
Flexible	Flexibility of Groups/Subgroup	*Fixed*
Low	**GRID**	**High**
Low	Social Mobility	*High*

5.5.2 The Cultural Orientations and What These Represent

Having begun to touch upon these above based just on the predicates of the dimensions, now I move to consider the quadrants which represent the cultural orientations. An individual, an institution and any group can lie at any point within the matrix. The precise position represents its/their cultural orientation. Individualism is viable with a low grid and low group positioning. Fatalism is viable with a low group and high grid positioning. Hierarchism is viable with high grid and high group positioning. Finally, egalitarianism is viable with low grid and high group positioning.

5.5.2.1 Myths of Nature and the Cultural Orientations

Before I turn to the main body of literature on Cultural Theory and the predicates provided therein for the cultural orientations, I take a few paragraphs to set out a related line of literature which was brought within CT-GG by Schwarz, Thompson, and Rayner. They incorporated[242] the typology of myths of nature which had previously been used by ecologists to analyse management of ecosystems through analysis of the managing institutions. The myths of nature, they say,[243] "describe how the relationship between society and the environment is configured".[244] These[245] "refer to the narratives, beliefs and social constructions that determine cultural interpretations about how nature… function(s)".[246] The diagram of the four myths is shown below in Figure 18. [247]

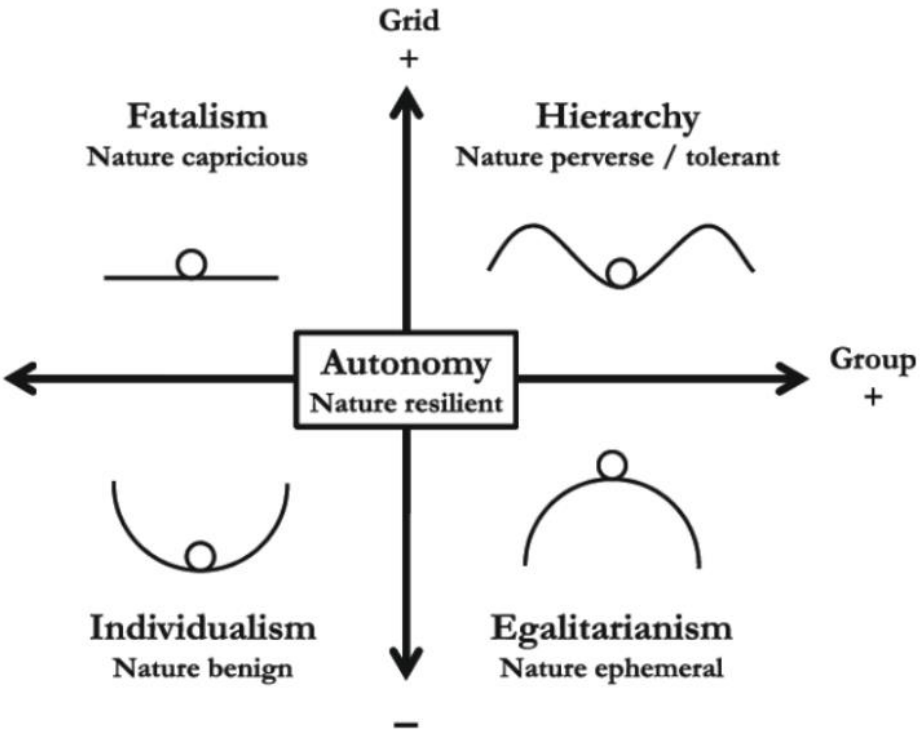

Figure 18 **The Four Myths of Nature**

Thompson, Ellis, and Wildavsky (1990)

242 Mamadouh (1999) at 402
243 Schwarz and Thompson (1990)
244 O'Riordan, Timothy, and Andrew Jordan. "Institutions, climate change and cultural theory: towards a common analytical framework." Global Environmental Change 9, no. 2 (1999): 81-93; Hulme, Mike. Why we disagree about climate change: Understanding controversy, inaction and opportunity. Cambridge University Press, 2009.
245 Thompson, Ellis, and Wildavsky (1990)
246 McNeeley, Shannon M., and Heather Lazrus. "The cultural theory of risk for climate change adaptation." Weather, climate, and society 6, no. 4 (2014): 506-519 at 507
247 Taken from Bellamy, Rob, and Mike Hulme. "Beyond the tipping point: understanding perceptions of abrupt climate change and their implications." Weather, Climate, and Society 3, no. 1 (2011): 48-60 at pg 50. In turn, adapted from Thompson, Ellis, and Wildavsky (1990), Thompson and Rayner (1998) and Douglas M., 1970: Natural Symbols, Explorations in Cosmology. Barrie & Rockliff, London

Rayner says that[248] certain forms of social organisation are correlated with the four worldviews taken from CT-GG.[249] Thus different perceptions of risk (and responses to risk) may reflect underlying cultural worldviews held by individuals and shared in groups.

In the view of Rayner, Schwartz and Thompson [250] for individualists: *"nature is benign, it is robust, it can take experimentation, trial and error, as the shape of the hill always brings the ball back to the best position."* Individualists consider that nature *"automatically adjusts to human actions."*[251] For fatalists**,** *"nature is capricious, it is a lottery, one does not know what to expect, one cannot learn from experience.* Mcneeley and Lazrus put it a slightly different way, they say the fatalist worldview corresponds with a myth of nature that it is *"capricious and fundamentally random and unpredictable".*[252] For hierarchists, "*nature is perverse/tolerant it is robust, but to a certain point, the shape of the hill brings the ball back to the best position, at least if it remains in the safe zone, if it goes too far, things go wrong. Therefore, this myth justifies the power given to experts as they are the ones who can evaluate the safety zone."* McNeeley and Lazrus add that hierarchists believe that nature is *"manageable and tolerant of some human influence and will thus accommodate human action to a point".*[253] For egalitarians, to Mamadouh, *"nature is ephemeral, it is fragile and the 'ball' should be as quiet as possible, any movement could lead to a fall from the top of the hill."*[254] To McNeeley and Lazrus Egalitarians believe *"nature is fragile and in a precarious balance with society"*[255] and thus they *"tend to view the relationship between humans and nature as lying in a delicate balance, prone to human influence leading to a collapse."*[256]

Applying these insights regarding the natural world to views on science and technology: one would expect a hierarchical culture to favour the use of technology to improve the quality of human life but only insofar as this use of technology is regulated through external prescriptions to make it safe to human beings and the environment in which they live. The individualist is likely to favour unregulated technology believing that the environment will adapt to human actions without the need for regulation. The egalitarian is likely to reject technology altogether whereas the fatalist does not consider that either technology, or its regulation, will matter to the quality of human lives.

Dake says that individualists *"believe that nature is resilient (or cornucopious) which comports well with the view that unfettered market mechanisms will increase abundance for all, thereby more than compensating for any environmental damage that is done."*[257] For Kahan, *"individualists see technology as a vehicle for unlimited individual enterprise"*[258] thus,

248 Rayner (1992).
249 McNeeley and Lazrus (2014) at 507
250 Mamadouh (1999) at 402
251 See Thompson, M. "Cultural discourses. Human Choice and Climate Change, Volume 1: The societal framework. S. Rayner and EL Malone. Columbus: Ohio." (1998): 265-344.
252 McNeeley and Lazrus (2014) at 508
253 Ibid. at 508
254 Mamadouh (1999) at 402
255 Jones, Michael D. "Leading the way to compromise? Cultural theory and climate change opinion." PS: Political Science and Politics 44, no. 4 (2011): 720-725. Douglas, Mary. Thought styles: critical essays on good taste. Sage, 1996.
256 McNeeley and Lazrus (2014) at 509
257 Dake (1991) at pg. 67
258 Ibid

according to him, individualists *"predictably dismiss claims of environmental risk as specious, in line with their commitment to the autonomy of markets and other private orderings"*[259] Dake says[260] Egalitarians *"claim that nature is fragile in order to justify equal sharing of what they see as one finite earth."* And thus where it comes to technology, egalitarians, *"who value strong equality of outcome in the sense of diminishing distinctions among people such as wealth, race, gender, authority etc. are predicted to perceive the dangers of technology to be great"* because *"an inegalitarian society is likely to insult the fragile environment just as it exploits the poor."*[261] Kahan says*, "egalitarians… are naturally sensitive to environmental risk, the reduction of which justifies regulating commercial activities that are productive of social inequality and that legitimise unconstrained self-interest."*[262] On the other hand, hierarchists, in the words of Dake believe that *"nature is perverse or tolerant: it will take as much, but only as much, damage as the experts and authorities say…"* and that this *"justifies having regulations and prescriptions flow down, just as obedience is supposed to flow up."*[263] Kahan says that Hierarchists *"believe that the hazards of technology can be managed by their experts in a way that improves the quality of human life."* Thus, hierarchists also dismiss claims of impending environmental disaster, seeing such claims as a threat to the competence and authority of scientific and governmental elites.

Thompson et al argued that – like the four cultural worldviews, the myths of nature too *"offer a partial representation of reality" i*.e. that they are each true taken in themselves. However, in time, each myth of nature – like the cultural orientations – will be *"surprised"*[264] by unexpected outcomes. Thompson et al also move from the myths of nature and the worldviews to extrapolate as to human nature[265] *"For individualists, human nature is extraordinarily stable and self-seeking. For fatalists, human nature is unpredictable, for hierarchists humans are 'born sinful but can be redeemed by good institutions whereas egalitarians see exact the opposite 'man is basically good but his nature is highly susceptible to institutional influences."*[266] This work by Thompson et al has been used on numerous occasions to analyse perceptions of the environment and nature.[267] I adapt it here in Chapter Six to apply it to views of the human body and thus to culturally analyse the institution of product risk perceptions. Below, where I develop predicates for the four cultural orientations, I include some of the insights set out in this section relating to science and technology.

259 Kahan and Braman (2006) at pg. 150
260 Dake (1991) at pg. 67
261 Ibid.
262 Kahan and Braman (2006) at 150
263 Ibid.
264 Mamadouh (1999) at 402
265 Thompson, Ellis and Wildavsky (1990) at pg. 33-37
266 Mamadouh (1999) at 403
267 Thompson (1997a) Grendstad, G., P. Selle, and K. Strømsnes. "Myths of nature and views on society." In *ECPR Joint Workshops: Cultural Theory in Political Science, Comparisons and Applications*. 1997. Davy B., 1997: Essential Injustice, When Legal Institutions Cannot Resolve Environmental and Land Use Disputes, Springer-Verlag, Wien

5.5.2.2 Individualism

Now, I draw upon the main body of CT-GG literature to develop predicates for each of the cultural orientations. Mamadouh says[268] that individualist groups (low grid, low group) are *"characterised by weak group incorporation and weak regulation or role prescriptions"* thus, she says, in these groups, *"the individual is free to enter transactions with others as (s)he wishes, as on a market. Boundaries are provisional. They are subject to renegotiation. Individuals are relatively free of control by others but their ability to control others is a measure of their position in the network."* Thus, one can expect to see *"the pursuit of personal rewards in a competitive environment"* and *"fairness consists of equality of opportunity."* In addition, *"blame is put on personal failure (or lack of competition)."*

For Dake, individualists *"support self-regulation, especially the freedom to bid and bargain"* and that *"the labyrinth of normative constraints and controls on behaviour that are valued in hierarchies are perceived as threats to the autonomy of individuals, who prefer to negotiate for his or herself"* therefore *"social deviance is a threat to individualistic culture only to the extent that it limits freedom, or is disruptive of market relationships."* This means that **"***Individualists are predicted to express concern about social deviance, but more for reasons having to do with risks to the market"* and they *"prefer to substitute self regulation for authority"* being also *"much more willing to permit behaviour which is the product of agreement"*. Thus, he contrasts the example of sex between consenting adults and violence against established institutions, with individualists more likely to be okay with the former but opposed to the latter. Furthermore, he remarks, *"individualists should be much more concerned than hierarchists about issues such as the stability of the investment climate, national debt and government overregulation."*[269] For Dake, individualists display, *"support for continued economic growth as the key to quality of life"* and hold a belief in *"private profit as the main motive for hard work"*. A belief that *"democracy depends fundamentally on the existence of free business enterprise"* and that *"the welfare state tends to destroy individual initiative."* He says that individualists will call for *"less government regulation of businesses"* and will *"endorse private wealth as just reward for economic endeavour"* believing that *"if a man has the vision and ability to acquire property, he ought to be allowed to enjoy it himself"*.[270]

For Grenstad, Selle, and Thompson, social relations which are individualistic are found where *"all boundaries are provisional and subject to negotiation."*[271] Thus, whilst individualists never see themselves as controlled by others, and where two individualists cooperate they do not control each other but rather do so for mutual gain, where an individualist cooperates with another of a different cultural orientation that may be coercive on the part of the individualist in the view of the other. And, they say, *"an individualists success is often measured by the size of the following commanded."*[272] Kahan says that an individualistic worldview *"coheres with*

268 Mamadouh (1999) at 400
269 Dake (1991) at pg. 66
270 Dake (1991) at pg. 69
271 Grendstad, Selle and Thompson (2003) at pg 4.
272 Grendstad, Selle and Thompson (2003) at pg 5.

an individualistic social order", in which, *"individuals are expected to secure their own needs without collective assistance."* And *"individual interests enjoy immunity from regulation aimed at securing collective interests."*[273] These predicates of individualism, taken from the literature, are summarised in Table 68 below, alongside some taken from the literature on the myths of nature, set out above.

Table 68 Predicates of Individualism in Groups and Individuals

Own table based on insights set out above

Individualism
Negotiable boundaries: no fixed social roles, high social mobility (low stratification)
Free transactions (decentralised regulation and self-regulation instead of government regulation)
Inequalities between individuals are permitted: fairness is equality of opportunity, not result
Free competition and retained profit as reward
Personal blame for failure and personal credit for success (popularity, reputation and following matters)
Opposition to welfare state: preference for self-sufficiency and personal responsibility
Support for innovation and scepticism of expertise in regulating technology

5.5.2.3 Hierarchism

As to hierarchist groups (high grid, high group) Mamadouh says[274] these are *"characterised by strong group boundaries and binding prescription"* which are justified (the prescriptions) by *"the importance of the whole over the parts, the collective over the individual"*. Thus, *"division of labour, differentiated roles, (and) hierarchical social relations"* will be found in these groups. Here, *"fairness consists of equality before the law"* and *"blame is put on deviants who do not endorse the established procedures".* These groups will place great trust in authority and expertise.[275] Kahan says, where the worldview is hierarchical, *"collective needs trump individual initiative, and… society is expected to secure the conditions of individual flourishing."* However, *"resources, opportunities, duties, rights, political offices and the like are distributed on the basis of conspicuous and largely fixed social characteristics – gender, race, class, lineage."*[276]

Dake says that hierarchists *"scrutinise social behaviour for acts of social deviance because they find insubordination to authority a threat to their preferred (superior/subordinate) form of social relations"* and that they *"should express great concerns about behaviours such as demonstrations and civil disobedience because they see these acts as disrespectful to the authority they wish to maintain."*[277] Thus Dake, in devising his survey measures to gauge

273 Kahan and Braman (2006) at pg. 150
274 Mamadouh (1999) at 401
275 Ibid
276 Kahan and Braman (2006) at pg. 150
277 Dake (1991) at pg. 66

individual cultural biases, draws the following links[278] for hierarchists: patriotism (*"I am for my country right or wrong"*) and a strong support for law and order. Strict ethical standards and a belief that there is *"little discipline in today's youth".* He also suggests a preference for centralisation (*"centralisation is one of the things that makes this country great"*).[279] According to Grenstad, Selle and Thompson where social relations are hierarchical[280] *"individuals are subject both to the control of their fellows and the demands of socially imposed roles"* whereas a group in which social relations are egalitarian can only expel members, groups where social relations are hierarchical *"has an armoury of different solutions to internal conflicts, including upgrading, shifting sideways, downgrading, resegregating and redefining."*[281] In these groups inequalities, and the exercise of authority which creates them, are justified *"on the grounds that different roles for* different people enable them all to live together more harmoniously than do alternative arrangements." The major predicates of hierarchism, taken from the literature, are summarised in Table 69 below, alongside those set out under the myths of nature section above.

Table 69 Predicates of Hierarchism in Groups and Individuals

Own table based upon insights set out above

Hierarchism
Fixed boundaries: rigid division of labour and low social mobility (high stratification)
Centralised government regulation of transactions
Inequalities between individuals are permitted: fairness is equality before the law
Restricted competition and redistribution of wealth and income
Accountability to specified superior rather than to the wider group (personal profile matters less)
Support for welfare state: group needs trump individual initiative
Expertise and experts trusted in managing technology, unregulated innovation mistrusted

5.5.2.4 Egalitarianism

Egalitarian (low grid, high group) groups are, *"characterised by strong group boundaries coupled with few regulations".* Mamadouh says[282] that the *"group is maintained through intensive relations between group members"* and that *"internal role differentiation is minimal"*. Here, *"fairness is equality of result"*. The group will have strong external boundaries and be impermeable, *"shared opposition to the outside world keeps such an egalitarian group together"* and *"blame is put on 'the system.'"* Meanwhile, for Dake, egalitarians *"abhor the role differentiation characteristic of hierarchy because ranked stations signify inequality"* and believe *"an unconscionably coercive system has no right to make demands or set standards"*

278 Dake (1991) at pg. 69
279 Ibid
280 Grendstad, Selle and Thompson (2003) at pg 4.
281 Douglas (1982b) at pg. 206
282 Mamadouh (1999) at 402

thus they *"reject the prescriptions associated with hierarchy and show much less concern about social deviance".*[283] For egalitarians, he says these will prioritise *"fairness and equality of conditions"* which means *"equality of outcomes".* Egalitarians would agree with the statement that, *"much of the conflict in this world could be eliminated if we had more equal distribution of resources among nations".* They would *"support federal efforts to eliminate poverty"* and also *"a tax shift so that the burden falls more heavily on corporations and persons with large incomes."* They would agree with the statement that *"what this world needs is a fairness revolution,"* that *"misuse of scientific and expert knowledge is a very serious problem in society today,"* and that *"the human goals of sharing and brotherhood are being hindered by current big institutions."*[284]

Kahan says that egalitarians, favour *"an egalitarian society, one that emphatically denies that social characteristics should matter in how resources, opportunities, duties and the like are distributed."*[285] Grenstad Selle and Thompson say social relations which are egalitarian are indicated by *"everyone transacting symmetrically with everyone else and no one transacting with the wider world"* and where *"there can be no internal authority structure."*[286] In addition, the only structure for the group is its external boundary (for it lacks internal stratification). They say the external boundary is, *"the 'wall of virtue'.. that separates the caring and vulnerable 'us' from the harsh and rapacious 'them.'"* Here, *"individuals can exercise control over one another only by claiming to speak in the name of the group: a claim that is supported only in those situations where everyone gives their support to a decision"* and as such, *"active participation, with decisions based upon direct consent is the only basis for legitimacy".* The major predicates of egalitarianism, taken from the literature, are summarised in Table 70 below.

Table 70 Predicates of Egalitarianism in Groups and Individuals

Own table based upon insights set out above

Egalitarianism
No internal boundaries: no differentiation in social roles, 'social mobility' meaningless (no stratification)
No regulation of transactions
Inequalities between individuals are not permitted: fairness is equality of result
No competition or private profit
Accountability to whole group, blame placed on outsiders/the wider system
Group needs trump individual initiative but not achieved through rules (sharing instead)
Expertise, technology, and innovation mistrusted

283 Dake (1991) at pg. 66
284 Dake (1991) at pg. 69
285 Kahan and Braman (2006) at pg. 150
286 Grendstad, Selle and Thompson (2003) at pg 4.

5.5.2.5 Fatalism

Fatalist (high grid, low group) groups are characterised *"by binding prescriptions in combination with weak group incorporation"*. Thus, *"these individuals have little to say about the ways they live their life"* which is *"organised from the outside."* For them, there is no such thing as *"fairness"* and blame is *"put on fate (bad luck)."*[287] As the fatalist worldview is not central to this research project, I do not go into further detail or develop a set of predicates for this cultural orientation.

5.5.2.6 The Fifth Cultural Orientation: Autonomy

Grenstad, Selle and Thompson explain[288] that hierarchical social relations are *"characterised by asymmetry and accountability"* whereas individualistic social relations are *"characterised by symmetry and the absence of accountability"* by that it is meant that *"buyers and sellers, bidders and bargainers, are endlessly switching roles, and no one can hold anyone else accountable."* Yet, as the prisoners dilemma shows, markets rely on trust: *"the tit-for-tat strategy that is 'uninvadeable' in the iterated prisoners dilemma"*[289] thus they have to *"rely on hierarchy to enforce the law of contract that is so vital to their viability."* Hence, these two worldviews rely on each other for their viability: without individualism there would be no negotiated transactions to regulate and without hierarchism there could be no negotiated transacting.

The two quadrants are tied to each other in their endorsement of control (manipulation, or grip). Symmetry and accountability are *"the defining characteristics of the egalitarian solidarity"*: here all relations are symmetrical and *"decisions require the direct consent of everyone"*. Then, *"asymmetry and the absence of accountability"* are the *"defining characteristics of the fatalistic solidarity"* and *"trustless interactions are sustained by fatalism."*[290] Fatalists thus seek to look after themselves and only their individual selves, constantly seeking to *"retaliate… first"* in their one-off prisoner's dilemma interactions with all other individuals in the world. Fatalists, hierarchists, egalitarians and individualists thus all seek to control where they conduct social interactions. They all seek to 'win' when they interact. The fifth type *"defines itself against"* this. The fifth type is autonomy. They say, *"its being is the hermit, because it stabilises itself by the deliberate avoidance of all coercive involvements."* This is where the fifth cultural orientation comes from, and because it appears in the literature it is necessary to explain this. However, I go no further than this because the fifth orientation is not relevant to my project here.

287 Mamadouh (1999) at 402
288 Grendstad, Selle and Thompson (2003) at pg 10-11.
289 Ibid
290 Ibid

5.5.3 Predicates of Hierarchism v Individualism

By contrast, the cultural orientations of hierarchism and individualism, and the differences between them, are central to the task undertaken in Chapter Six. In this research project I look specifically at the diagonal between individualism and hierarchism, claiming that the EU (as a whole) is relatively hierarchical as compared to the relatively individualistic US. Below I set out, in Table 71, the predicates of individualism and hierarchism taken from the literature reviewed above. I will use these for the purposes of analysing groups, organisations, and institutions in the Chapter Six. I have given a label to each of the pairs of predicates which I have adopted, and I have also included here the relevant predicates based on the dimensions set out in Table 67 above. In the paragraphs below I provide a preliminary indication of how I apply these to analyse the groups, organisations, and institutions, in Chapter Six.

The coupled pairs in Table 71 below are not the values and norms of culture. They are merely predicates of those values and norms. The values and norms of culture in this case are simply: 'individualism' or 'hierarchism' – these are the institutional logics, the basic institutions. What the predicates in Table 71 below indicate is that where a rule of group behaviour (a formal or informal institution) accords with one of the predicates (be that, in the pair, the hierarchical one or the individualistic one), then that rule (institution) itself indicates that cultural orientation in the group.

Table 71 Predicates of Hierarchism v Predicates of Individualism

Own table based upon insights set out above

Individualism	Hierarchism
Social Roles and Social Mobility	
Negotiable boundaries: no fixed social roles, high social mobility (low stratification)	Fixed boundaries: rigid division of labour and low social mobility (high stratification)
Regulation of Transactions	
Free transactions (decentralised regulation and self-regulation instead of government regulation)	Centralised government regulation of transactions
Equality and Inequality	
Inequalities between individuals are permitted: fairness is equality of opportunity, not result	Inequalities between individuals are permitted: fairness is equality before the law
Competition and Profit	
Free competition and retained profit as reward	Restricted competition and redistribution of wealth and income
Accountability and Blame	
Personal blame for failure and personal credit for success (popularity, reputation and following matters)	Accountability to specified superior rather than to the wider group (personal public profile matters less)
Welfare State	
Opposition to welfare state: preference for self-sufficiency and personal responsibility	Support for welfare state: group needs trump individual initiative
Innovation and Expertise	
Support for innovation and scepticism of expertise in regulating technology	Expertise and experts trusted in managing technology, unregulated innovation mistrusted
Subgroups	
Subgroups exist and boundaries of subgroups are permeable	Subgroups exist and boundaries of subgroups are fixed

5.5.4 Applying the Predicates to Analyse Groups, Organisations, and Institutions

5.5.4.1 Methodology Adopted in Chapters Six and Seven

The first step in Chapter Six is to arrive at a preliminary cultural positioning for the jurisdictions relative to each other. Jurisdictional culture is likely to affect and reflect the culture of all relevant (sub) groups, (including organisations), and institutions within the jurisdictions.[291] I identified which groups, organisations and institutions were proximate to the various divergences in Chapters Two to Four. Therefore, in Chapter Six - after first arriving at the preliminary cultural positioning of the jurisdictions - I culturally analyse the proximate groups, organisations, and institutions to assess their cultural orientation in each case. I do this using the predicates for hierarchism v individualism set out in Table 71 above. As set out above where I analyse subgroups (such as the professions, pharmaceutical industries, and regulatory agencies), I first consider the behaviour of those groups: what they seek to achieve and how they go about achieving it. I have already done this in Chapters Two to Four in relation to the FDA, the EMA and the NAs and US and EU consumers, doctors, lawyers, pharmacists, and pharmaceutical industries. There, I have identified key characteristics (of behaviour and objectives) in each case. From this, I say, I can deduce an institution which governs the behaviour of the group, and then I can culturally analyse that institution. Although I do not explicitly refer to the predicates each time and I do not explicitly walk through the process of identifying an institution (based upon a behaviour or practice), in each case, this is what is being done.

By way of example, I have provided evidence in Chapter Two that US doctors compete to retain consumers. From this I can deduce an institution governing the intra-group relations of US doctors which states that there is free competition within the group. Then, I can place that institution somewhere on the hierarchism-individualism diagonal using the predicates which I have developed in this Chapter. Hence, having observed that EU/EUMS doctors relatively less often compete to retain patients, I can deduce an institution which says that there is not free competition within this group. As I can see from the predicates in Table 71 that free competition is a predicate of individualism and restricted competition is a predicate of hierarchism, then this is one data point guiding me towards the conclusion that the group culture of US doctors is individualistic (or relatively low-grid, low-group 'rLGLG') relative to the group culture of EU/EUMS doctors which is hierarchical (or relatively high-grid, high-group 'rHGHG').

In addition to this, as set out above in the comments regarding institutional theory and institutional logics, I can expect that the culture of the subgroup is likely to have affinity to the culture of the jurisdiction – the wider group within which the subgroup operates. Hence, when

291 It is likely that there will be inconsistencies in some places between the preliminary cultural positioning and the regulatory positions taken in divergence, however, if cultural theory is able to provide further explanation to the extant theories in the case of regulatory divergence here, then these inconsistencies will be capable of reconciliation by considering the cultural orientation of the relevant groups, organisations, and institutions which were proximate to shaping the regulatory position. This is illustrated in (the concluding) Chapter Seven.

considering the subgroups I also often consider how the characteristics (the behaviour) of the subgroup is shaped by the 'institutional framework' in which it operates. That institutional framework, now, is separate from the subgroup itself. For example: the institutional framework in which the subgroup of US lawyers operate, is the US common law legal system. The institutional framework here is a jurisdiction-wide institution, and thus when analysed culturally, the cultural orientation of this institution also adds a data point in support (or against) the preliminary cultural positioning of the jurisdictions. In doing this, I draw out the point made in the institutional theory and institutional logics literature, that subgroups within a wider group must abide by (what I call) the basic institution (or institutional logic) of culture in order to be able to interact with other groups and individuals within the jurisdiction.

Occasionally, I look at jurisdiction-wide institutions separately, without first considering how these shape the behaviour of subgroups. In these cases, I say the jurisdiction-wide institution has affected the regulatory divergence (regulatory position taken in one of the jurisdictions) by constraining or widening the choices available to interest groups, or to regulators. In these cases, I can culturally analyse the institution directly, using the predicates in Table 71.[292]

5.5.4.2 Examples: Application of the Predicates

Because, in Chapter Six, I do not routinely refer to the predicates in Table 71, I finish this Chapter by providing solid examples of how the predicates there are used, in Chapter Six, to assess the cultural orientation of the groups, organisations and institutions. I do this by reference to the eight pairs of predicates on the hierarchism-individualism diagonal.

Social Roles and Social Mobility

I have identified that a rLGLG group will have negotiable boundaries and thus few fixed social roles. As such, there is little stratification and potentially a high level of social mobility. Conversely, in a rHGHG society there are fixed boundaries, with a rigid division of labour. There is thus a lot of stratification and a low level of social mobility. In Chapter Six these predicates are linked, in the case of the professions (doctors, lawyers, and pharmacists) to a preference in a rHGHG culture to enter these professions in order to seek social status and esteem. In turn, in some cases, it is relatively important for the rHGHG professional groups to

292 The best example of this is the formal legal institution of free speech protections, which I discuss in the context of licensing and direct to consumer advertising (DTCA). In these cases I analyse the institution directly. Thus, for example, the US caselaw on free speech protections indicates a relatively greater adherence to the 'marketplace of ideas' theory of Holmes. Whereas the caselaw of the European Court of Human Right (ECtHR) instead indicates adherence to the 'checking value' theory of free speech. Because the marketplace of ideas theory is one which implies few limits upon the freedom to transact in ideas, whereas the 'checking value' and 'self-governance' theories of free speech do place limits upon this freedom, and in doing so draw a sharp distinction between public and private speech - suggesting that only certain 'types' of speech are fit for protection - then by reference to my predicates from Table 71 (under 'Regulation of Transactions') I come to the conclusion that the US institution of free speech protections is rLGLG relative to the EU institution of free speech protections which is rHGHG.

hold on to their occupational task roles as experts and advisers, or to maintain a hierarchical relationship between the professional and the consumer.[293]

Regulation of Transactions

I have identified that in a rLGLG jurisdiction there will be a high level of freedom to enter into transactions and that there will be relatively less centralised government regulation of transactions and relatively more self-regulation or at least decentralised regulation of transacting. In a rHGHG jurisdiction, there will be stronger centralised (governmental) regulation of transacting. This pair of predicates is used in many ways in Chapter Six. First, the preliminary positioning of the jurisdictions is based directly around a score pertaining to the freedom to enter transactions. It is also based upon observations about levels of authoritarianism and on religion in the jurisdictions and clusters, and the latter two are linked to the question of centralisation. Elsewhere in Chapter Six, some aspects of the jurisdictions which are closely linked to freedom of markets and transacting are analysed. Stronger labour market regulation is linked to the predicate of centralised government regulation. Neoliberalism - which is the opening of markets and the moving of transactions from the public to the private sphere - is also analysed. The significance of money in the two jurisdictions is also considered. I say there that in rLGLG jurisdictions with a high level of economic freedom (to transact) money will be a relatively good medium of exchange for the satisfaction of individual preferences, because relatively more can be bought and sold. Whereas, in a rHGHG jurisdiction where, for example, social mobility is low, it may be more likely that individuals will seek social esteem and status over monetary payment, the latter which will not so easily translate into a new social position.[294]

293 In addition, in Chapter Six, I make some observations about consumers in the US and the EU. I argue that in a 'consumer society' it is more likely that an individual will seek to obtain a new social position through consumption. Thus, for example, the purchase and consumption of branded goods (including pharmaceutical products) is seen relatively more frequently in the rLGLG jurisdiction, where social status may be changed at the individual's initiative.

294 Where I consider aspects of the legal systems, I note, for example, that a rLGLG jurisdiction would attach relatively more importance to the principle of 'freedom of contract', than would a rHGHG society. Hence, the historical importance, in rLGLG jurisdictions of a contractual nexus being present in order for liability for defective products to take effect. RHGHG jurisdictions too can be expected to enforce property rights and uphold agreements (this is a core characteristic of hierarchism, external prescriptions) however, in these jurisdictions the legal system is more likely to interfere with the *substance* of agreements – e.g., to hold that the seller has some duty to take care of the buyer, because this follows from the predicate that for hierarchists the good of the group as a whole trumps individual initiative. In addition, in rHGHG jurisdictions the appropriation of individual property by governments through taxes, for redistribution (to strengthen the group as a whole), is relatively more acceptable than it is in rLGLG jurisdictions. A preference for *written* rules over unwritten rules is also linked to individualism via this pair of predicates, because clear written rules allow individuals to self-regulate rather than there being a need to rely on second- and third-party enforcement of rules and norms. By contrast in rHGHG societies there are expected to be more *unwritten* rules and conventions. These regulate day to day conduct and compliance with them is judged by other member of the group in addition to through formal third-party legal enforcement. This pair of predicates is also applied in Chapter Six in some less obvious ways. The preference for decentralised or self-regulation over centralised (potentially governmental) regulation is linked to shame, guilt, and transparency in public administration, as well as to the usefulness of public apologies in avoiding litigation. Finally, the concept of addiction is linked, in Chapter Six, to a preference for self-regulation over second- or third-party regulation.

Equality and Inequality

The main difference between the two predicates in this pair is that in rLGLG cultures equality of opportunity is key. When coupled with the unwillingness of rLGLG cultures – relative to rHGHG cultures – to redistribute wealth and income through (e.g.) taxes, what is expected to result is a wider level of inequality in the distribution of wealth and income in the jurisdiction having a rLGLG culture. In Chapter Six, for the preliminary positioning of the jurisdictions, I use the Gini coefficient as an indication that the more unequal US has a rLGLG culture compared to the rHGHG EU where the Gini coefficient generally indicates a more equal distribution of wealth and income.

Competition and Profit

Here I say that in a rLGLG jurisdiction there is free (unrestricted) competition, and that profit is the incentive to compete, whereas in a rHGHG jurisdiction there are greater restrictions upon competition and profit acts less as an incentive to compete. That is because it is likely to be redistributed anyway, for the good of the whole group. This, again, is why I use the Gini coefficient to undertake a preliminary positioning of the two jurisdictions. The preference for free competition in the rLGLG US is repeatedly referred to through Chapter Six in relation to the professions, and to the pharmaceutical industry.

Accountability and Blame

I have identified that in a rLGLG jurisdiction there will more often be personal blame for failure and personal credit for success; and that reputation and following - and thus individual public profile - will matter relatively more than it will in a rHGHG jurisdiction. This is because in a group with a rLGLG culture, there is relatively less accountability to a specific superior (in a hierarchy) but, nevertheless, to maintain one's position in the network, and options for transacting with others, it is important to maintain a good reputation within the whole group, and to be popular – just as the FDA is with consumers. In the case of a rHGHG jurisdiction, there will be relatively more accountability to a specific superior except where there is no superior. In these cases, accountability of the individual to the whole group will matter less. This pair of predicates is also relevant to the convention of ministerial responsibility, and to the public profile of bureaucrats working in agencies.[295]

Welfare State

The pair of predicates relating to the welfare state speaks for itself, and it is clearly linked, in Chapter Six to certain jurisdiction-wide institutions such as: socialised versus private healthcare, state funded legal aid expenses versus the US 'costs' rule, and the comprehensive welfare state in the EUMS.

Innovation and Expertise

Here I have identified that a rLGLG cultural orientation is linked to support for innovation, and scepticism of expertise in regulating technology. Whereas in a jurisdiction with a rHGHG culture, expertise and experts are trusted in managing technology, but unregulated

295 It is also linked to the historical aspect of legal systems which in some cases (rLGLG jurisdictions) protects certain interests concerning reputation more strongly – hence the historical fact of punitive damages to compensate for insult and outrage.

innovation is mistrusted. This pair of predicates comes in directly in Chapter Six particularly in relation to the differences between the FDA and the EMA/NAs.[296]

Subgroups

I have said that the main difference between rLGLG and rHGHG cultures when it comes to subgroups within the jurisdiction, is that the boundaries of subgroups in rLGLG cultures are more likely to be permeable. In rHGHG cultures they are relatively more likely to be fixed. This is linked, in Chapter Six, to the prevailing political structure in the two jurisdictions: corporatist and neo-corporatist political structures in the rHGHG jurisdiction but more pluralistic structures in the rLGLG jurisdiction.[297]

5.6 Conclusions

In this Chapter I have adopted an approach to culture which is based around institutions, and which treats culture as the shared values and norms which provide the basic institution, or institutional logic, in any given group. I have added content to this institutional approach by adopting the dimensions and cultural orientations taken from the Cultural Theory of Risk and the Grid-Group typology. I have then operationalised both the institutional approach to culture, and the selected dimensions and cultural orientations, for the purposes of the task in Chapter Six.

296 It is also relevant to the institution of product risk perceptions in the cases of specific pharmaceutical products. The preference for innovation in rLGLG cultures is linked also to innovation amongst US lawyers and in the US pharmaceutical industry.

297 It is also linked, there, to the ability and tendency for groups such as the professions to split and specialise in different roles and to expand and contract depending upon market forces in rLGLG jurisdictions, as opposed to being insulated from those forces because of stratification in rHGHG jurisdictions.

Chapter Six: Applying Culture

6.1 Introduction

At the conclusion of Chapters Two through Four, I had determined that public interest theory, private interest theory and institutional analysis together did not fully explain the divergences in: licensing and direct to consumer advertising (DTCA), pharmacovigilance and product liability, and sale classification and generic substitution. My research question asks whether cultural theory can provide further, supplementary explanation for these regulatory divergences. My hypothesis is that it is capable of providing a consistent, underlying explanation for all of the divergences when considered alongside the extant theories. In this Chapter I apply the cultural framework developed in Chapter Five to see if this hypothesis is correct.

In the case of the first two pairs of divergences I concluded that the two areas of regulation together form a system of regulation in each jurisdiction, and that the system in each jurisdiction is configured differently. In the case of licensing and DTCA, the United States (US) system exhibits caution in licensing whilst the European Union (EU) system exhibits caution in DTCA. Both systems – though differently configured – were justifiable from a public interest perspective. In the case of pharmacovigilance and product liability – I had concluded that there was both transatlantic divergence between the US and the EU and system divergence between the US/EU and a suggested public interest system. In this case neither the US system nor the EU system – despite being differently configured – seemed well justified in public interest terms. In the case of licensing and DTCA I identified that the divergent configurations result from an interaction between the underlying public interest, and the strength and objectives of the various groups and organisations which lobby for regulation of, or actively regulate, these areas. The efforts and options of all are constrained or expanded by jurisdiction-wide institutions in each case. The relevant interest groups were doctors and consumers, and the relevant organisations were the European Medicines Agency (EMA), the US Food and Drug Administration (FDA) and the EU Member State (EUMS) national agencies (NAs). The relevant institutions were socialised healthcare and legal protections of free speech.

In the case of pharmacovigilance and product liability I identified that both the transatlantic divergences and the system divergence (from the Suggested Public Interest (SPI) system) were also likely due to the lobbying influence of certain interest groups and the behaviour of the regulatory organisations. The behaviour of these groups and organisations interacted with certain institutions to shape the regulation in both jurisdictions and helped to account for both system and transatlantic divergence. The relevant interest groups were the pharmaceutical industry in the EU (EUPI) and in the US (USPI) and lawyers, the relevant organisations the FDA, EMA and NAs, and the relevant institutions in/of the respective legal systems and theories of justice, socialised healthcare, and the social norm of litigiousness. At the conclusion of Chapter Four I determined that public interest theory and private interest theory and institutional analysis together could not fully explain the transatlantic nor the intra-EU divergences in sale classification and generic substitution. Here the major interest group affecting the development of the regulation was pharmacists - be those predominantly in independent pharmacy (IP) in the EU/Southern EUMS (SEUMS) or dominated by large retail pharmacy (LRP) in the US - and the organisations impacting upon the regulation were once

again the FDA, EMA, and NAs. The most relevant institutions were product perceptions and price regulation.

In this Chapter I make use of the institutional approach to culture, adopting the typology of culture drawn from the Cultural Theory of Risk and Group-Grid (CT-GG), which was selected in Chapter Five. I use these to culturally analyse the jurisdictions, groups, organisations, and institutions relevant to each pair of divergences. I begin in Section 6.2 by setting out the methodology adopted in this Chapter. Then, in Section 6.3 I make the case for a preliminary cultural positioning for the jurisdictions which is relatively low grid-low group (rLGLG) for the US and relatively high grid-high group (rHGHG) for the EU. Following this, in Section 6.4-Section 6.6, I take each pair of divergences in turn – respectively - and I culturally analyse the groups, organisations, and institutions using the predicates set out in Table 71 from Chapter Five.

6.2 Methodology

To reiterate, I am not making the claim that culture c*aused* the regulatory divergences, and I do not need to establish where the respective jurisdictional cultures came from in the first place.[1] I also do not need to show a linear causal relationship between jurisdictional culture, and the culture of groups, organisations, and institutions. I have sought to make this clear already in setting out my approach to culture in Chapter Five. I also do not seek or need to show that cultural theory provides an *alternative* far less a *superior* explanation for regulatory divergence, I claim only that the explanation provided by cultural theory is supplementary, and that its supplementary value is found in the fact that it discloses a *consistent* account, linked to the cultural orientations, across the several regulatory divergences.

Table 72 Jurisdictions, Organisations, (Sub)Groups, and Institutions to be Analysed Culturally

JURISDICTIONS	
United States	European Union *NEUMS Cluster* *SEUMS Cluster*
ORGANISATIONS	
FDA	EMA
	NAs
GROUPS	
US Doctors	EU Doctors
US Consumers	EU Consumers
US Pharmaceutical Industry	EU Pharmaceutical Industry
US Lawyers	EU Lawyers
US Pharmacists (dominated by LRP)	EU Pharmacists (more IP)
INSTITUTIONS	
US Free Speech Protections	EU Free Speech Protections
Private Healthcare	Socialised Healthcare
US Common Law	EU Legal System
No Price Regulation	Price Regulation
Norm of Litigiousness	Norm against Litigiousness
US Product Perceptions	EU Product Perceptions

1 I refer back to the multiple equilibria argument outlined in Chapter Five

CT-GG is used so that cultural orientations can be legitimately divided into a workable limited number: hierarchical, egalitarian, fatalist and individualistic. This enables me to identify whether there is a broadly consistent cultural picture within each jurisdiction, and to compare culture between the two jurisdictions. Within the jurisdictions, the question of causation is not so important. It is accepted here that culture, institutions, and regulation are mutually co-produced, as per the analysis set out in Chapter Five. Furthermore, in this Chapter I only culturally analyse the groups, organisations, and institutions, leaving cultural analysis of the regulations themselves to Chapter Seven, where I seek to show that the relationship between culture and regulatory divergence was only made possible by also considering public interest, private interest and institutional perspectives first and, as such, cultural theory truly adds *supplementary* explanation for regulatory divergence (rather than an alternative explanation). I argue there, also, that the value of the addition of cultural theory is that it provides a consistent, underlying account for the regulatory divergences across all six considered, but only when considered in tandem with the public interest, private interest, and institutional approaches.

In addition to the jurisdictions and the Clusters, the proximate groups, organisations, and institutions are set out above in Table 72. I assess the cultural orientation of these institutions, organisations and groups using CT-GG. I do this using the predicates for hierarchism and individualism set out (again) below in Table 73. Bear in mind that where I consider groups (including organisations) I perform the cultural analysis by looking at the behaviour of those groups and deducing their most basic institution of culture based upon these behaviours, the latter which disclose the institutions governing and guiding the behaviour of the group and its members. Neither the behaviours nor the predicates listed in Table 73 below are the basic institutions of culture, which are instead: Hierarchism, Egalitarianism, Individualism and Fatalism. Rather, the predicates set out in Table 73 below and gathered from the CT-GG literature assist me in allocating a particular institution governing group behaviour, to one of the cultural orientations, thus assisting me in identifying the cultural orientation of the group (or, if considering an institution directly, the institution).

I will therefore consider myself to have found some evidence in support of the hypothesis that cultural theory can add further explanation to the extant theories in the case of transatlantic pharmaceutical regulatory divergence if, upon application of the predicates in Table 73 to the relevant groups, organisations and institutions, a consistent within-jurisdiction cultural orientation is manifest across all institutions, groups and organisations, and a consistent between-jurisdiction cultural difference is found, across all divergences considered.

Before I culturally analyse the groups, organisations, and institutions. I begin by arguing the case for a preliminary cultural positioning of the jurisdictions.

Table 73 Predicates of Hierarchism v Predicates of Individualism (2)

Individualism	Hierarchism
Social Roles and Social Mobility	
Negotiable boundaries: no fixed social roles, high social mobility (low stratification)	Fixed boundaries: rigid division of labour and low social mobility (high stratification)
Regulation of Transactions	
Free transactions (decentralised regulation and self-regulation instead of government regulation)	Centralised government regulation of transactions
Equality and Inequality	
Inequalities between individuals are permitted: fairness is equality of opportunity, not result	Inequalities between individuals are permitted: fairness is equality before the law
Competition and Profit	
Free competition and retained profit as reward	Restricted competition and redistribution of wealth and income
Accountability and Blame	
Personal blame for failure and personal credit for success (popularity, reputation and following matters)	Accountability to specified superior rather than to the wider group (personal public profile matters less)
Welfare State	
Opposition to welfare state: preference for self-sufficiency and personal responsibility	Support for welfare state: group needs trump individual initiative
Innovation and Expertise	
Support for innovation and scepticism of expertise in regulating technology	Expertise and experts trusted in managing technology, unregulated innovation mistrusted
Subgroups	
Subgroups exist and boundaries of subgroups are permeable	Subgroups exist and boundaries of subgroups are fixed

6.3 Preliminary Cultural Positioning of Jurisdictions

I begin by seeking a preliminary cultural positioning for the jurisdictions and Clusters. The preliminary positioning is only, and can only be, a relative one. Many empirical studies have been undertaken, and much data produced, on the culture of the US and the EUMS.[1] It is accepted that the US (the jurisdictional culture of the US) is one of the most individualistic of any jurisdiction.[2] This was also recognised by Hofstede and by numerous subsequent empirical enquiries. I begin by positioning the US in the bottom left corner of the matrix and, after considering the cultural positioning of the EU, I come back later to justify the relative cultural positioning of the US to the EU.

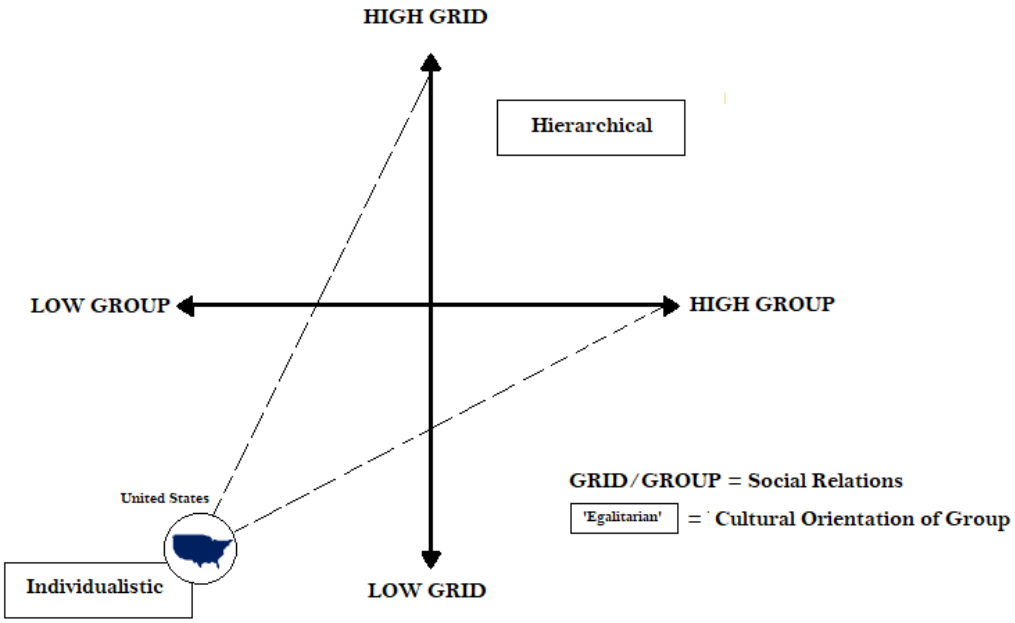

Figure 19 **CT-GG Jurisdictional Cultural Positioning of the US**

Own Figure based upon the CT-GG Matrix

1 Hofstede, Geert. Culture's consequences: International differences in work-related values. Vol. 5. Sage, 1984.
2 See e.g. Gabrielidis, Cristina, Walter G. Stephan, Oscar Ybarra, Virginia M. Dos Santos Pearson, and Lucila Villareal. "Preferred styles of conflict resolution: Mexico and the United States." *Journal of Cross-Cultural Psychology* 28, no. 6 (1997): 661-677. Earley, P. Christopher. "Social loafing and collectivism: A comparison of the United States and the People's Republic of China." *Administrative science quarterly* (1989): 565-581. Kim, Ken I., Hun-Joon Park, and Nori Suzuki. "Reward allocations in the United States, Japan, and Korea: A comparison of individualistic and collectivistic cultures." *Academy of Management Journal* 33, no. 1 (1990): 188-198. Ting-Toomey, Stella. "Intimacy expressions in three cultures: France, Japan, and the United States." *International Journal of Intercultural Relations* 15, no. 1 (1991): 29-46. Oetzel, John, Stella Ting-Toomey, Tomoko Masumoto, Yumiko Yokochi, Xiaohui Pan, Jiro Takai, and Richard Wilcox. "Face and facework in conflict: A cross-cultural comparison of China, Germany, Japan, and the United States." *Communication Monographs* 68, no. 3 (2001): 235-258. Han, Sang-Pil, and Sharon Shavitt. "Persuasion and culture: Advertising appeals in individualistic and collectivistic societies." *Journal of experimental social psychology* 30, no. 4 (1994): 326-350. Gelfand, Michele J., and Sophia Christakopoulou. "Culture and negotiator cognition: Judgment accuracy and negotiation processes in individualistic and collectivistic cultures." *Organizational Behavior and Human Decision Processes* 79, no. 3 (1999): 248-269.

The EU is not yet given a specific position on the matrix, due in party to its cultural diversity. Instead, in Figure 19 above I have (between the dashed line) indicated a zone where the EU will fall if it, as a whole, has a jurisdictional cultural orientation which is less individualistic than that of the US. Before I justify that assumption, I first must consider how to analyse the culture of the EU.

6.3.1 Analysing the Jurisdictional Culture of the EU

There is greater intra-EUMS cultural diversity than there is intra-US cultural diversity. This was stressed in Chapter Four where I analysed intra-EUMS divergences in sale classification and generic substitution. Moreover, in addition to there being intra-EUMS cultural diversity, the EU itself as a jurisdiction has a supranational nature. This makes it - as a jurisdiction - culturally distinct from the EUMS, albeit due to more than 50 years of its existence, the jurisdictional culture of the EU will have affected the jurisdictional culture of the EUMS to some extent.

The EU is comprised of 27 (formerly 28) distinct jurisdictions, and the separate jurisdiction of the EU - which is comprised of its organs and agencies - interacts with these. Therefore, to analyse the EU, culturally, I need to consider the cultural orientation of the EUMS and assign these a preliminary positioning as well as analyse the cultural orientation of the EU organs and agencies. Then, I need to consider how these together indicate a cultural positioning for the EU as a whole, relative to the US. Thus, below, first I analyse the EUMS, then I analyse the EU organs and agencies, and finally I justify a positioning of the EU as a whole relative to the US. This approach is acceptable because – as was seen in Chapter Four - whilst the regulatory positions differ widely across the EU on the face of them, culture across the EU member states does not differ so widely and, it is submitted, there is less intra-EU diversity in culture as there is between the EU and the US as a whole in culture.

6.3.1.1. Cultural Analysis of the NEUMS and SEUMS Clusters

The EUMS – as was the approach adopted in Chapter Four – can be loosely 'clustered' according to their regulatory positions, and according to their cultures. With the differences between the culture of one Cluster and another being smaller than the difference between (aggregate/average) EU culture (comprising the culture of the two clusters of EUMS, plus the culture of the EU organs and agencies) and that of the US. I justify the preliminary cultural positioning of the Northern EUMS (NEUMS) and Southern EUMS (SEUMS) cultures based on three considerations: 1) levels of economic freedom; 2) levels of authoritarianism; and 3) religion.

Levels of Economic Freedom

A high level of economic freedom indicates a rLGLG culture in a jurisdiction. This follows directly from the predicates set out in Table 73 above: 'Regulation of Transactions'. Socialism is a political system in which the state intervenes heavily in the market (supposedly) in the interests of the whole group, and it is thus associated with a low level of economic freedom. Socialism has a stronger history in the EUMS than it does in the US. It also has had a stronger

presence historically in the SEUMS Cluster than in the NEUMS Cluster. Countries with low economic freedom, which may have a stronger tradition in socialism, generally have higher taxes and a relatively high proportion of property held by the state for the public benefit. As to the history of socialism as a political system in EUMS: historically the Socialist Democratic Party in Germany was Europe's largest and is Europe's oldest socialist party, however the ideals of what would later become socialism were first expressed during the French Revolution in the late 18th Century. European socialist parties which adopt a 'third way' between capitalism and socialism should be distinguished from socialist parties which advocate state ownership of property and strong redistribution of wealth, and the latter are found – in strength – in the South of Europe including Italy, Spain, and France.[3]

Table 74 NEUMS and SEUMS Clusters Including Economic Freedom Score 2020

	GSALE[4]	NRPs[5]	NRPs PO[6]	GSub[7]	CCsent GSub[8]	Chain Pharma[9]	Phmcicts[10]	Phmcies[11]	EFree 2020[12]
NEUMS Cluster	**YES**	**YES**	**NO**	**NO**	**NO**	**YES**	**-100**	**-25**	**+70**
Sweden	YES	YES	NO	NO	NO	YES	-100	-25	74.9
UK	YES	YES	NO	NO	N/A	YES	-100	-25	79.3
Netherlands	YES	NO	NO	YES	NO	YES	-100	-25	77
Germany	YES	NO	NO	NO	NO	NO	-100	-25	73.5
Denmark	YES	NO	NO	NO	NO	NO	-100	-25	78.3
Finland	YES	YES	NO	NO	NO	NO	-	-	75.7
Ireland	YES	YES	NO	NO	N/A	YES	+100	+25	80.9
Austria	YES	NO	NO	NO	N/A	NO	-100	-25	73.3
Belgium	NO	NO	NO	NO	N/A	YES	+100	+25	68.9
Italy	NO	NO	NO	NO	NO	NO	+100	+25	63.8
Greece	NO	NO	YES	YES	NO	NO	-	-	59.9
Portugal	NO	NO	YES	YES	NO	NO	-100	+25	67
Spain	NO	NO	NO	YES	YES	NO	+100	+25	66.8
France	NO	NO	YES	YES	YES	NO	+100	+25	66
SEUMS Cluster	**NO**	**NO**	**YES**	**YES**	**YES**	**NO**	**+100**	**+25**	**-70**

Each year, the Fraser Institute and the Economic Freedom Network publish a report called the 'Economic Freedom of the World Index.' According to this institute, some hallmarks of economic freedom include: the importance of personal choice over collective choice, and the extent to which there exists voluntary exchange coordinated by markets rather than allocation via the political process as well as the level of freedom to enter and compete in markets.[4] In Table 74 above I have taken Table 59 from Chapter Four and have added – in the final column – the Economic Freedom Index Score from 2020 in the final column. In that column I have shaded values below 70 in dark grey and values above 70 in light grey. As one moves toward the geographic south of Europe, the EUMS seem to have an economic freedom score which becomes lower. The identification of the EUMS oriented towards the SEUMS cluster in Chapter Four is consistent with a score of economic freedom below 70. The most important examples from the SEUMS cluster: Italy, Spain and France all score well below 70 on the index, whereas the best examples of EUMS from the NEUMS cluster all score well above 70. Taken together with the remarks made about socialism in the EUMS, this provides evidence in support of two things: 1) that there exist two distinct cultural clusters which match

3 Socialism has also been prevalent in Eastern Europe throughout the latter half of the twentieth Century, but the analysis here focuses on EUMS in Western Europe.

4 https://en.wikipedia.org/wiki/Economic_Freedom_of_the_World

the NEUMS and SEUMS orientation for the regulatory positions analysed in Chapter Four, and 2) that the SEUMS Cluster is likely to have a cultural orientation which is high group relative to the NEUMS cluster.

Authoritarianism

Another hallmark of high group cultures is authoritarianism. I define this here as the extent to which individual rights and preferences are overridden by group rules, which is high-grid by definition and hierarchical by reference to the predicates set out in Table 73 above.

Authoritarian governments in Europe have - in recent history - either been socialist authoritarian or right-wing (nationalist) authoritarian. Both types represent high-grid, high-group political systems. The focus of some authoritarian political systems (right wing, nationalist) is limits on individual social freedoms and rights rather than limitations on economic freedoms and rights. In the case of authoritarian socialist systems, both economic and social rights are likely to be limited. Freedom House produces an annual report called, 'Freedom in the World' in which "individual freedoms – ranging from the right to vote to freedom of expression and equality before the law – can be affected by state or nonstate actors." The rankings from its 2020 report[5] are shown below in the final column of a new version of Table 74 – now Table 75, below. I have shaded a score of 94 or above in light grey and a score of 93 or below in dark grey.

Table 75 NEUMS and SEUMS Clusters Including Freedom Ranking 2020

	GSALE	NRPs	NRPs PO	GSub	CC GSub	Ch Ph	Phmcs	Phmcst	EF 2020	FS 2020
NEUMS Clust.	**YES**	**YES**	**NO**	**NO**	**NO**	**YES**	**-100**	**-25**	**+70**	**+94**
Sweden	YES	YES	NO	NO	NO	YES	-100	-25	74.9	100
UK	YES	YES	NO	NO	N/A	YES	-100	-25	79.3	94
Netherlands	YES	NO	NO	YES	NO	YES	-100	-25	77	99
Germany	YES	NO	NO	NO	NO	NO	-100	-25	73.5	94
Denmark	YES	NO	NO	NO	NO	NO	-100	-25	78.3	97
Finland	YES	YES	NO	NO	NO	NO	-	-	75.7	100
Ireland	YES	YES	NO	NO	N/A	YES	+100	+25	80.9	97
Austria	YES	NO	NO	NO	N/A	NO	-100	-25	73.3	93
Belgium	NO	NO	NO	NO	N/A	YES	+100	+25	68.9	96
Italy	NO	NO	NO	NO	NO	NO	+100	+25	63.8	89
Greece	NO	NO	YES	YES	NO	NO	-	-	59.9	88
Portugal	NO	NO	YES	YES	NO	NO	-100	+25	67	96
Spain	NO	NO	NO	YES	YES	NO	+100	+25	66.8	92
France	NO	NO	YES	YES	YES	NO	+100	+25	66	90
SEUMS Clust.	**NO**	**NO**	**YES**	**YES**	**YES**	**NO**	**+100**	**+25**	**-70**	**-94**

Again, EUMS oriented towards the NEUMS cluster score higher on this index and EUMS oriented towards the SEUMS Cluster score lower.

In addition, I consider the history of right-wing authoritarian governments across Europe. These have been more frequent in the south of Europe. Italy's fascist authoritarian regime under Mussolini from 1922-1945, Spain under the Spanish Patriotic Union from 1923-1930

5 https://freedomhouse.org/countries/freedom-world/scores?sort=desc&order=Total%20Score%20and%20Status

and then under the dictatorship of Francisco Franco from 1939-1975. Greece and its succession of military dictatorships between 1925-1926, then 1936-1941, from 1941-1944 in collaboration with Nazi Germany and again from 1967-1974. Portugal too with military dictatorships in 1915, then 1917-1918, again from 1926-1933 and then from 1933-1974. Austria from 1932-1938 prior to union with Nazi Germany. And Germany between 1933 and 1945. France and the Netherlands too, it should be noted, established authoritarian governments (whilst under occupation or threatened by it) which collaborated with the authoritarian Nazi regime. Authoritarianism is thus not entirely historically limited to the SEUMS Cluster; however, I note that I see no evidence of authoritarian right wing nor authoritarian socialist governments in the Nordic countries nor in the British Isles.

Taken together with the Economic Freedom Scores set out in Table 74 and Table 75 above, again I treat this as evidence of the existence of two cultural Clusters, correlated with geographical positioning, and that the SEUMS Cluster is relatively high group as assessed by CT-GG.

Religion

I believe that organised/established religion is a key indicator of the group axis positioning of the EUMS.[6] Considering the predicates set out in Table 73 above, Roman Catholicism is linked to a high group cultural orientation relative to Protestantism. The dogma of Catholicism teaches universality and group cohesion.[7][8] Moreover, in the view of Catholicism everyone is a member of the group, whether they wanted to be so or not.[9] The Catholic Church uses relatively more symbols – such as statues, shrines, icons etc - which some philosophers argue have the purpose of group cohesion.[10] Unlike the decentralised Protestant church, the Catholic Church is uniform and centralised. Prayers, hymns, the order of service, the layout of

6 For general support see: Castles, Francis G. "On religion and public policy: Does Catholicism make a difference?." In Religion and Politics, pp. 529-550. Routledge, 2019. See also: Manow, Philip, and Kees Van Kersbergen. "Religion and the western welfare state: The theoretical context." Religion, class coalitions, and welfare states (2009): 1-38.

7 I.e., everyone who strays from the group must be brought back to the group and may re-enter the group through the possibility of redemption (the central tenet of Catholicism – you can still be forgiven for your sins and re-enter heaven).

8 See Becker, Sascha O., and Ludger Woessmann. "Social cohesion, religious beliefs, and the effect of Protestantism on suicide." Review of economics and statistics 100, no. 3 (2018): 377-391, at 379, *"Durkheim (1897) emphasized that Protestant doctrine encourages independent thought and religious individualism, decreasing social cohesion relative to a more unified Catholic community, which tends to protect people from committing suicide. If there is mutual interdependence in preferences, the fact that there are others who would suffer from a person's suicide will tend to discourage people from committing suicide. In terms of our simple economic model of suicide, the lower cohesion of the Protestant community leads to the prediction that suicide rates would be higher in Protestant communities than in Catholic communities."*

9 See Pope Pius XII, Encyclical Mystici Corporis Christi (Vatican City, 1943). See also: Marshner William H. Membership in the Church: Fundamental Questions FAITH & REASON The Journal of Christendom College Winter 1976 Vol. II No. 3, *"Hence the Second Vatican Council rightly observed that ecumenical approaches to non-Catholic Christians are not based on sentimentality but on the solid fact that the separated brethren already participate, to a greater or lesser degree, in those treasures. But many theologians have attempted to draw from this fact radical implications for ecclesiology itself. They do not hesitate to maintain that the Church must be understood henceforth as a concentric affair, within which the Roman Catholic body is only the innermost circle; that non-Catholic denominations are, therefore, "elements" within the total reality of the Church; and that the separated brothers themselves are thus in some way (or in some degree) already "members" of the Church."*

10 See McDonald, H. D. "The Symbolic Theology of Paul Tillich." *Scottish Journal of Theology* 17, no. 4 (1964): 414-430. Weber, Max, and Stephen Kalberg. *The Protestant ethic and the spirit of capitalism*. Routledge, 2013.

churches etc are all required to be the same from place to place across the world. Again, this emphasises togetherness and group identity. By contrast, Protestantism does not have a centralised bureaucratic structure. It teaches a relationship directly between individuals and God.[11] It states that salvation/redemption is not necessarily achieved through collective means (such as confession and reconciliation)[12] but sometimes only as a result of predestination[13] which places importance upon the signalling of one' individual virtuous qualities.[14] You are only a Protestant Christian, in the eyes of Protestants, if you are baptised as a Protestant and those who are not baptised are not considered Protestants. The structure of the Protestant church is decentralised. There is little or no emphasis on uniformity except in so far as the Bible is concerned. There is no central organisational structure for Protestantism as a whole. Protestantism makes much less use of symbol, statues and icons etc.[15] Overall, Protestantism is much more about the individual relationship with God, without need for an organised church, and a group identity[16] within an organised church, to ensure this.

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11 See Hager, Anselm. "Protestant Missionaries Are Associated With Reduced Community Cohesion." Sociology of Religion 83, no. 2 (2022): 252-279, (abtract): *"…Protestant missionaries propagate an individualist faith, and they provide an identity along which communities may separate. The effect of Protestant missionaries on community cohesion is thus unclear. To make headway on these conflicting theoretical predictions, we study variation in missionary activity in southeastern Peru. We document that villages with Protestant missions show lower levels of community cohesion compared to non-missionized, Catholic villages. "*

12 Davidson, James D., Joseph A. Schlangen, and William V. D'Antonio. "Protestant and Catholic perceptions of church structure." Social Forces 47, no. 3 (1969): 314-322

13 In its more extreme versions, it teaches that some cannot and could never be redeemed – i.e. Calvinism and predestination.

14 Arruñada, Benito. "Protestants and Catholics: Similar work ethic, different social ethic." The Economic Journal 120, no. 547 (2010): 890-918, *"In contrast, Protestant theologies, especially Calvinism before Arminianism… emphasized predestination: salvation is achieved by "grace" alone—God chooses who goes to heaven and who goes to hell. Since Max Weber,however, many writers have considered that Catholic salvation by works and faith produces inferior economic incentives to Protestant beliefs. The rationale is twofold. First, the availability of forgiveness through Catholic confession of sins to a priest eliminates the potential effect of a pure system of salvation by works. Second, even Calvin complemented mere predestination—which, in itself, does not seem very motivating—by emphasizing that believers must examine their own hearts because, without good works, there can be no faith and no salvation. This introspection could easily be interpreted by believers as a way of knowing that they have been chosen to be saved. A reinforcement of self-examination is therefore to be expected. Calvinist theology may thus produce not only motivation for good works but also an emphasis on methodic self-examination, which should make individuals more rational and self-restrained. Good conduct does not warrant salvation, but merely serves as a signal to the believer, who is therefore moved to constant self-examination, with increased moral awareness. This emphasis on the signaling function of good works, often coupled with worldly success, is also present in Lutheranism."*

15 Martin, David A. "Religion and public values: A Catholic-Protestant contrast." Review of Religious Research (1985): 313-331 at 327: *"I began with the suggestion that the Catholic presence is everywhere more massive, more tight knit, with more explicit norms formulated ecclesiastically… The Catholic sector in what were once homogenous Catholic cultures develops parties, unions, associations for the defence of religious norms and for leisure activity… By contrast, Protestant cultures exhibit a less distinctively Christian iconography with little by way of an independent ecclesiastical power base or developed and articulated political norms."*

16 Cohen, Adam B., and Peter C. Hill. "Religion as culture: Religious individualism and collectivism among American Catholics, Jews, and Protestants." Journal of personality 75, no. 4 (2007): 709-742 at p736: *"In several studies, using quite different measures, we have shown that the religious and spiritual identities, motivations, and experiences of Catholics and Jews are more socially and community oriented than those of Protestants, who are more religiously individualistic."*

Catholicism is prevalent in the south of Europe. The Roman Catholic church was established in Rome and is still strongest and most authoritative (within Europe) in the Southern European states of Italy, Spain, and France. Protestantism began in the North of Europe with Martin Luther's efforts in Germany and spread across the whole of the north of Europe, including Sweden, Denmark. The Netherlands and England and Scotland in the following centuries, still finding its strongest European presence in these places. Significant Catholic populations exist in Austria, Belgium, France, Western and Southern Germany, Ireland, Italy, the East and South of the Netherlands, Portugal, and Spain. The largest Protestant populations in Europe live in Denmark, Finland, central, eastern and northern Germany, Sweden, the central and northern part of the Netherlands and the UK (Anglicanism). Calvinism is the strain of Protestantism found in much of the Protestant Netherlands and also in parts of Germany and in Scotland. Lutheranism is found in the Nordic countries of Sweden, Denmark, Finland, and Northern and western Germany.[17]

The prevalence of Protestantism within the NEUMS Cluster and Catholicism within the SEUMS Cluster is thus offered here as evidence: 1) of the existence of two distinct cultural Clusters and 2) that the SUEMS Cluster is high group relative to the NEUMS Cluster when considered from the perspective of CT-GG. Having considered economic freedom, authoritarianism, and religion, I conclude that the SEUMS Cluster is likely to have a cultural orientation which is high group relative to that of the NEUMS Cluster. This is shown in Figure 20 below, which is not an absolute positioning, but a relative one only.

Next, I consider the cultural positioning of the EU organs and agencies, and then from this, the cultural positioning of the EU (comprised of the NEUMS and SEUMS Clusters and the EU organs and agencies).

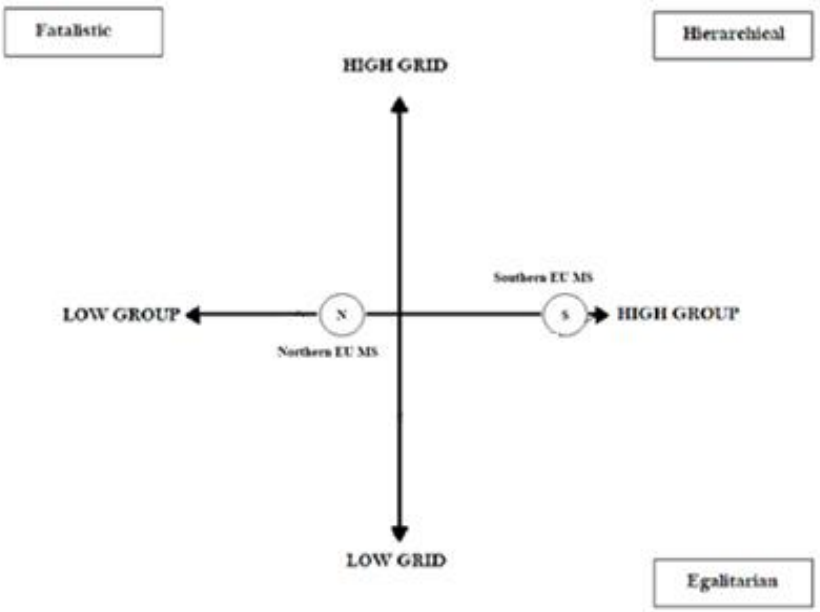

Figure 20 **Preliminary Cultural Positioning of NEUMS and SEUMS Clusters**

17 See Cipriani, Roberto. "Religions in Europe." Religion 39, no. 2 (2009): 109-116.

6.3.1.2 Cultural Analysis of the EU Organs and Agencies

I argue that the cultural positioning of the EU organs and agencies is higher on the grid axis than that of the NEUMS and SEUMS Clusters. In Europe (the continent and surrounding islands) there are several groups, or nations, each of which has an individually recognisable culture and for which cultural differences within the group (nation) are smaller than cultural differences between the groups (nations). However, I have also said there are two Clusters of groups or nations for which it is also true to say – of these two clusters – that the cultural differences within the Cluster are smaller than the cultural differences between the Clusters. The NEUMS Clusters is low group relative to the SEUMS Cluster. In 1957 six of these nations/groups – some from the SEUMS Cluster (e.g., Italy and France) and some from the NEUMS Cluster (e.g., Germany and the Netherlands) sought to cooperate with each other on an intergovernmental level through the Treaty of Rome. Over time, this cooperation expanded in geographical scope to include more group (nations) from the SEUMS Cluster and from the NEUMS Cluster. This cooperation began to expand beyond the intergovernmental sphere to become transnational and later supranational in nature. For this purpose, fixed institutions were established through formal legal institutions for regulating, decision-making and law-making.

These institutions were the organs, and later the agencies. These were always staffed and operated (so far as possible) with decision makers which were taken in equal proportion from EUMS oriented towards both Clusters. The institutions were established to be culturally neutral between the two Clusters. Because they needed to serve the interests of both clusters, the institutions could not be excessively high group in their outlook (i.e., harsh on private enterprise and always expanding the welfare state) nor excessively low group (always

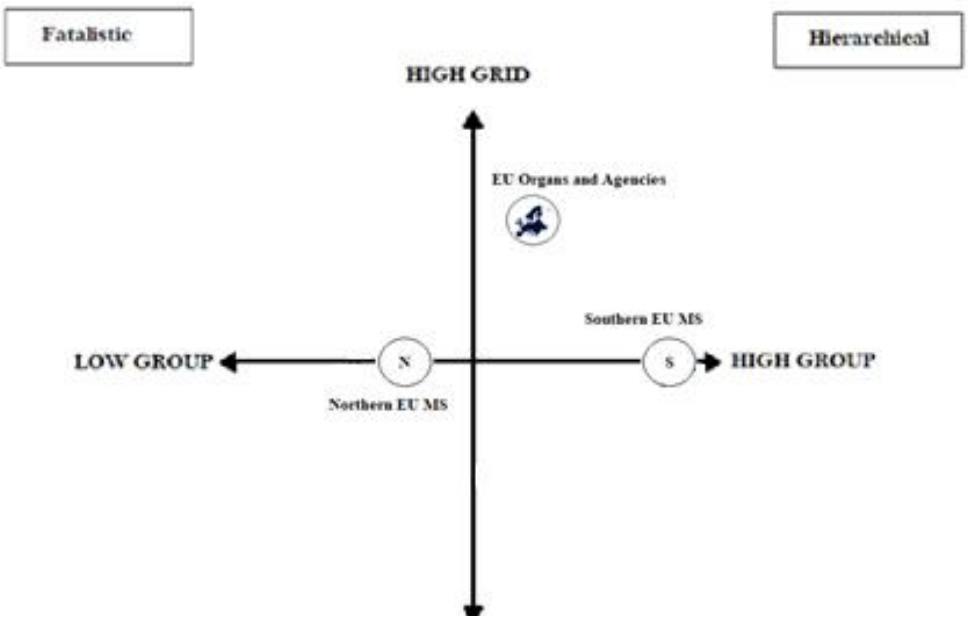

Figure 21 **Cultural Positioning of NEUMS and SEUMS Clusters and EU Organs and Agencies**

Own Figure using Group-Grid Matrix

prioritising private enterprise). As the scope of EU law-making, decision-making and regulation became wider, the organs and agencies were faced with differences of opinion which could not be reconciled amongst the EUMS governments and decision makers from the NEUMS and SEUMS staffing the organs and agencies. The need to find solutions which would be acceptable to all, pushed the EU organs and agencies higher up the grid axis in their cultural orientation. Instead of compromising in the sense of choosing between a high group or a low group approach, instead the decision would usually be made on the basis of technical expertise. The resultant approach is high-grid – as indicated by the predicates set out in Table 73 above - and the cultural orientation of the organs and agencies is high grid relative to those of the NEUMS and SEUMS Clusters. This is shown in Figure 21 above.

Key to this is that on the group axis the EU organs and agencies will fall somewhere in between the NEUMS and SEUMS Clusters. I have already identified the NEUMS and SEUMS Clusters to be low group and high group, respectively, relative to each other. According to the logic of the argument above, because the EU as a supranational organisation, had to compromise between relatively low group NEUMS positions and relatively high group SEUMS positions, it would necessarily fall in between the two on the group axis (at least). Again, where it has been placed specifically is not an absolute or concrete positioning, it is just representative of the fact that the organs and agencies fall in between the NEUMS and SEUMS Clusters on that axis. On the grid axis, because compromise was made possible by adopting a scientific-technocratic approach – which is characteristic of a high grid approach (decision making governed by rules relating to expertise, conventions, and consensus, not directed by pluralistic politics), the EU organs and agencies must be positioned higher up on the grid axis.

A detailed example of how an EU agency adopts a high-grid, technocratic-scientific approach has already been set out in Chapter One and Chapter Two in relation to the EMA. Particularly in its characteristic of, 'science excludes politics' which is contrasted to the US FDA approach of 'politicised science'. That argument is developed further below in this Chapter. In relation to the EU organs and agencies generally: these have historically been characterised as depoliticised and technocratic in nature.[18] The logic is that - because there is a democratic deficit between the EU populace on one hand, and the EU organs and regulatory agencies on the other - then the social frame of reference spoken about by Simon[19] is likely to act less strongly as a premise for decision making for bureaucrats in those agencies than it would (for example) for bureaucrats in US regulatory agencies. As argued above, the reliance upon technical expertise is by design. In constructing a supranational organisation to achieve regulatory harmonisation, the scope for political disagreement amongst EUMS was wide. For the project to be feasible[20] it was required to isolate the agencies and organs to some extent from direct democratic pressure. As such, decision making based on technical expertise became the preferred way of doing things.

18 Radaelli, Claudio M. "The public policy of the European Union: whither politics of expertise?." Journal of European public policy 6, no. 5 (1999): 757-774. Although, as Radaelli notes, we need to be careful what we mean when we use the term, 'technocracy', and reliance upon expertise does not necessarily mean that an issue is depoliticised.

19 Simon, H. A., and James March. Administrative behavior organization. New York: Free Press, 1976.

20 Radaelli (1999).

6.3.1.3 Cultural Positioning of the EU as a Whole

However, the EU as a whole is comprised of more than just its organs and agencies. There are some decisions which can only be made in the Council of Ministers at the intergovernmental level, where ministers directly accountable to the demos in their individual EUMS would and do advocate a high and low group position (variously) on political issues that cannot be answered through expertise. Similarly, individual justices in the Court of Justice of the European Union express their culturally laden interpretation of EU law undoubtedly culturally conditioned by the culture of the EUMS from which they are drawn. In addition to this, political debate does now take place in the European Parliament between the high group and low group approaches which often (broadly) follows the north-south high-low group divide, although its impact on EU policymaking and law-making is limited.

The true 'EU' cultural orientation when it comes to the laws it produces, is therefore some aggregate-average of the relatively high-grid position of the agencies and organs, the relatively high group position of the SEUMS Cluster, and the relatively low group position of the NEUMS Cluster. Thus, I have a positioning for the NEUMS Cluster, the SEUMS Cluster and the EU organs and agencies. The cultural orientation of the EU as a whole – as explained above – is comprised of the cultural orientations of the EUMS plus its own organs and agencies and thus the cultural orientation of the EU falls somewhere in between the three circles representing the Clusters and the organs/agencies, in the shaded triangle shown in Figure 22 below.

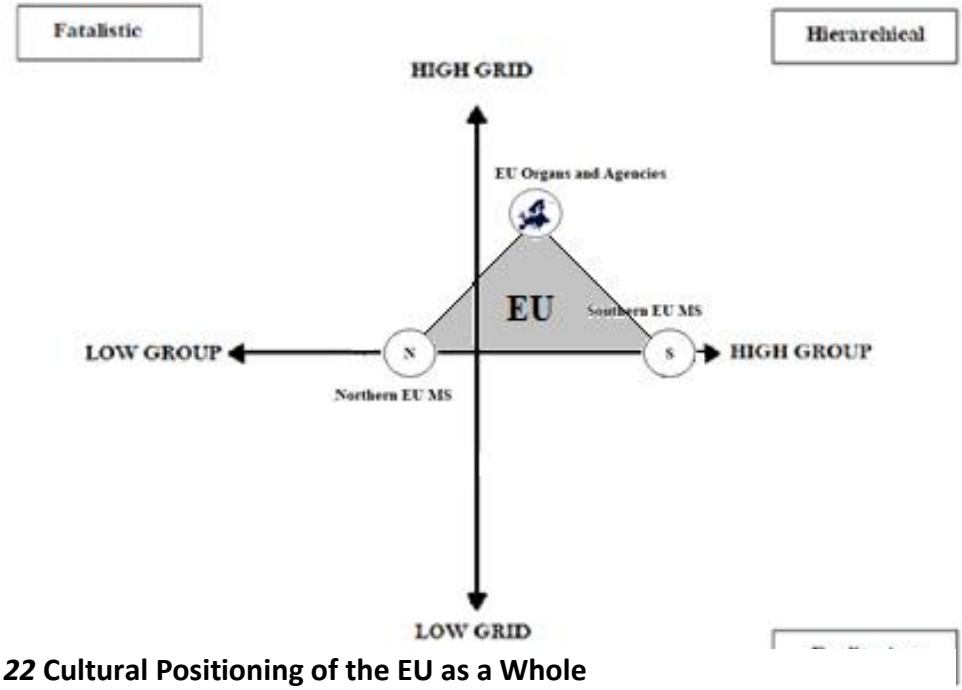

Figure 22 **Cultural Positioning of the EU as a Whole**

Own Figure using the Group-Grid Matrix

To complete the preliminary cultural positioning of the jurisdictions I now need to justify placing the US as low grid and low group relative to the EU as a whole.

6.3.2 Cultural Analysis and Positioning of the US Relative to the EU

I have already stated, above, that the US is agreed by scholars to be one of the most individualistic jurisdictional cultures on earth. There are several additional reasons why I consider it acceptable to position the US as low grid and low group relative to the EU. The first and most important is the level of economic freedom in the US. This is higher than the majority of EUMS and the US is consistently ranked highly in such indices. The ranking of the US relative to the 14 sampled EUMS on the Economic Freedom Index is set out below in Table 76. [21]

Table 76 Economic Freedom Index Score with US and Sampled EUMS

Own table with data taken from fraserinstitute.org

Country	**Economic Freedom Index Score 2020**
Ireland	80.9
UK	79.3
Denmark	78.3
Netherlands	77
UNITED STATES	**76.6**
Finland	75.7
Sweden	74.9
Germany	73.5
Austria	73.3
EU (14) AVERAGE	**71.8**
Belgium	68.9
Portugal	67
Spain	66.8
France	66
Italy	63.8
Greece	59.9

21 https://www.fraserinstitute.org/economic-freedom/map

In addition to economic freedom, I consider a measure of income and wealth inequality. I say that – according to the theoretical insights set out in Chapter Five, and the predicates adopted in Table 73 above under 'Equality and Inequality' – an individualistic jurisdiction is likely to have a more unequal distribution of income and wealth. That is because 1) money is not a perfect medium of exchange for all goods and 2) an individualistic jurisdiction will not take active steps to redistribute income/wealth or to ensure equality of outcomes.[22]

In a rHGHG culture, there may be more barriers to social mobility and less economic freedom (due to external prescriptions holding an individual within a particular place in society). However, one is also more likely to see external prescriptions present which take the wealth of individuals and apply it for the benefit of the group. Whilst in an extreme example of a rHGHG jurisdictional culture this is likely to fix hierarchies in the distribution of wealth and income, these are not so likely to grow over time as in the case of a rLGLG society where the state will avoid interfering in the market to redistribute wealth and income.[23] Therefore, I say that relatively hierarchical and egalitarian cultures are likely to have a lower level of wealth and income inequality overall, than are individualistic cultures. The Gini coefficient[24] represents the distribution of income and wealth within a country. A low coefficient means that income and wealth are evenly distributed (to be expected from relatively high group cultures) and a low coefficient means they are likely to be unevenly distributed, with relatively few holding a larger proportion of wealth and income. The Gini coefficients for the sampled EUMS and the US as of 2021 shown in Table 77 below. The highest and lowest Gini coefficients worldwide are added as a point of reference.

22 In jurisdictional cultures which are relatively egalitarian (relatively low grid and relatively high group) one would expect to see lower levels of income and wealth inequality than in jurisdictional cultures which are rHGHG. However, one would also expect to see both cultures have lower levels of wealth and income inequality than in a jurisdictional culture which is rLGLG. If money were a perfect medium of exchange with which every possible type of good could be bought and sold in satisfaction of unique individual preferences, then in a perfect example of an individualistic culture there would be little or no inequality in levels of wealth and income. That is because markets (of all possible types) would be perfectly competitive, and competition would eradicate differences in levels of wealth and inequality between individuals. Money is not a perfect medium of exchange, however, as certain goods cannot be assigned prices. As such, within individualistic societies those whose preferences favour goods which can be assigned prices are likely to seek maximum income in order to spend it on those goods (because the market is free in a rLGLG culture and these goods are available on the market). There will also be those whose preferences favour the good of wealth itself (the security, satisfaction, or status which comes with being 'rich') and they will amass wealth. Meanwhile, those whose preferences favour non-priced (or non-priceable) goods will seek money less and other things more – e.g. leisure time, interpersonal relationships etc. Meanwhile, because in an individualistic culture the state will not strongly interfere in the market to redistribute wealth between individuals and will respect the preferences of individuals whichever of the three categories they fall in to, one would expect to see relatively large differences in wealth and income. This logic holds even without requiring barriers to social mobility. In a society where it is possible to amass income and wealth (no barriers) you can, at least to some extent, but not everyone will chose to, and the result will be big differences in wealth and income.

23 Meanwhile, in an egalitarian society, the state is likely to actively intervene to remove barriers to social mobility and to promote the poor and weak, in order that outcomes for individuals are relatively equal across the group.

24 https://data.worldbank.org/indicator/SI.POV.GINI

Table 77 Gini Coefficient US, 14 Sampled EUMS, and Comparators

Own table with data taken from World Bank

Jurisdiction	**Gini Coefficient 2021**
Slovenia	24.2
Average of 14 Sampled EUMS	**31.46**
US	**41.1**
South Africa	63

The difference of over 10 is significant, showing that the US has a considerably more unequal distribution of income than the sampled EUMS. I argue that – taken together with the economic freedom score – this is evidence that the US has a jurisdictional culture which is individualistic relative to the jurisdictional culture of the EU.

The final reason comes from history.[25] The US started out as a colonial project of (what later became) the NEUMS. In 1620 when the Mayflower sailed for the American continent it contained settlers from England (then a part of the Kingdom of Great Britain) and sailed from the Netherlands. These settlers were not only Protestant but were separatist Protestants breaking away from established Anglicanism in England due to its links with Catholicism. These settlers, prior to embarking on their voyage, lived in exile in the Netherlands, which at the time had a high level of religious freedom – a key low-group low-grid individualistic right. They established Plymouth Colony which later became a part of the British colony of Massachusetts. Similar journeys were made for similar reasons by Dutch settlers, not only seeking religious freedom but free economic opportunities.

According to my institutional approach to culture, detailed in full in Chapter Five, and in particular how groups come to have identifiable, distinct cultures, a group will form institutions reflecting the cultural orientation at the time it created the institution. Because those institutions are persistent, and newcomers to the group interact with others in the group according to those institutions, group culture remains relatively fixed and stable over time.[26] This is precisely what was done when these colonies were found in the North-Eastern corner of what is now the US. Institutions were created protecting religious and economic freedoms. Those institutions were persistent and shaped the individual cultural biases of newcomers who arrived over the subsequent decades. Certainly, the origins of the modern US are more complex than just the Mayflower. However, it is historical fact that this cluster of colonies on the Eastern seaboard of the modern US came to dominate the entire territory as it stands today, over the following four centuries.[27] Whilst French colonies and Spanish

25 Walls, Stephanie M. Individualism in the United States: a transformation in American political thought. Bloomsbury Publishing USA, 2015.

26 Although certainly not permanently fixed and stable

27 On the relationship between westward expansion and culture: Bazzi, Samuel, Martin Fiszbein, and Mesay Gebresilasse. "Frontier culture: The roots and persistence of "rugged individualism" in the United States." Econometrica 88, no. 6 (2020): 2329-2368, *"The presence of a westward-moving frontier of settlement*

colonies were founded in the South and mid-west and the West respectively – presumably having a more high-group and catholic culture - it was the English colonies which came to dominate. The US, as originally declared and founded in 1776, was comprised of the 13 English colonies using the English language and having institutions which protected social and economic freedoms (individualistic institutions).

Once the US was founded, it came to absorb and dominate the French and Spanish colonies, the culture, and institutions of which did not supplant the culture and institutions of the original English colonies. The Louisiana purchase of 1803 took large areas of French territory for the US, but these territories had to meet the standards defined by the US constitution which was written by individuals from the original English colonies, to be admitted to the US as States. Spanish, and later Mexican territories, were similarly absorbed in later wars and diplomatic moves. It is historically accurate to say, therefore, that the US, today, as a group, is dominated still by those original persistent institutions created by English (and Dutch) settlers in the Northeast of the Country. This further supports a view of the US as individualistic relative to the EU taken as a whole – which is a combination of the high-grid, high-group organs and agencies, the high-group south and the relatively low-group north.

The civil war of 1861-1865 was fought for several reasons, the abolition of slavery being the most cited, and the abolition of slavery was one outcome of the war.[28] Slavery is an archetypal high-grid institution – the complete limitation of individual freedom by external prescriptions.[29] On another level it was a victory for one faction within the US of 1865 – one which supported less stratification in society and greater economic freedom. At this time, the northern cities were becoming urban and industrialised, making value-added products from raw materials which were extracted in the US or imported from abroad.[30] The south was agrarian, and rural, extracting raw materials (famously cotton)[31] using slave labour. Not only was the institution of slavery high grid, but the whole culture of the south was high grid. There were strict social hierarchies and etiquette – informal social rules dictating how individuals of different classes and status may interact with each other.[32] The victory of the Union in the

shaped early U.S. history. In 1893, the historian Frederick Jackson Turner famously argued that the American frontier fostered individualism. We investigate the "frontier thesis" and identify its long-run implications for culture and politics. We track the frontier throughout the 1790–1890 period and construct a novel, county-level measure of total frontier experience. Historically, frontier locations had distinctive demographics and greater individualism."

28 Woodworth, Steven E. Cultures in Conflict--the American Civil War. Bloomsbury Publishing USA, 2000.

29 For a general discussion of the institution and its nature see: Patterson, Orlando. "Recent studies on Caribbean slavery and the Atlantic slave trade." Latin American Research Review 17, no. 3 (1982): 251-275 and Reynolds E., 1993: Stand the storm: a history of the Atlantic slave trade. Chicago (IL): Elephant Paperbacks.

30 The classic argument is set out in: Beard, Charles Austin, and Mary Ritter Beard. The rise of American civilization. Vol. 2. Macmillan, 1927.

31 See Ang, James B. "Agricultural legacy and individualistic culture." Journal of Economic Growth 24 (2019): 397-425: *"This paper presents evidence on the relationship between traditional farming practices and the emergence of individualistic culture. It hypothesizes that agricultural legacies have a persistent effect on the prevalence of modern-day individualistic traits. Individualism emerged in societies engaged in the farming of less labor-intensive crops, whereas interdependence emerged in societies engaged in the farming of more labor-intensive crops. The empirical analyses establish that agricultural legacies have shaped the formation of individualist traits among individuals, pre-industrial ethnic groups, and countries."* Cotton was a highly labour-intensive crop, hence the prevalence of slavery in the deep South and the Confederacy.

32 See Vandello, Joseph A., and Dov Cohen. "Patterns of individualism and collectivism across the United States." Journal of personality and social psychology 77, no. 2 (1999): 279 (abstract): *"The authors created an*

civil war, the abolition of slavery, as well as the victory of the US in the revolutionary war and the abolition of monarchy 100 years previously, become a part of the cultural 'myth' of the US. One of the symbols –a storytelling institution – through which individuals within the group (the jurisdiction) of the US interact with each other.

Preliminary Cultural Positioning of Jurisdictions

History, as well as a present survey of economic and social freedoms, and the scholarly consensus that the US is an individualistic culture thus justify the placement of the US as individualistic relative to the EU. This is shown finally in Figure 23 and Table 78 below.

Armed with this preliminary cultural positioning for the jurisdictions, I now turn to each of the pairs of divergences. Here, I culturally analyse the proximate groups, organisations, and institutions to identify whether the cultural orientation of these matches the preliminary cultural positioning of the jurisdictions set out in this section.

eight-item index ranking states in terms of collectivist versus individualist tendencies. As predicted, collectivist tendencies were strongest in the Deep South, and individualist tendencies were strongest in the Mountain West and Great Plains"

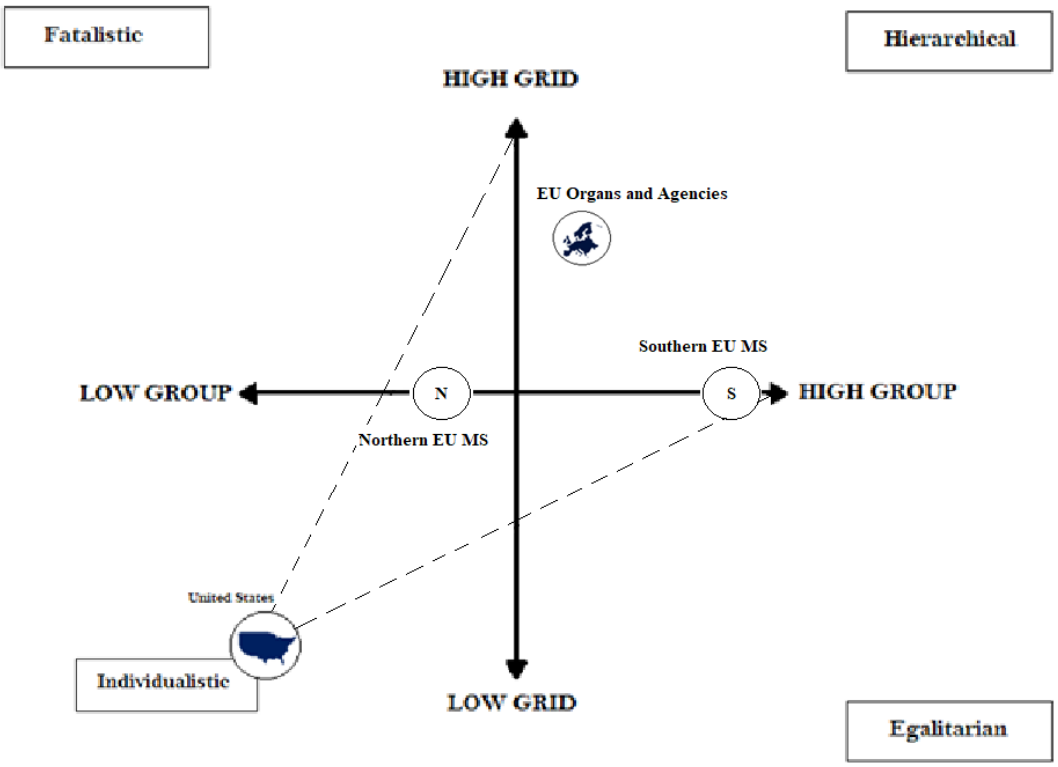

Figure 23 **Preliminary Cultural Positioning of Jurisdictions**

Own Figure using Group-Grid Matrix

Table 78 Preliminary Relative Cultural Orientation of Jurisdictions

Cultural Positioning	JURISDICTIONS		Cultural Positioning
RLGLG	United States	European Union	*RHGHG*

6.4 Licensing and Direct to Consumer Advertising

6.4.1 Proximate Groups, Organisations, and Institutions

Now I must consider the cultural orientation of the organisations, institutions and groups which were proximate to shaping the regulatory positions on licensing and DTCA in the US and the EU. The work of identifying these was complete by the end of Chapters One and Two. The most important groups identified to impact upon the regulation were doctors and consumers in the US and the EU. The proximate organisations are the FDA in the US and the EMA/NAs in the EU/EUMS. The proximate institutions are legal protections of free speech in the US and the EU, and socialised (EU) versus private (US) healthcare.

6.4.2 Culture and the Proximate Groups, Organisations, and Institutions

6.4.2.1 The FDA, the EMA and the NAs

In Chapter One I set out some key characteristics of the FDA, the EMA and the NAs and I show these again in Table 79 below. In this subsection I consider the cultural orientation of these organisations by analysing those characteristics using CT-GG and the predicates set out in Table 73 above.

Table 79 The FDA, the EMA and the NAs Key Characteristics (5)

FDA	NAs/EMA
'Direct to Consumer Accountability'	'Double' (NAs) and then 'Treble' (EMA) 'Insulation'
Relative Resistance to Industry Influence	Capture by Default
Politicised Science	Science Excludes Politics

To recap, 'Direct-to-consumer accountability' and 'politicised science' at the FDA contribute to a cautious approach in licensing because they make the FDA responsive to consumer demands. Because consumers – more than scientists availed of empirical data and statistical techniques – are likely to be susceptible to the cognitive biases set out in Chapter Two, the combination of these two characteristics causes the FDA to be cautious in licensing. In the EU/EUMS, at the EMA/NAs, 'double and treble insulation' for health ministers from consumer accountability, coupled with 'science excludes politics' means that the EMA and NAs do not

have to be responsive to consumers who suffer from those cognitive biases, and instead accommodate industry by default.

Direct-to-Consumer Accountability at the FDA v Treble Insulation at the EMA

Direct-to-consumer accountability at the FDA is assisted by high levels of transparency at the organisation, which make it accessible to consumers. By contrast, the EMA and NAs have long been accused of a lack of transparency, and this contributes to the characteristic of treble insulation. A rLGLG organisation would be expected to be more transparent and thus invite higher levels of public participation than a rHGHG organisation. Velayutham[1] has argued,[2] that relatively high group cultures,[3] struggle with ensuring transparency. By reference to psychological and sociological studies,[4] she links the emotion of shame with high group cultures. In these, second and third party enforcement of social norms is the status quo, and it is paramount to conceal mistakes in order to avoid losing face in public. By contrast, in relatively low group cultures, such as the US, the emotion of guilt is predominant, first party enforcement of social norms is the status quo and there is no impediment to transparency as a means of accountability. She also links hierarchism specifically to a preference for secrecy. One would therefore expect the FDA, if it is a rLGLG organisation, to be more transparent in its procedures than the EMA/NAs and, based upon the analysis of direct-to-consumer accountability and double/treble insulation in Chapters One and Two, this seems to be the case. It is also clear how these behaviours of the organisations disclose institutions which are rLGLG in the case of the FDA and rHGHG in the case of the EMA/NAs according to the predicates set out above in Table 73, in particular under the heading 'Accountability and Blame'.

Direct-to-consumer accountability at the FDA is also facilitated by clear administrative procedures which make public participation possible. Clear, written and published, procedures are expected from a rLGLG organisation. Consumers may access these in order to understand how to become involved in the process, and courts may mediate any dispute between consumers, the agency and other actors, according to these rules.[5] Gelfand notes that highly specific rules (in the form of written law) are more commonly found in individualistic (rLGLG) societies, where they reflect the desire of individuals to be able to plan their own affairs according to a fixed reference point for standards of behaviour. This is in contrast to a rHGHG culture in which there are relatively more standards governing individual behaviour and in which many of these are unwritten and are communicated to individuals through group symbols and behaviour.[6] I noted in Chapter One how many EU agencies suffer from 'multiple accountabilities disorder' and that the result is that chains of accountability are underused because the accountability process as a whole is unclear. This is also caused by the

1 Velayutham, Sivakumar, and M. H. B. Perera. "The influence of emotions and culture on accountability and governance." Corporate Governance: The international journal of business in society 4, no. 1 (2004): 52-64

2 By reference to the lack of transparency which concealed the financial mismanagement which caused the Asian financial crisis.

3 Such as many of those found in East Asia.

4 Velayutham and Perera (2004).

5 Gelfand, Michele J., Beng-Chong Lim, and Jana L. Raver. "Culture and accountability in organizations: Variations in forms of social control across cultures." Human Resource Management Review 14, no. 1 (2004): 135-160.

6 Velayutham and Perera (2004)

highly technical-scientific approach at the EMA which makes it difficult for consumers to understand the process. I concluded that legal rules applicable to the EMA which hold it to substantive decision-making standards[7] have the effect of making the agency less accountable either to the EUMS governments or to consumers because compliance with those standards becomes a technical-scientific question answerable only by the Committee on Medicinal Products for Human Use (CMPH) itself. As such, treble insulation (and a lack of direct-to-consumer accountability) at the EMA is facilitated by a lack of clear rules (accessible to those outside of the agency) governing the EMA's procedures, and this is to be expected from a rHGHG agency.[8] It is clear how these observations are linked to the predicates set out above in Table 73, in particular under the headings, 'Regulation of Transactions,' 'Accountability and Blame,' and 'Innovation and Expertise'.

Politicised Science at the FDA v Science Excludes Politics at the EMA/NAs

A significant factor preventing direct-to-consumer accountability at the EMA/NAs is the technical-scientific approach adopted there. At EU agencies there is a clear preference for accepting the views of experts over those of laypeople. One reason for this is set out above: there is a need to compromise in EU policymaking between EUMS of different cultural orientations, and policymaking would not be possible if every issue were permitted to become politicised. As such, the strategy of EU decision makers has been to base decision-making on supposedly neutral and rational (quantitative, rather than qualitative) scientific expertise, which insulates decision-making against politics.[9] The preference for expert decision-making is also *directly* linked to rHGHG culture. Cultural theory establishes a link between rHGHG worldview and preference for 'expert' decision making.[10] A rLGLG worldview, on the other hand, rejects the notion of 'independent' expert decision making, believing that all scientific research is ultimately coloured by the normative disposition of the researcher.[11] This worldview tends to believe that expert consensus is a hierarchical effort to impose the views and preferences of the group upon the individual. Individualists would, therefore, be much more amenable to lay public input into regulatory decision making.[12] This is what we see in the US at the FDA with *'politicised science'*. The use of a qualitative (not quantitative) framework for evaluating products – for example - reflects a culture which believes that

7 Gehring, Thomas, and Sebastian Krapohl. "Supranational regulatory agencies between independence and control: the EMEA and the authorization of pharmaceuticals in the European Single Market." Journal of European Public Policy 14, no. 2 (2007): 208-226.

8 See Gelfand, Lim, and Raver (2004)

9 Wiener, Jonathan B., and Alberto Alemanno. "Comparing regulatory oversight bodies across the Atlantic: The office of information and regulatory affairs in the US and the Impact Assessment Board in the EU." (2010).

10 Peters and Slovic (1996). Dake, Karl. "Orienting dispositions in the perception of risk: An analysis of contemporary worldviews and cultural biases." Journal of cross-cultural psychology 22, no. 1 (1991): 61-82. Dake, Karl. "Myths of nature: Culture and the social construction of risk." Journal of Social issues 48, no. 4 (1992): 21-37. Slovic, Paul, James H. Flynn, and Mark Layman. "Perceived risk, trust, and the politics of nuclear waste." *Science* 254, no. 5038 (1991): 1603-1607. Kahan, Dan M., Hank Jenkins-Smith, and Donald Braman. "Cultural cognition of scientific consensus." *Journal of risk research* 14, no. 2 (2011): 147-174. Barke, Richard P., and Hank C. Jenkins-Smith. "Politics and scientific expertise: scientists, risk perception, and nuclear waste policy." *Risk Analysis* 13, no. 4 (1993): 425-439.

11 See Mostert, Erik. "The challenge of public participation." Water policy 5, no. 2 (2003): 179-197.

12 Ibid.

politics can and should affect decision making, alongside science. These insights are reflected in the predicates set out in Table 73 above under the heading 'Innovation and Expertise.'

Conclusions: FDA, EMA and NAs

These two characteristics (in each case) are also shaped by the wider jurisdictional culture in which these organisations operate. Double and treble insulation at the NAs/EMA has been necessitated partly by a strong convention of ministerial responsibility in EUMS governments for the reasons set out in Chapter One.[13] The convention essentially embodies the whole ministry within the minister. It says that the entirety of the ministry is collectively responsible and makes the minister accountable. When the minister resigns, that is not understood to be an admission of personal fault, but of the failure of the ministry as a whole.[14] This convention means that bureaucrats within a ministry (or an agency underneath the ministry) keep a relatively low public profile compared to those in the US. In addition, ministerial responsibility[15] results from a centralised, or corporatist or (neo-corporatist) political structure, the former of which was common across the (now) EUMS in the first half of the 20th century and the latter which became common in the second half of the 20th century. These political structures[16] are rHGHG compared to pluralist political structures, which one would expect to find in a rLGLG jurisdictional culture. In these, there are fewer categories of subgroup into which ordinary people may organise and, as such any organisation may challenge government and make use of a free and pluralistic media to do so. In the same way, the role of individuals within these subgroups takes on greater significance, and these individuals have a higher public profile – for example, the head of the FDA. By rendering individuals within an agency accountable to the public through the media, the pluralistic structure enhances direct to consumer accountability of the agency itself by incentivising its bureaucrats accordingly. The effects of the pluralistic structure in the US are also seen in the organisation of women activists during the progressive era (outside of trade unions and established political parties); in the organisation of consumers *as consumers* from the beginning of the new consumer movement; and, from their later organisation as disease specific consumer groups from the 1980s onwards. This was all facilitated by the pluralistic political structure in the US.

A pluralistic political structure, focusing on individuals, their identifiable personal faults, or successes, and aided by free information provided through the media to consumer who may organise independent of established political structures, reflects a rLGLG underlying culture in the political system. It affects the characteristics of the FDA because it necessitates the FDA's responsiveness to consumers. The ability of the NAs and EMA to escape accountability to consumers ('*double and treble insulation'*) in turn results from the convention of ministerial

13 This is argued there to be the reason why the licensing functions were removed from government departments to agencies from the 1980s onwards, and why consumers bring their anger over scandals to ministries and ministers rather than to the agencies in the EU/EUMS.

14 Hence the political significance of ministerial resignations.

15 The convention of ministerial responsibility says the minister must accept blame (and resign) even where he was not at fault directly. Responsibility at the ministry is centralised and falls upon the minister.

16 Strong, centralised, and hierarchical structures of government and/or corporatist structures whereby society must organise into specific groups comprised of factions such as labour, and industry mediated between by government, are high group by definition in cultural terms.

responsibility, and the centralised or corporatist/neo-corporatist structure. In these, ordinary people express political discontent more often through e.g. established political parties and/or trade unions. These aspects of the EU/EUMS political structures are rHGHG compared to the US political structure and they affect the characteristics of the EMA and NAs by making it possible for these to avoid direct-to-consumer accountability. All of the observations in these paragraphs are linked to the predicates in Table 73 above including those under 'Accountability and Blame', 'Regulation of Transactions' and 'Subgroups'.

Underlying jurisdictional culture has helped to shape the cultural orientation of these agencies partly through the institutional structure in which they operate. Key characteristics of the agencies are also directly linked to underlying cultural orientation. 'Direct-to-consumer accountability' and 'politicised science' are clear manifestations of an individualistic cultural orientation at the FDA, and 'double and treble-insulation' and 'science-before-politics' evidence an underlying hierarchical culture at the EMA/NAs. The licensing divergence can therefore be attributed to underlying culture, because it is these characteristics which cause relatively more caution at the FDA and relatively less caution at the EMA and NAs.

6.4.2.2 Doctors, Consumers, and the Doctor-Consumer Relationship

In the case of doctors and consumers, I first analyse each group (in both the US and the EU) finding that US doctors and consumers as groups have rLGLG underlying cultural orientations and that there is a rHGHG cultural orientation for the EU groups. Then, I consider an associated institution, which is the relationship between doctors and consumers in the US and the EU. That institution is shaped by the characteristics of the groups themselves, and those characteristics, I argue, reflect the underlying culture of the groups.[17] In the EU I find that this relationship is hierarchical. In the US I find that this relationship is individualistic. I conclude by explaining how the cultural orientation of the groups, and of the institution, have contributed to the regulation of DTCA and licensing in the US and the EU.

<u>Doctors</u>

In Chapters One and Two I set out some key characteristics of the interest group of doctors in the US and the EU, respectively. These are shown again in Table 80 below.

Table 80 Doctors in the US and EU/EUMS and Relationships/Autonomy (3)

	US	**EU**
Autonomy v the State (hospitals/agencies)	High	Low
Autonomy v Pharmaceutical Industry	Low	High
Autonomy v Consumers	Low	High
Consumer Autonomy	High	Low

17 Arguably, the institution constitutes one characteristic of the groups i.e., what makes US doctors distinct from EU doctors is that they more often accommodate consumers. See Chapter Five for the full explanation of the relationship between groups, institutions (including those which guide group behaviour) and culture.

History explains the characteristics set out in Table 80. In Europe, many centuries ago, physicians generally were of noble birth and would only treat wealthy high-social status patients.[18] They had no reason to journey to the American colonies in the 1600s or the 1700s. There was little to offer them there in terms of economic opportunity and social status that they did not already have in Europe.[19] What this meant on the north-eastern American continent was that for the 1600s, 1700s and much of the 1800s, there were very few qualified and educated medical practitioners. At this time, according to Daniels,[20] (summarising Starr)[21] *"during early American history and through most of the nineteenth century, the medical profession lacked the cultural authority and power it now enjoys…."* There was no licensing or regulation of access to the profession, and Daniels asks how an interest group with the current power of US doctors avoided capture by hospitals.

The argument of Starr is that US doctors were able to coordinate effectively, and Daniels contrasts this with the position in Europe where doctors were not able to do so, despite their strong barriers to entry. Daniels argues that this is because, "*European physicians were often divided into a hospital-based group, an aristocracy among physicians, and general practitioners. Focus on their different interests may well have blocked them from finding common solutions to the problem of incorporation by hospitals…".* He attributes the failure of European doctors to coordinate as due to their *"more rigidly class-divided history."* Thus the relatively low level of barriers to entry (stratification of the profession) on the American continent amongst doctors in the 1600s to 1800s actually assisted them in gaining power later on. To Daniels' and Starr's argument that US doctors effectively *coordinated* as a result of this, I add the observation that they were also obliged to *compete* with each other, too. They competed *downwards* for consumers and coordinated *upwards* vis a vis the state (hospitals/agencies). European doctors, who did not compete for their wealthy patients, stratified into classes and weakened themselves in efforts to coordinate against the state in later centuries. US doctors maintained their autonomy against the state and European doctors lost it. The implications of this, however, were that US doctors had to offer high levels of autonomy to consumers in their healthcare, whilst European doctors did not.

These behaviours exhibited by the historical and current groups of US and EU/EUMS doctors reflect several of the predicates set out in Table 73 above. In particular, those listed under 'Social Roles and Social Mobility', 'Regulation of Transactions', 'Competition and Profit',

18 Kronus, Carol L. "The Evolution of Occupational Power: An Historical Study of Task Boundaries between Physiclans and Pharmacists." Sociology of Work and Occupations 3, no. 1 (1976): 3-37.

19 With their high (blood based) barriers to entry and refusal to innovate and expand their client base, these noble doctors in Europe eventually put themselves out of business and social change in Europe in the 1800s and 1900s meant that pharmacists (then: apothecaries) who had few scruples about treating the poor found that they could treat the poor and earn a lot of money from doing so as a result of the large number of clients available (and the fact that the formerly poor were experiencing greater levels of wealth and income as these centuries progressed). In the north of Europe (particularly the UK) these apothecaries simply took over from 'noble' doctors and became the modern General Practitioners. In the south they became modern pharmacists but with a much higher social status and aura of 'expertise' than the pharmacists found in the modern United States (who instead were absorbed into large retail operations). Kronus (1967).

20 Daniels, Norman. "Understanding physician power: A review of the social transformation of American medicine." Philosophy & public affairs (1984): 347-357.

21 Starr, Paul The Social Transformation of American Medicine (New York: Basic Books, I983)

'Welfare State' and 'Subgroups'. One would expect a rLGLG group of doctors to coordinate and to compete with each other, on equal terms as individuals, rather than under the umbrella of the state through its control over hospitals and socialised healthcare agencies. Competition is a hallmark of individualistic cultures, as is individual autonomy. In the EU/EUMS, stratification – in the form of elite hospital doctors and community gatekeeper doctors – reflects an underlying rHGHG culture for this group of doctors. Their eventual employment or control by the state through hospitals and agencies also reflects underlying rHGHG culture. This resulted both from the institutional structure in which EU/EUMS doctors operate (socialised healthcare) and from the group preferences of EU/EUMS doctors themselves, who voluntarily coordinated in two (hierarchical) groups and submitted to state control through socialised healthcare. Conversely, the institutional structure in the early United States – a frontier environment lacking stratification or regulation – shaped the development of US doctors as a rLGLG group.The rLGLG cultural orientation of US doctors is evidenced currently by several of their characteristics. Their autonomy vis a vis the state is one. Their successful protection of their right to prescribe off-label is another.

The partial vertical integration (close alliance, or capture) of US doctors with/by the US Pharmaceutical Industry (USPI) is also reflective of rLGLG culture. This is shown in the seeking and receipt of kickbacks from detailers, through sponsorship of products in the media as scientific 'opinion-leaders', through cooperation with USPI in conducting privately contracted clinical trials and the other examples of medical neoliberalism set out in Chapters One and Two. All of these will be expected from a group comprised of individuals who consider there to be few limits (and for whom, in fact, there are few limits) on their economic freedom to bid, bargain and transact in satisfaction of their preferences. The relative preference of US doctors for monetary payment over social esteem in remuneration of their work is also influenced by the institutional structure. Where DTCA is permitted and therefore the advice of the doctor is relatively more often questioned by consumers, and where market forces compel doctors to accommodate consumers demands to retain consumers, then those entering the profession are relatively less likely to do so out of a desire to obtain social status and esteem. US doctors have tacitly chosen money, instead, over the course of their history. Although, indeed, in a rLGLG society wealth itself may be the final determinant of social status, in contrast to a rHGHG society where noble birth or educational qualifications may matter more. In the EU/EUMS where doctors have much less economic freedom to enter into the medical neoliberal arrangements seen in the US, the importance of the status of doctors as experts whose advice is to be taken and not negotiated, is relatively more important. This, too, is a product of the institutional structure in the EU/EUMS, with socialised healthcare, a lack of competition between doctors for patients, and a lack of DTCA. I conclude that US doctors as a group have a rLGLG cultural orientation compared to EU/EUMS doctors which have a rHGHG cultural orientation as a group.

Consumers

In Chapters One and Two I set out some key characteristics of the interest group of consumers in the US and the EU, respectively. These are shown again in Table 81 below.

Table 81 Consumers in the US & EU/EUMS: Characterisation/Relationships (2)

	US (activist)	**EU (passive)**
Relationship with Government	Vigilance/activism	Passive acceptance of benefits
Relationship with Agencies	Activism: use of media	Focal point is Ministers instead
Relationship with Doctors	Market power/autonomy	Social esteem/accept advice

The institutional structure has shaped the cultural orientation of consumers as a group in the US and the EU. The US is a clearer example of a consumer society than many EUMS – as set out in Chapter One. And the extent to which a society is consumerist is correlated with the salience to consumers within that society of their position as consumers. Thus, in a strongly consumerist society consumers easily see their potential to organise and lobby as consumers. Consumer society is linked to a high level of economic freedom, which is linked in turn to an underlying rLGLG culture – see the predicates listed in Table 73 above under 'Regulation of Transactions'. This is less the case in many EUMS, which have a rHGHG culture. In addition, a rLGLG pluralist political structure in the US allowed ordinary people to organise outside of, and express political discontent through other means than, established political parties and trade unions. A rHGHG centralised, corporatist or neo corporatist political structure in the EU/EUMS meant that most ordinary people did so through established political parties and/or trade unions, and the convention of ministerial responsibility in the EUMS governments meant that health ministers became a focal point for outrage over any pharmaceuticals scandal.[22] See also the predicates set out in Table 73 above under the heading 'Subgroups'.

Now I analyse the active-passive characteristic of consumers shown above in Table 81. This, too, has resulted from the institutional structure in each case. A lack of socialised healthcare and comprehensive welfare state in the US necessitated vigilance and activism on the part of US consumers. Also, their objectives as a group were narrowed to the liberal market-oriented focus of accurate price-quality combinations in products due to the McCarthyism era forbidding more radical objectives. Similarly, in the EU/EUMS, the provision of benefits in the form of socialised healthcare, the welfare state and consumer protection legislation passed by the EUMS in tandem with the EU meant that EU/EUMS consumers have had less reason than their US counterparts to be vigilant or activist. Ministerial responsibility, socialised healthcare, the welfare state and much of EU consumer protection legislation are rHGHG institutions. In addition to the rLGLG pluralist political structure in the US, vehement political opposition to communism and socialism in the 1950s reflects a political structure which is committed to liberalism and individualism, indicating that it is rLGLG. Both the predicates listed under, 'Welfare State' and 'Subgroups' in Table 73 above are relevant here.

22 This was reinforced by the fact of socialised healthcare which meant that the minister was de facto in charge of all of healthcare in the EUMS.

However, I consider that the activism of US consumers is also directly linked to an underlying rLGLG cultural orientation. I believe this is evidenced by the tradition of consumer activism in the US which stretches back well beyond the 20th century. As Glickman notes,[23] consumer activism in the US results from the understanding that individual consumers have of their importance in a market network and the power they wield through individual consumption choices. He describes this as *"almost exaggerated*." This indicates underlying values in those individuals – and shared values in their group cultural orientation – which attach great significance to the act of transacting in the market. This act, and freedom to undertake this act, is the core characteristic of the individualistic worldview. It is low group because it prioritises individual preferences over group preferences: the individual may swap something he values less for something he values more with another individual who values those things the opposite way around, even if society values both things equally. It is low grid because there is no restriction at all placed on the freedom to transact. The individualist is free to seek or offer any price he wishes. He is entitled not to part with the thing which is sought unless his own valuation is met – because the thing is protected for him by a property right and thus, he can exclude others from use or possession of it. Clearly this is linked to the predicates in Table 73 above under the heading 'Regulation of Transactions'.

The act of transacting therefore has a special status in a rLGLG society. One would thus expect that in a rLGLG society individuals would also make use of this act to wield political power. That is what was happening in the earlier examples of consumer activism, where boycotts and buycotts sought to achieve various socio-political objectives. In the era of the new consumer movement, again the individualist understands the significance of his position as a consumer transacting for goods and services. Now, however, the salience of this position and of the act of transacting highlights his vulnerability vis a vis other actors in the marketplace. This prompts his vigilance and activism, to fight for price and quality combinations in products which are accurate, which is what US consumers did through Senator Kefauver in 1959-1962. In a rHGHG culture the position of the ordinary person as an individual consumer, and the significance – to him - of his act of transacting, is relatively less salient. If he seeks political change he goes through political parties or takes to the streets in protest. If he feels vulnerable, he accepts the welfare of the state. If, to finance this, the state is required through external prescriptions to tax transactions, redistribute wealth or otherwise interfere in the marketplace, then this is acceptable in his worldview for the good of the group. That is relatively more often outlook of the ordinary individual in a rHGHG culture than in a rLGLG culture.

My conclusion therefore is that US consumers as an interest group have the activist characteristic because it reflects an underlying rLGLG cultural orientation for that group, which in turn is partly shaped by the institutional structure of the jurisdiction in which the group operates. In the EU/EUMS, in relative terms, the passive characteristic is shaped by the institutional structure and the corresponding cultural orientation is rHGHG.

23 Glickman, Lawrence B. *Buying power: A history of consumer activism in America*. University of Chicago Press, 2009. See also Glickman, Lawrence B. "" Buy for the Sake of the Slave": Abolitionism and the Origins of American Consumer Activism." *American Quarterly* 56, no. 4 (2004): 889-912.

The Doctor-Consumer Relationship

The interaction between doctors and consumers in the US and the EU forms and is governed by the associated institution of the doctor-consumer relationship. This institution has helped to shape the transatlantic divergence in licensing and DTCA. First, I consider that institution, and then I consider how it has shaped the divergence.

The doctor-consumer relationship in the EU/EUMS is rHGHG compared to the doctor-consumer relationship in the US.[24] Because – as set out in Chapters One and Two – EU/EUMS consumers passively accept the advice of EU/EUMS doctors and EU/EUMS doctors have no need to compete with each other for consumers, there is a clear power dynamic between doctors and consumers in the EU/EUMS.[25] Consumers have nothing to threaten doctors with: they have relatively little choice over the identity of their doctor, and doctors mostly do not rely on consumers directly for fees. There is little scope for the consumer to negotiate the doctors advice. Neither does the consumer wish to negotiate that advice. The consumer's attitude is shaped both by the institutional structure – socialised healthcare -and also by the consumer's own cultural worldview (rHGHG) which tells her that the doctor's advice, as an expert, is to be accepted and acted upon. I argue in a later section of this chapter that a relatively high group cultural worldview moves a holder to perceive all synthetic pharmaceutical products as inherently dangerous, and as such the advice of experts is key. It is not for those of a rHGHG worldview to ask the doctor for anything specific. Neither would the rHGHG consumer want a source of information other than the doctor: no one else is more 'expert' in giving this advice and, anyway, the doctor's advice is completely free at the point of provision in many EUMS. For their part, doctors in the EU/EUMS most likely entered medicine in the first place to a greater extent than a US doctor had, for reasons of seeking social esteem.[26]

Thus, in the US, patient centred medicine was produced by the market as the form of medical service preferred by consumers – an individualistic (rLGLG) conception of the doctor-consumer relationship whereby each party transacting for the service is seen as an individual transacting for that service on equal terms. In the EU/EUMS the relationship is more hierarchical (rHGHG). These observations are linked to the predicates set out in Table 73 above under the subheadings, 'Innovation and Expertise', 'Welfare State', and 'Social Roles and Social Mobility' as well as to the insights developed relating to the myths of nature as set out in Chapter Five (concerning consumer perceptions of pharmaceutical product risks).

The transatlantic differences between this institution have contributed to the divergence in DTCA and licensing. First, the existence of DTCA in addition to the individualistic doctor-consumer relationship places pressure on the FDA to be cautious in licensing. That is because doctors cannot be so strongly relied upon to act as safety gatekeepers as they can in the EU/EUMS. The advice of US doctors is always up for negotiation with patients who wield market power and thus doctors are incentivised to take risks in prescribing (on the demands

24 Dent, Mike, and Majda Pahor. "Patient involvement in Europe–a comparative framework." Journal of Health Organization and Management no. 5 (2015)

25 See Gelfand (2004)

26 Real incomes of most EU/EUMS doctors are lower than for US doctors. EU/EUMS doctors receive part of their compensation in the social esteem they receive and their acknowledgment as experts in society. I develop this point further in relation to EU/EUMS pharmacists below.

of consumers exposed to DTCA). This leads to a potential for catastrophic type II errors and so the FDA must exercise additional caution.[27] Secondly, in relation to licensing in the EU, the EMA is enabled to be relatively fast when licensing new products, knowing that rHGHG EU/EUMS doctors will ensure additional safety oversight through their consumer-product matching process, and that EU/EUMS consumers will abide by this. The cultural orientation of doctors and consumers, therefore, is one key element in understanding why the US chooses the configuration which it does. The FDA cannot be less cautious in licensing because it cannot rely so much upon doctors to act as safety gatekeepers. The opposite is true at the EMA/Nas.

6.4.2.3 Free Speech Protections

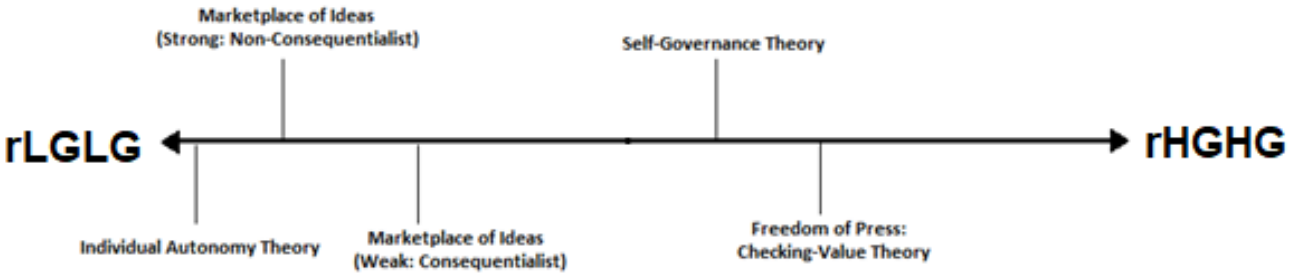

Figure 24 **Culture and Theories of Free Speech**

In Chapter Two I set out crucial differences between the US and the EU in terms of the legal institution of free speech protection. I also considered differences in the theoretical underpinnings of the free speech jurisprudence in the US and the EU. I now turn to consider whether these differences reflect underlying cultural differences. I conclude that they do. The strong version of the marketplace of ideas theory[28] trusts in human rationality a priori. The weak version does not, but it stops short of banning commercial speech based on paternalistic principles. Thus, the marketplace of ideas theory as a whole subjects human actions to fewer external prescriptions than the self-governance theory, which would accept restriction of commercial speech as it is merely 'private' speech. The marketplace of ideas theory is thus rLGLG compared to the self-governance theory as it is more trusting in individual autonomy and rationality and does not accept restriction of that individual autonomy for the good of the group. The various theories of free speech are set out above in Figure 24, and placed on a spectrum between rLGLG and rHGHG approaches.

The caselaw of the US Supreme Court (SCOTUS) is certainly closer to the marketplace of ideas theory than is that of the European Court of Human Rights ECtHR. The caselaw in the US is thus rLGLG to that of the EU. The ECtHR caselaw and free speech protections in the EU in general are associated with the self-governance and checking-value theories. These are rHGHG approaches. The basic purpose of the checking-value and self-governance theories is a high group one. It is the preservation of the democratic system as a whole which matters

27 It does this through licensing rather than by curbing DTCA for the reasons set out below relating to free speech.
28 Also, the more extreme theory of individual autonomy (which focuses on the speaker, rather than the listener).

here, rather than the autonomy of any given individual to receive or to broadcast ideas. As such, a legal institution of free speech based upon these ideas is more willing to set out limits to free speech through legal prescriptions in order to secure group goals.[29] This is a rHGHG approach. The jurisprudence of the ECtHR is less closely related to the theories giving prominence to individual autonomy such as the marketplace of ideas theory, and this reflects a distrust of individual human rationality and autonomy. It is thus further away from individualism than the approach of SCOTUS. The differential adoption of the theories of free speech in the jurisprudence of SCOTUS and the ECtHR reflects the predicates set out in Table 73 above under 'Regulation of Transactions' where the market regulated in this case is the market in ideas.

As set out in Chapter Two, the form of the free speech institution in the US and the EU has contributed to each jurisdiction's choice of configuration (the divergence) because it makes it difficult for the FDA to legally ban or restrict DTCA. In the EU, a move to overturn the ban on DTCA on free speech grounds would be unlikely to succeed due to the form of the free speech institution there.[30] Necessarily, therefore, the US opts for the configuration in which it exercises caution in licensing instead, and also relevant to this is the fact that the FDA cannot rely to a great extent on doctors to act as safety gatekeepers). In the EU, the initial choice of configuration, however, is likely to be due to the institution of socialised healthcare, which means that DTCA would place a strain on healthcare budgets. In the final subsection below, therefore, I consider the cultural orientation of the institution of socialised healthcare v private healthcare.

6.4.2.4 Socialised Healthcare v Private Healthcare

A rHGHG culture is more likely to implement systems of social insurance for the provision of healthcare. This is because those with a rHGHG worldview have been shown to feel less individual responsibility,[31] whilst those in individualistic cultures feel strongly personally responsible for meeting their own needs.[32] As such, a rLGLG group is more likely to implement a system whereby the individual bears responsibility for their healthcare costs directly via private insurance, as is the case in the US. In the rHGHG EU, private insurance is often heavily subsidised and often healthcare is made free at the point of use - paid for through general taxes. A rLGLG culture prizes the ability for individuals to transact on the market. They therefore reject monopoly power, which harms the market.[33] Meanwhile, in many EU systems, supply is centrally matched to demand by a monopsony buyer of doctors' services

29 Parmet, Wendy E., and Jason A. Smith. "Free speech and public health: A population-based approach to the First Amendment." Loy. LAL Rev. 39 (2006): 363.

30 I additionally point out that the ECtHR's style of reasoning in applying the margin of appreciation doctrine is high group, as it considers what the group of member states of the Council of Europe have in common, as an input to the interpretation of the meaning of European Convention on Human Rights (ECHR) rights.

31 See Gelfand (2004). Velayutham and Perera (2004)

32 See Kemmelmeier, Markus, Edina E. Jambor, and Joyce Letner. "Individualism and good works: Cultural variation in giving and volunteering across the United States." Journal of Cross-Cultural Psychology 37, no. 3 (2006): 327-344.

33 Kemmelmeier (2006) As such, in the individualistic US there is widespread competition between doctors for patients and between hospitals for both doctors and patients.

and monopoly supplier of healthcare funding in socialised healthcare systems.[34] This latter approach reflects a culture in which some goods are seen as not appropriate for being left entirely to the market, and in which case government has a crucial role in provision. This is typical of high group cultures.[35] The effect of socialised healthcare in the EU is to shape the doctor-consumer relationship (which itself shapes the regulatory divergence) and, also to make it financially difficult to permit DTCA in the EUMS because this would lead to serious budget pressures either directly or through subsidy of private health insurance. I conclude that socialised healthcare is a rHGHG institution whilst private healthcare is a rLGLG institution, and that the shape of these institutions in the US and EU has contributed to the divergences in licensing and DTCA. Clearly, both institutions are linked to the predicates in Table 73 above under the subheadings of, 'Welfare State', 'Competition and Profit', 'Equality and Inequality' and 'Regulation of Transactions'.

My conclusion for licensing and DTCA is that the groups, organisations and institution which are most proximate to the shaping of the regulatory position in each jurisdiction have a cultural orientation which - in each case – matches the preliminary cultural positioning of the jurisdiction in which they exist. As such, CT-GG has provided additional explanation to that provided by the extant theories in the case of licensing and DTCA, and that explanation – i.e., the underlying cultural orientation - is consistent across both divergences

34 There is, of course, a range of systems within the EU.
35 By definition.

6.5 Pharmacovigilance and Product Liability

6.5.1 Proximate Groups, Organisations, and Institutions

The most important groups identified to impact upon the regulation in pharmacovigilance and product liability were the pharmaceutical industry and lawyers in the US and the EU. The proximate organisations are the FDA in the US and the EMA/NAs in the EU/EUMS. The proximate institutions are the legal systems in the US and – as I argue below – the theories of justice backing up those legal systems. In addition, there is the norm of litigiousness in the US (and the opposite in the EU/EUMS) and socialised healthcare in the EU/EUMS versus private healthcare in the US. I have already culturally analysed the organisations and socialised/private healthcare as institutions, so here I focus on the remaining objects for cultural analysis.

6.5.2 Culture and the Proximate Groups, Organisations, and Institutions

6.5.2.1 The Pharmaceutical Industry

In Chapter Three I set out how USPI and the EU Pharmaceutical Industry (EUPI) have affected the regulation of pharmacovigilance and product liability in their respective jurisdictions. I said that this resulted from differences in their lobbying priorities as set out in the final column of Table 82 below.

Table 82 Pharmaceutical Industry in the US and the EU (3)

Institutional Framework	Relationships	Business Model	Lobbying Priorities
United States (USPI) No price regulation Less socialised healthcare DTCA	**Adversarial** Intense competition intra-USPI Arms-length with FDA Tolerated by consumers BUT: Allied with US Doctors	**Blockbuster Model: USPI** More innovation less manufacturing Blockbuster products Profit maximise	**Embrace risk:** Permit high punitive damages but liability must be tied to fault
European Union (EUPI) Price regulation Socialised healthcare No DTCA	**Corporatist** Avoid intense intra-EUPI competition Cooperate with EMA/NAs Estranged from consumers	**Stability Model: EUPI** More manufacturing less innovation Stable returns on capital in EU Profit satisfice	**Avoid risk:** Harmonise EUMS regulation of product liability Cap total damages but EUPI will act as insurer of last resort for consumers even without fault

In these paragraphs I assume that the institutional framework in each case reflects underlying jurisdictional culture. This has already been argued to be the case above for DTCA and socialised healthcare and is argued to be the case below for price regulation. Before turning specifically to USPI and EUPI I first ask what one would expect – based upon theoretical insights – the business model and relationships of a pharmaceutical industry interest group would be where it operates in a rLGLG and rHGHG jurisdictional culture, respectively. Then, having assumed that the institutional framework reflects underlying jurisdictional culture, I ask how the real-world relationships and business models of USPI and EUPI are 1) shaped by that institutional framework and 2) directly influenced by jurisdictional culture. Finally, I ask whether the expected position matches the position in reality.

United States Pharmaceutical Industry

Beginning with the business model and relationships: one would expect a high degree of inter-firm (intra industry) competition from a group which operates in a rLGLG jurisdictional culture. This is because individualism places no or few constraints upon the economic freedom of a firm to compete and allows those who compete to retain the rewards of successful competition. Incentives are thus set to compete and to win. Because innovation - by extending the production possibility frontier for any given firm – grants a competitive advantage to that firm, then a relatively high degree of competition based upon innovation is expected. Because

success in the market is measured in profits, the reason for innovating will be the maximisation of profit. This will skew the type of innovation towards those products which are likely to return the maximum profit on investment in innovation. As such one would expect a pharmaceutical industry interest group operating in a rLGLG jurisdictional culture to develop a business model based around profit maximising blockbuster products. These aspects of the behaviour of USPI disclose institutions governing that group which are linked to the predicates in Table 73 under 'Competition and Profit,' 'Regulation of Transactions' and 'Innovation and Expertise'.

On relationships: the expected level of competition intra-industry (inter firm) is high, for the same reasons. Because close cooperation with the regulator will put any given firm at a competitive disadvantage vis a vis other firms, and because it is difficult for all firms in the industry to coordinate with each other and agree a fixed level of cooperation with the regulator. The danger of defection granting a competitive advantage to the defector is also present. Therefore, it is expected that the industry interest group will have a relatively uniform arms-length relationship with the regulator in the case of each firm. An adversarial network of relationship will thus develop both intra-industry and between the industry and the regulatory agency and the consumers which the agency protects. To some extent this aspect of the behaviour of USPI is linked to the Table 73 predicate of 'Regulation of Transactions'.

This (as is set out in Chapters One and Three and in Table 82 above) is observed to be the case for USPI, its business model and its internal relationships, and its external relationships with the FDA and consumers. How is this also shaped by the institutional framework? The lack of price regulation increases incentives to USPI to compete (through innovation) by declining to cap the financial rewards for innovation. The permission of DTCA raises the potential reward from innovation. Finally, the lack of socialised healthcare leads to increased competition because it removes the safety net of guaranteed demand for the industry.[1] Competition thus becomes competition for survival, and innovation - being the key to competition - becomes a necessity for survival. These aspects of the institutional framework are linked to the Table 73 predicates under 'Regulation of Transactions' (DTCA) and 'Competition and Profit' and 'Welfare State' (price regulation/lack of socialised healthcare).

I wish to introduce two further aspects of the institutional framework here, which I say also contribute to the high level of innovation and which I say are also shaped by jurisdictional culture. The first is labour market regulation. For a rHGHG firm within a rHGHG industry (group) individual employment is likely to be long term relative to that found in a rLGLG firm within a rLGLG group. That is because in a jurisdiction with rHGHG culture labour regulation will encourage relatively fixed and stable long-term employment within one firm on one career path.[2] By contrast, in a rLGLG culture labour market regulation will be weaker, and the labour market will be more flexible. This is clearly linked to the Table 73 predicates under 'Regulation of Transactions'.

As a result in the latter individuals who specialise as researchers are more likely to move between firms within the industry and other organisations related to the industry which

1 From the bulk purchase of products by government for the healthcare system.

2 See Douglas J. Institutions of the Third Kind: British and Swedish Labour Markets Compared. Journal of General Management. 1989;14(4):34-52. doi:10.1177/030630708901400403

specialise in research such as universities. The high turnover of individuals between firms and research organisations encourages collaborations between the two and leads to specialisation which is efficient and raises overall levels of innovation. By contrast in a rHGHG culture there will be less labour mobility between firms and other organisations and more lifelong employment within a given firm due to the stronger labour regulation. This will lead to more in-house innovation which is less likely to be efficient than collaborative innovation between other organisations and industry firms. Kneller has suggested that this is the case in Japan, where the culture of the industry is rHGHG to either the US or the EU and the innovation level of the Japanese pharmaceutical industry is low compared to both. He puts this down to a tendency for innovation to take place in-house.[3] This is also more often the case in the EU due to stronger labour market regulation[4] which makes it more difficult to hire and fire workers relative to the situation in the US. This encourages a practice of in-house innovation in EUPI firms relative to USPI firms and leads to lower innovation in EUPI firms relative to USPI firms. This shows how overall levels of innovation in EUPI vis a vis USPI is linked to an underlying rHGHG group culture in the former via the mediating influence of labour market regulation, one part of the institutional framework.

The second is jury-determined punitive damages awards in product liability cases. This is a part of the institutional framework and in Chapter Three I have set out the differences between the US and EU approaches. I said there that punitive damages awards in product liability suits against pharmaceutical firms represents court based 'backup' mediation of the relationship between US consumers and USPI, where the FDA has failed (or, rather, has been unable) to protect consumers. The possibility of very high punitive damages affects the extent to which USPI will cooperate with the regulator, particularly on pharmacovigilance. Cooperation will risk the revealing of information which would later provide evidence for a claimant consumer in a product liability claim, and thus the institutional framework disincentivises close cooperation. However, punitive damages are necessary within this adversarial matrix of relationships. The lack of price regulation coupled with a lack of socialised healthcare mean that USPI wins very large profits which are highly salient to consumers who face high private insurance premiums. This is not sustainable in the long run where consumers have the ultimate political power in a democracy. Punitive damages give consumers a reason not to demand price regulation. These keep the adversarial matrix of relationships in equilibrium, and they too contribute to the business model of USPI in that ever greater innovation and profit maximisation is required in order to protect against the liability risk posed by punitive damages awards. The US legal system's reliance upon individual initiative to seek legal remedies rather than reliance upon the welfare state (including own payment of legal fees) is linked to the Table 73 predicates under 'Welfare State' and 'Accountability and Blame' as well as 'Regulation of Transactions'.

I have speculated as to what the relationships and business model of a pharmaceutical industry interest group, operating in a rLGLG jurisdictional culture would be, based on the core theoretical insights of individualism.[5] I have described how the business model and

3 Kneller, Robert. "Autarkic drug discovery in Japanese pharmaceutical companies: insights into national differences in industrial innovation." *Research policy* 32, no. 10 (2003): 1805-1827.

4 See Standing, Guy. "Globalization, labour flexibility and insecurity: the era of market regulation." European Journal of Industrial Relations 3, no. 1 (1997): 7-37 and Rhodes, Martin. "The future of the social dimension: labour market regulation in post-1992 Europe." J. Common Mkt. Stud. 30 (1992): 23.

5 As set out in Chapter 5: Cultural Theories

relationships of USPI are shaped by the institutional framework which is assumed (and shown above and below) to be shaped by the rLGLG jurisdictional culture. I have introduced and explained also how the institutions of labour market regulation and jury determined punitive damages awards in product liability cases form a part of the institutional framework, how these are shaped by jurisdictional culture, and how these contribute to the business model and relationships of USPI. I conclude that there is a match between what is expected from a pharmaceutical industry interest group operating in a rLGLG jurisdictional culture based upon theory, and the reality of the business model and relationships of USPI. I therefore conclude that USPI is a rLGLG group. Further, its underlying rLGLG culture sits underneath its lobbying priorities as set out in Table 82 above, and these have contributed to the transatlantic and system divergences.

European Union Pharmaceutical Industry

Turning to the EU, to EUPI and what one would expect based upon theory, much of this is the inverse of what is set out above for rLGLG USPI on business model and relationships. One expects less competition due to the rHGHG jurisdictional culture in which a group such as EUPI operates. Partly due to this one also expects less innovation and that it will be easier – due to reduced relative competitive pressure – for any given firm in that group, as well as the group, to cooperate with the regulatory agency.

This – as set out in Chapters Three and One and in Table 82 above - is observed to be the case for EUPI, its business model and its corporatist relationships both inter-firm (intra industry), and with the EMA, the NAs and with consumers. How is this also shaped by the institutional framework? Socialised healthcare reduces competitive pressure by providing a guaranteed market and guaranteed demand. Price regulation is the backup threat which prevents EUPI from abusing that safety net and thus the two institutions interact to keep the EU system in equilibrium. Price regulation and socialised healthcare together, too, mean that EUPI can expect only reasonable (politically determined) returns on capital, and talk of profit maximisation thus means something very different here than it does in the US. Price regulation and socialised healthcare together force EUPI, the EMA/NAs and the government of the EUMS to cooperate closely and this, too, results in an estrangement of EUPI from consumers who – if they are aggrieved over a healthcare issue – address those grievances to the EUMS governments who administer socialised healthcare, as an alternative to demonising EUPI. Jury determined punitive damages awards in product liability suits are thus, logically, absent here. These aspects of the behaviour of EUPI and its relationships are linked to the Table 73 predicates of 'Regulation of Transactions', 'Competition and Profit', 'Innovation and Expertise', and 'Welfare State.'

I will elaborate on the institution of labour market regulation and how this affects the business model of EUPI. The spread of resources made by individual firms between manufacturing operations and research and development (innovation) operations will be affected by labour regulation, which in turn is affected by jurisdictional culture. Tighter labour market regulation – typical of rHGHG cultures – will make it difficult for firms to outsource manufacturing operations from their home jurisdiction to other parts of the world. This may also result from government subsidies to protect manufacturing jobs within the home jurisdiction (which are inefficient and stifle innovation in the long run) and which are also to be expected from rHGHG cultures where the focus will be placed upon maintaining the place of individuals within the

groups where they belong – such as within one factory and one firm. Where an industry – for these reasons – continues to apply some of its resources to manufacturing operations even though manufacturing could be done much cheaper elsewhere, where the costs of labour are lower – then this is likely to be detrimental to innovation in the industry because fewer resources are left over for innovation. This is the case for EUPI which still focuses on manufacturing to a much greater extent than USPI which has outsourced manufacturing to other parts of the world.[6] This is reflective of rLGLG group culture of USPI. The comments made above regarding USPI and the predicates from Table 73 are inverted here in the case of EUPI (i.e. the same pairs of predicates apply, but the opposite one applies in the case of EUPI vis a vis USPI).

I asked what the relationships and business model of a pharmaceutical industry interest group would be (operating in a rHGHG jurisdictional culture) based on the core theoretical insights of hierarchism.[7] I have described how the business model and relationships of EUPI are shaped by the institutional framework which was assumed (and was/will be shown above and below) to be shaped by the rHGHG jurisdictional culture. I have introduced and explained also how the institution of labour market regulation forms a part of the institutional framework, how this is shaped by jurisdictional culture, and how this contributes to the business model of EUPI meaning that it focuses relatively more on manufacturing than does USPI. I conclude that there is a match between what is expected from a pharmaceutical industry interest group operating in a rHGHG jurisdictional culture based upon theory, and the reality of the business model and relationships of EUPI. I therefore conclude that EUPI is a rHGHG group. Further, its underlying rHGHG culture sits underneath its lobbying priorities as set out in Table 73 above and these have contributed to the transatlantic and system divergences.

6.5.2.2 Lawyers

In Chapter Three I set out how lawyers in the EU and the US tend to influence law-making in these jurisdictions, and their impact upon the development of the regulation of pharmacovigilance and product liability. Below I summarise this again in Table 83. As was the case for USPI and EUPI above, here too jurisdictional culture has shaped the institutional framework (the legal systems) which in turn shape the culture of the interest group of lawyers in the US and the EU.

Through the private interest mechanisms set out in Chapter Three, these lawyer interest groups have partly shaped the regulation in each jurisdiction, and thus the transatlantic and system divergence. For the purposes of these paragraphs, I assume that the institutional framework has been shaped by the jurisdictional culture – this is substantiated in detail below. Here, I begin by asking what one would expect an interest group of lawyers to do, and what one would expect them to seek to achieve, in a rLGLG and a rHGHG jurisdictional culture, respectively. Then, I turn back to Table 83 and identify what it is that the interest group of lawyers in the US and the EU do and seek to achieve (in reality) tying this to the institutional

6 See https://www.efpia.eu/media/361960/efpia-pharmafigures2018_v07-hq.pdf See also https://www.lygature.org/sites/lygature/files/atoms/files/Escher-Report_12-10-08.pdf

7 As set out in Chapter 5: Cultural Theories

features listed in the first column of Table 83.[8] I then ask whether the expected behaviour and objectives (based on theory) match the actual behaviour and objectives, and thus conclude whether the groups are rLGLG and/or rHGHG relative to each other.

Table 83 Lawyers and their Impact on Lawmaking in the US and the EU (2)

Institutional Framework	Impact on Lawmaking	Objectives
United States Common law system Inductive reasoning Adversarial procedure	**US Lawyers** As practicing lawyers/judges: bottom-up development of law through case-specific arguments adopted by judges drawn from interest groups of claimant and defendant lawyers	**US Lawyers** Seek to maximise individual fee income and prestige through lobbying as organized groups (e.g. ATLA) or court-based arguments. Seek substantive and/or procedural legal changes to benefit fee income of group
European Union/EUMS Mostly civil law systems Deductive reasoning Inquisitorial procedure EU Bureaucratic organisation EU law must be implemented EU law must be neutral	**EU Bureaucrat Lawyers** As bureaucrats in Council, Parliament, and other organs: drafting law, according to logical, rational, and non-ideological approaches to law-making. Implemented top-down. **EU Practising Lawyers** As practicing lawyers/judges, top-down through interpretation of EU Law before or in the CJEU or national courts in a centralised way leaving little scope for divergent national interpretations.	**EU Bureaucrat Lawyers** Seek to maximise the competences of the organs and the EU by integration 'through' law. **EU Practising Lawyers** Seek to maximise the authority of the CJEU and/or ensure the supremacy of EU law.

US Lawyers

I begin with the expected behaviour and objectives of an interest group of lawyers operating in a rLGLG jurisdiction. One would expect such lawyers to align their interests with those of their client first and the court second. This is because lawyers in a rLGLG jurisdictional culture would not identify primarily with the group – the court system – which they interact with, but

8 Which are later culturally analysed themselves in Subsection below.

rather as individuals. Second, one would expect lawyers in a rLGLG jurisdictional culture, if they identify with any group, to identify only with a group of individuals whose interests are closely aligned with their own. This is first because a high level of specialisation will take place within the professions in a rLGLG jurisdictional culture, necessitated by competitive conditions between lawyers. This is also because in a rLGLG culture cooperation with others in a group is only seen as useful to the individual in so far as it advances the interests of the individual. It will be relatively infrequent that the individual will suppress his own interests to prioritise the greater good of a larger group, e.g. the court system as a whole, or 'lawyers' as a whole. One expects, therefore, to see lawyers in a rLGLG jurisdictional culture organise in subgroups most earnestly only where those subgroups are comprised of other lawyers representing the same type of clients, in the same position (i.e. defendant/claimant) and in the same type of cases (i.e. personal injury, white collar crime, environmental offences etc.). However, even where they identify and cooperate to some extent with similarly positioned lawyers, they are expected to be in a high degree of competition with those other lawyers, to obtain the business of the same pool of clients. These observations are linked to the Table 73 predicates under 'Subgroups'.

Thus, in a rLGLG jurisdictional culture one would also expect members of the interest group of lawyers to assert an individual personality, to advertise their services, and to give interviews to the media. They will do this ultimately because to do so will increase their fee income, which they seek to maximise. By raising their public profile through advertisement, media appearances and personal branding they differentiate their product within a competitive market for legal services, providing them with some power over the price (fees). They are also to be expected to innovate – particularly in their court-based arguments – to gain a competitive advantage over other lawyers within their subgroup. Also, to elevate their overall trial or settlement success rate, which will be the benchmark of success for lawyers in a rLGLG jurisdictional culture. As a proven high success rate is the best way of differentiating their services and gaining a competitive advantage, the objectives of the lawyer and the interests of his client in this jurisdictional culture are very closely aligned, and probably closer aligned than the objectives of the lawyer and the interests of the court system or a wider conception of justice.[9] Lawyers in a rLGLG jurisdictional culture therefore, too, can be expected to seek substantive legal changes in court which will systematically favour 'their type' of client in 'their type' of case because such legal changes will also systematically favour the fee income of the lawyer. These observations are linked to the Table 73 predicates listed underneath 'Accountability and Blame', 'Competition and Profit' and 'Innovation and Expertise'.

As set out in Chapters Three and One and in Table 83 above, this is indeed the reality in the US more so than in the EU. Lawyers in the US have often organised in subgroups with other lawyers who represent the same type of clients in the same type of cases – an example is ATLA – the American Trial Lawyers Association. Lawyers in the US do advertise[10] and do compete for clients to a high degree.[11] They often give interviews to the media where they express

9 See below on the difference between distributive and corrective justice.

10 See https://www.americanbar.org/groups/professional_responsibility/resources/professionalism/crossroads/

11 See Garoupa, Nuno. "Regulation of legal and medical professions in the US and Europe: A comparative analysis." See also: Domberger, Simon, and Avrom Sherr. "The impact of competition on pricing and quality of legal services." International Review of Law and Economics 9, no. 1 (1989): 41-56.

personal views on cases. In addition, they innovate. Garoupa and Ulen have argued[12] that greater competition in the legal academy has caused legal academics in the US to be more innovative relative to academics in the EU where the legal academy is less competitive. The same can arguably be observed for lawyers themselves. Lawyers in the US will seek innovative arguments to support their individual cases knowing that legal changes brought about through judge made precedent, will systematically favour the interests of their clients and thus their own interests. This tendency towards innovation is, it is submitted, reflective of the tradition of legal realism in the US.[13] Oliver Wendell Holmes Jr identified the divergence between the interests/priorities of the court (and the law) and the interests and priorities of those who use the legal system in his 'prediction theory of law'. It follows from his view of the legal system – widely taught in US law schools - that US lawyers representing Holmes' 'bad man'[14] are most interested in whatever argument will support his client. There is relatively little concern for the internal cogency and consistency of the common law. That does not indicate a disrespect for the law itself, but is a feature of the US legal system – the common law through its adversarial procedure and inductive reasoning is trusted to develop over time in a cogent and consistent way even where precedent is overruled.

So, in legal practice, courts are relatively more willing to hear consequentialist or policy arguments than they are in the EUMS. And, there is a less restrictive force imposed by general principles of law upon what arguments may be advanced by lawyers in US courts than in the courts of the EUMS. One example of a consequentialist argument is that offered by Landes and Posner for the placing of strict liability upon producers for defective products[15] and the attendant incentive effects.[16] Innovative US claimant lawyers in personal injury cases seized upon this consequentialist argument in the 1950s and 1960s not because it was cogent with existing common law precedent but because it was a compelling argument which the court was likely to accept. And, if the court did accept it, then this benefitted both those lawyers and their clients. In addition to seeking change through court-based argument, in their organisation in the subgroups described above, US lawyers have also sought legal change by direct lobbying of government. For example, ATLA's lobbying for the lifting of restrictions upon class action suits in the 1960s, and the response of defendant personal injury lawyers in lobbying to seek punitive damages caps in some US states in the 1980s.

How is the behaviour of US lawyers and their objectives also shaped by the institutional framework?[17] Chase argues[18] that differences between US and German lawyers are attributable in part to the bureaucratic structure of civil law systems – making use of inquisitorial rather than adversarial procedure. The bureaucratic structure of civil law systems is inherently rHGHG. By contrast, the rLGLG adversarial common law system places more focus on the role of practicing lawyers. Bureaucratic and inquisitorial civil law systems place the task of interpreting the law in its application to a specific case solely with the judge. In

12 In relation to legal academia see: Garoupa, Nuno, and Thomas S. Ulen. "The market for legal innovation: law and economics in Europe and the United States." In Comparative Law and Economics. Edward Elgar Publishing, 2016.

13 See Holmes Jr, Oliver Wendell. *The path of the law.* The Floating Press, 2009.

14 Any client with specific interests diverging from those of the law itself.

15 I argue below that really this is as a reversal of an evidential burden.

16 See Chapter Three.

17 Which is assumed at this stage (and explained fully below) to reflect jurisdictional culture.

18 Chase, Oscar G. "Legal processes and national culture." Cardozo J. Int'l & Comp. L. 5 (1997): 1.

adversarial common law systems claimant and/or defendant play a significant role in the interpretation of the law through the arguments which they choose to advance in court to support their case. The judge in these systems will often merely accept one or more of these arguments when giving judgment. The focus of common law inductive reasoning is on doing justice on the facts of each case. This allows US lawyers to seek legal change based on the facts of their current case. The adversarial procedure and the inductive reasoning together allow them to align their interests with those of their client very closely, and to maximise their fee income in doing so by winning legal precedent which supports their type of client in their type of case systematically, over time. The centralised bureaucratic institutional framework of the EU/EUMS Civil Law systems is linked to the Table 73 predicates of 'Regulation of Transactions', 'Accountability and Blame' and 'Innovation and Expertise'. The converse is true in each case for the US Common law system.

In the foregoing paragraphs I have considered what one would expect the behaviour and objectives of an interest group of lawyers to be, based upon their operating in a rLGLG jurisdictional culture based upon the key theoretical insights of individualism. I have set out the real-world behaviour and objectives of US lawyers and also how this is shaped by features of their institutional framework.[19] I conclude that there is a match between what one would expect based on theory, and the real world position. I therefore conclude that US lawyers have a rLGLG cultural orientation as a group. That rLGLG cultural orientation helps to explain their behaviour in furtherance of their objectives and their behaviour – as set out in Chapter Three and in Table 83 above. And, it helps to explain the transatlantic and system divergences, through the private interest mechanisms.

EU Lawyers

What one would expect for EU lawyers (EU/EUMS lawyers and EU bureaucrat lawyers) based upon theoretical insights regarding hierarchism, is the inverse of what was expected and observed above in the case of US lawyers. US lawyers organise along adversarial lines in subgroups, asserting individual personalities, competing heavily with each other (even within subgroups, for clients), and aligning their interests first with the client and second with the court. This is all done to maximise fee income. One would expect an interest group of lawyers operating in a rHGHG jurisdiction to organise more often as a whole profession (not along adversarial lines) to maintain a lower public profile, to compete less with each other (perhaps relying instead upon strong barriers to entry to the profession to protect the profession as a whole)[20] and to align their interests just as strongly with the court system/the legal system as they do with their specific clients. The predicates from Table 73 linked to US lawyers are also therefore linked to the EU lawyers but, clearly, the opposite predicate in each pair applies in this case.

This is what is seen, particularly at the EU level. I deal first with the EU bureaucrat lawyers described in Chapter Three. These are often fully employed by the EU organs which they

19 Which is assumed at this stage to reflect underlying rLGLG culture.

20 See Garoupa, Nuno. "Regulation of legal and medical professions in the US and Europe: A comparative analysis."

serve.[21] They keep a low public profile – as bureaucrats only, not politicians.[22] That is linked to the predicates in Table 73 under 'Accountability and Blame'. They identify with their class (of bureaucrat lawyers) instead of splitting along adversarial lines.[23] This is linked in the predicates in Table 73: 'Social Roles and Social Mobility', 'Regulation of Transactions' and 'Subgroups'. Their interests are aligned with the EU organs, and they seek to maximise the competences of the organs in the process of 'integration through law',[24] whereby they produce harmonising EU law which is acceptable to all EUMS and which gradually supplants domestic law. These lawyers do not innovate in the sense that I have described US lawyers innovating above. There is, first, little reason to innovate because EU bureaucrat lawyers are not directly in competition with each other but work together within the organs for the benefit of the organs. Moreover, the style of law-making in which they engage at the organs is not rLGLG consequentialist but rHGHG technocratic. At its most basic, the process of law-making draws from the legal traditions of all EUMS, but it is presented to the EUMS in the intergovernmental sphere as 'expert' law-making: rational, logical and non-ideological. That is a rHGHG approach to law-making, it is linked to the Table 73 predicates under the heading 'Innovation and Expertise'.

This is seen to be the case with the EU Product Liability Directive 1985 (PLD). The PLD comes from an EU/Council of Europe push for consumer protection. But this political mission, and the body of law created under it are drawn from legal traditions common to all EUMS (or at least, most of them). As set out in Chapter Three, and below in more detail – consumer protection is drawn from legal traditions found in French and German legal systems which require the seller of goods to consider the interests of the buyer at the point of sale – different to the English and later American Common Law doctrines of 'Caveat Emptor'. Having taken legal traditions common to all or most EUMS as the fundamental basis for the substance of EU law, these concepts are 'rebranded' to ensure they remain neutral from the specific legal traditions of any one EUMS. The most effective way for bureaucrat lawyers at the EU to achieve this has always been to replace the national and the traditional with the logical and the rational – i.e. 'scientific' lawmaking – which can most easily be presented as non-ideological and therefore acceptable to all EUMS. This accounts for EU bureaucrat-lawyers' use of technical law-making, drawing upon fields such as law and economics, and competition law, where 'neutral' numbers do not lie. This is a rHGHG approach to law-making undertaken by a rHGHG group of EU bureaucrat lawyers. This is also how the institutional framework feature that 'EU law must be neutral' (see Table 83 above) helps to shape the cultural orientation of EU bureaucrat lawyers, their behaviour, and their objectives.

Turning to EU/EUMS lawyers, I am now referring to those court based practising lawyers at the EUMS level which practice specifically in the field of EU law. Here, these lawyers – taken from all EUMS –do not split along adversarial lines. They organise as one group, most strongly within each individual EUMS but also across national boundaries.[25] Their interests are aligned

21 See Vauchez (2008) and Schepel and Wesseling. "The legal community: judges, lawyers, officials and clerks in the writing of Europe." European Law Journal 3, no. 2 (1997): 165-188.

22 See discussion in this Chapter above.

23 The latter which is not possible anyway since these lawyers are not engaged in adversarial proceedings.

24 See Vauchez, Antoine. "'Integration-Through-Law': Contribution to a Socio-History of EU Political Commonsense." (2008).

25 See Garrett, Geoffrey. "The politics of legal integration in the European Union." International Organization 49, no. 1 (1995): 171-181. See also Schepel and Wesseling (1997).

with the objective of the expansion of EU law because – due to their specialisation – the expansion of EU law and its competences/supremacy over domestic law will enhance their status as experts and advisers. They cooperate closely, coordinating that cooperation based on the judgments of the Court of Justice of the European Union (CJEU) – where many of them will appear as advocates and where some of them will end up sitting as judges.[26] In doing so, they orchestrate the implementation of EU law in each EUMS in a controlled, centrally supervised way, which permits little room for divergent national interpretations of law. These behaviours are linked to the Table 73 predicates entitled 'Social Roles and Social Mobility', 'Regulation and Transactions', 'Accountability and Blame', 'Innovation and Expertise' and 'Subgroups'. This is a rHGHG approach to law-making and legal interpretation, different from the bottom-up approach taken in the US Common Law system.

How does the institutional framework in which EU/EUMS lawyers operate[27] help to shape their behaviour and objectives? I begin with the following aspect of the institutional framework: that 'EU law must be implemented'. On the EU level, the process mandated in the Treaties for the implementation of EU law[28] necessitates a rHGHG approach by EU/EUMS lawyers. They must make arguments based always on the wording of the primary and secondary EU legislation, adopting an 'autonomous' approach to the law quite removed from legal realism's consequentialist perspective. The preliminary reference procedure set out in the Treaties[29] requires the involvement of EU/EUMS lawyers at the domestic court stage which – due to their incentives – will draw the maximum possible number of domestic cases to the CJEU for resolution. This is in part because the sui generis public law of the EU itself (as set out by the CJEU in its earliest cases) is purposive in its reasoning.[30] EU/EUMS lawyers are therefore faced with a large number of domestic cases which *may* be sent to the CJEU and they have personal incentives to argue that a preliminary reference should be made – for the reasons given above.

Once the preliminary reference has been made, the purposive reasoning of the CJEU then brings the maximum possible number of these cases within the scope of EU law for resolution. At the domestic level specifically, the fact that most EUMS have civil law systems with inquisitorial procedures and deductive reasoning shapes the behaviour of EU/EUMS lawyers before these domestic courts. The deductive reasoning enables these lawyers to place the

26 Consider also the role of the Advocate General before the CJEU. See Clément-Wilz, Laure. "The Advocate General: A Key Actor of the Court of Justice of the European Union." Cambridge yearbook of European legal studies 14 (2012): 587-613.

27 Assumed at this stage to reflect the rHGHG jurisdictional culture of the EU.

28 See the Treaty on European Union and the Treaty on the Functioning of the European Union

29 Article 267 TFEU: Article 267 of the Treaty on the Functioning of the European Union provides: *"The Court of Justice of the European Union shall have jurisdiction to give preliminary rulings concerning: (a) the interpretation of the Treaties; (b) the validity and interpretation of acts of the institutions, bodies, offices or agencies of the Union; Where such a question is raised before any court or tribunal of a Member State, that court or tribunal may, if it considers that a decision on the question is necessary to enable it to give judgment, request the Court to give a ruling thereon. Where any such question is raised in a case pending before a court or tribunal of a Member State against whose decisions there is no judicial remedy under national law, that court or tribunal shall bring the matter before the Court. If such a question is raised in a case pending before a court or tribunal of a Member State with regard to a person in custody, the Court of Justice of the European Union shall act with the minimum of delay"*

30 For further explanation see Pollicino, Oreste. "Legal reasoning of the court of justice in the context of the principle of equality between judicial activism and self-restraint." German Law Journal 5, no. 3 (2004): 283-317. See also Fennelly, Nial. "Legal interpretation at the European Court of Justice." Fordham Int'l LJ 20 (1996): 656.

court's focus squarely on the wording of the EU law instruments, which provides them with the best opportunity to expand the scope of EU law itself. The inquisitorial procedure permits them, as judges, to favour the application of EU laws over the application of domestic law.[31] This approach at the EUMS level and at the EU/CJEU level is rHGHG compared to the rLGLG bottom-up, inductive reasoning and adversarial procedure of the US Common Law. The EU Practising Lawyers' behaviour and the institutional framework is linked to the Table 73 predicates entitled 'Social Roles and Social Mobility', 'Regulation and Transactions', 'Accountability and Blame' and 'Innovation and Expertise'.

Here I have considered what one would expect the behaviour and objectives of an interest group of lawyers to be - when operating in a rHGHG jurisdictional culture - based upon the key theoretical insights of hierarchism. I have set out the real-world behaviour and objectives of EU lawyers and also how this is shaped by features of an institutional framework which is assumed – at this stage – to reflect underlying rHGHG culture. I conclude that there is a match between what one would expect based on theory, and the real-world position. I therefore conclude that EU lawyers have a rHGHG cultural orientation as a group. That rHGHG cultural orientation helps to explain their behaviour in furtherance of their objectives and their behaviour – as set out in Chapter 3 and in Table 83 above – helps to explain the transatlantic and system divergences, through the private interest mechanisms.

6.5.2.3 Legal Systems and Theories of Justice

Now I move away from the groups and turn to the institutions. I have already outlined how the cultural orientation of the groups is influenced by the cultural orientation of the institutions which comprise the regulatory framework in which they operate. Here I argue that the US Common Law is rLGLG because of and causing its commitment relatively more to corrective justice. I argue that the EU legal system is rHGHG because of and causing its commitment relatively more to distributive justice. I begin by making this overall argument about the legal systems and theories of justice, then I move to consider each system separately in more detail. In the case of the US, I look at specific institutional features of the common law system and culturally analyse these to explain further.

Corrective and Distributive Justice

I say corrective justice is rLGLG because it focuses on the individual, the harm done to the individual and the remedy available to the individual. The harm done to the individual must always be corrected, so long as there is fault on the part of the injurer. The fault on the part of the injurer is crucial otherwise - if they are held liable to correct the harm - then it is the injurer and his or her individual interests which are being harmed by the legal system. Corrective justice is therefore individualistic.[32] The Common Law, through its inductive reasoning and its insistence upon doing justice on the facts of each case, is committed to corrective justice. Aspects of the law and the legal system which deter harm fit within the

31 Which, when combined with the purposive institutional style of EU law and the CJEU, tends towards systematic expansion of EU law to the detriment of domestic national law.

32 See Weinrib, Ernest J. "Corrective justice." Iowa L. Rev. 77 (1991): 403. See also Benson, Peter. "The basis of corrective justice and its relation to distributive justice." Iowa L. Rev. 77 (1991): 515.

model of corrective justice although are slightly separate from it.[33] Deterrence is achieved as a by-product of the threat of the corrective remedy being imposed (liability).[34] It is the corrective remedy and the ability of the individual victim to access it which is paramount. A compensatory role for the law is also a by-product, but a by-product only,[35] of this focus on the corrective remedy. This aspect of US common law and corrective justice is clearly linked to the Table 73 predicates of 'Accountability and Blame'.

Distributive justice is, I say, rHGHG. Here, compensation takes centre stage. What is most important is that no member of the group is left wanting, and it is the responsibility of the group to look after all members of the group. Fault is therefore less important, because the need for provision to be made for the injured is considered a good enough reason on its own to impose liability, and for the legal system to redistribute wealth from sectors of the group with the ability to pay, to those who are injured.[36] The choice of which subgroup from which to redistribute wealth to those in need is coordinate by law. A reason, but not necessarily a fault-based reason, may serve this purpose. The identification of a subgroup which has profited from the sale of the products which caused the harm may represent a good coordinating 'reason' but the crucial element is the latter subgroup's ability to pay, and the former subgroup's need. The opposite predicate from the pair listed in Table 73 under 'Accountability and Blame' applies here. This general argument is set out below in Table 84.

Table 84 US Common Law, EU Legal System, Theories of Justice and Cultural Orientation

Own table based upon the literature set out in this section

	Theory of Justice	Purpose	Cult. Ort.
US Common Law	Corrective	Correction: provide a remedy where fault	rLGLG
EU Legal System	Distributive	Redistribution: provide for injured party	rHGHG

Corrective and Distributive Justice and Strict Liability for Defective Products in the US and EU

Going from the legal systems generally to the specific case of liability for defective products, now I argue that the approach taken to strict liability for defective products in the US seeks relatively more to bring about corrective justice, whereas the system of strict liability under the EU PLD seeks relatively more to bring about distributive justice. Owen argues[37] that historically the US Common Law was very insistent upon a contractual nexus between claimant and defendant as a prerequisite for any form of liability for defective products. One would expect this from a rLGLG legal system. Contract law is the law facilitating the voluntary creation of obligations between individuals which the law enforces according to the intention

33 See Schwartz, Gary T. "Mixed theories of tort law: affirming both deterrence and corrective justice." Tex. L. Rev. 75 (1996): 1801. See also Howells, Geraint G., and Mark Mildred. "Is European products liability more protective than the restatement (third) of torts: products liability." Tenn. L. Rev. 65 (1997): 985.
34 See also Howells and Mildred. (1997).
35 Ibid.
36 Ibid.
37 See Owen, David G. "Punitive damages in products liability litigation." Michigan Law Review 74, no. 7 (1976): 1257-1371.

of the parties, based upon the principle of freedom of contract.[38] This institution is inherently individualistic. Here, the law does not interfere in the substance of an agreement but only upholds it. Law facilitates and coordinates private bargaining for the creation of wealth, it does not redistribute wealth itself.[39] Hence, privity of contract – the legal doctrine in common law requiring the contractual nexus between the parties before any liability could be imposed – was especially strong in US Common Law.[40] However, as the US industrialised and consumer goods flooded on to the market,[41] pressure grew to ensure that consumers would always have a remedy. Corrective justice requires a remedy where there is fault. However, individualism also rejects the imposition of non-voluntary obligations upon individuals wherever possible. This led to the emergence of the concept of a "duty of care' in *English* Common Law. The duty of care doctrine (negligence) is a fault-based standard.[42] One party may be liable to another party, which they did not directly contract with, through an indirect route. The logic is that – even without contract – the first party can assume some responsibility to the unknown second party where it is foreseeable that the act or omission of the first party may cause harm to the second party which must be corrected.

This was the case for manufacturers who placed defective products on the market which harmed ultimate consumers. In Scotland, Mrs Donoghue would have been left without a remedy because – even under an implied contractual term or warranty guaranteeing the safety of her ginger beer – it was the friend whom Mrs Donoghue met at the café in Paisley who purchased the drink and gave it to Mrs Donoghue. It was the friend, therefore, who was privy to the contract with the seller. Mrs Donoghue[43] would have been left with no remedy if liability were restricted to cases where a contractual nexus existed between seller or manufacturer and victim.[44] Corrective justice could not allow this.[45] Similarly, but 16 years previously, in New York, when Mr MacPherson was injured by a defective wheel in his Buick automobile, the car dealership from which he purchased the vehicle did not have sufficient funds[46] to provide correction (a remedy) and so a remedy was required against the manufacturer directly. Thus, Lord Atkin in *Donoghue* and Benjamin Cardozo in *MacPherson* advanced the concept of duty of care (English Common Law) and/or removed the privity requirement (US Common Law) to provide corrective justice which was still based in fault: negligence liability.

Strict liability for defective products came later in the 20th Century in US Common Law. On first blush strict liability seems to not fit with the rLGLG justification for negligence liability set out above. In the US strict liability for defective products followed from Justice Traynor's concurring opinion in *Escola*[47] at the Supreme Court of California in 1944. Judgment was given

38 See Owen, David G. "The evolution of products liability law." Rev. Litig. 26 (2007): 955.
39 See Hart, Herbert Lionel Adolphus, Herbert Lionel Adolphus Hart, and Leslie Green. The concept of law. oxford university press, 2012.
40 See Owen (1976).
41 With remote chains of supply from manufacturer to ultimate consumer.
42 See Owen (1976) and Owen (2007).
43 *Donoghue v Stevenson* [1932] UKHL100
44 See Getzler, Joshua. "Richard Epstein, Strict Liability, and the History of Torts." Journal of Tort Law 3, no. 1 (2010).
45 *Donald C. MacPherson v. Buick Motor Company* 111 N.E. 1050, 217 N.Y. 382
46 Or likely did not, hence Mr MacPherson's decision to sue Buick.
47 *Gladys Escola, Respondent, v. Coca Cola Bottling Company of Fresno (a Corporation), Appellant.* 24 Cal.2d 453, 150 P.2d 436

there for the consumer based on *res ipsa loquitir* – a doctrine in Common Law which makes it much easier for a claimant to establish breach in negligence where the very nature of the accident or injury 'speaks for itself'. In that case, the claimant is not required to directly prove breach and instead the defendant must prove it did not breach the duty of care: a full or partial reversal of the evidential burden of proof. In Traynor's concurring opinion, a rule of strict liability should be imposed on manufacturers whose products cause injury to consumers. His argument focused upon the deterrent effects of such a rule – a consequentialist, public policy argument. Escola itself, however, was decided based on *res ipsa loquitir.* As such, Epstein argues[48] that – cogent with the corrective justice approach of the US common law - strict liability is fault based. He sees strict liability in US Common Law as a reversal of the evidential burden of proof. Instead of the injured party having to prove breach by the manufacturer the manufacturer must show that they did not. The need for this reversal of the evidential burden comes from a place of corrective justice and therefore still reflects the underlying rLGLG culture of US Common Law. Without this reversal in the burden of proof – as Traynor pointed out in *Escola* - claimants could almost never recover, because defendants had such control and knowledge over their own production processes that – in an adversarial system – claimants would not be able to produce evidence that breach had occurred.

The key to understanding the difference between strict liability as a reversal of the evidential burden of proof, and strict liability which in theory had been introduced on a rHGHG wealth redistribution (compensatory) basis is to look at what happens – according to the law – where the defendant can show that it could have done *nothing* to prevent the product harming the claimant. This is the case for unknown and unknowable latent defects and US Common Law does not impose liability in these circumstances, whereas it is possible under the EU PLD to do so.[49] Strict product liability in US law therefore is shown – via the medium of corrective justice and the reversal of the evidential burden of proof – to reflect rLGLG underlying culture. Just like the concept of duty of care before it, it seeks to ensure foremost that a corrective remedy is available, but, it will not go so far as to impose liability where there was no fault on the part of the producer.

In the civil law legal systems of the EUMS, there is a different tradition, which comes from Roman Law[50] and Aquinas' natural law,[51] where the seller of the product implicitly has a duty to take care of the buyer. This is the opposite of the Caveat Emptor doctrine which came to US Common Law via the Common Law of medieval England. However, it found its way into the legal tradition of the EUMS to become the basis of a body of law known at the EU level as 'consumer protection' law, one instrument from that body of law being the PLD. Consumer protection law at the EU level comes from distributive justice, the most abstract and

48 See Epstein, Richard A. "A theory of strict liability." *The Journal of Legal Studies* 2, no. 1 (1973): 151-204. See Epstein, Richard A. "The path to" The TJ Hooper": the theory and history of custom in the law of tort." *The Journal of Legal Studies* 21, no. 1 (1992): 1-38. See also Posner, Richard A. "Epstein's Tort Theory: A Critique." *The Journal of Legal Studies* 8, no. 3 (1979): 457-475.

49 By derogation from the Article 7 defence.

50 See Getzler (2010), Owen (1976) and Owen (2007).

51 See Velasquez, Manuel, and F. Neil Brady. "Natural Law and Business Ethics." Business Ethics Quarterly 7, no. 2 (1997): 83-107. Accessed April 1, 2021. doi:10.2307/3857300. See also Reitz, John C. "A History of Cutoff Rules as a Form of Caveat Emptor: Part II-From Roman Law to the Modern Civil and Common Law." The American Journal of Comparative Law 37, no. 2 (1989): 247-299.

fundamental concept uniting the civil law legal systems of the EUMS which EU law is at once required to mirror whilst at the same time appearing separate: logical, rational, and ideologically neutral. A different approach is taken under a distributive theory of justice.[52] Thus, the seller must deal bona fides with the buyer.[53] He must reveal known latent defects before sale, and he will be held liable if he does not.[54] None of these is the case in the legal doctrines of US common law. Under distributive justice, where some members of the group are harmed, it is reason enough that some other members of the group profited because of the sale which led to that harm, to require a redistribution of wealth (compensation) from the latter group to the former group. Thus, for unknown and unknowable latent defects in pharmaceutical products it may be enough simply that the industry benefitted from the sale even where it cannot be described as being at fault in any way. Strict liability under EU law therefore comes from a different place to where it comes from in US Common Law. Howells describes distributive justice as the 'grand theory'[55] which EU lawyers have been preoccupied with whilst their US counterparts were much more concerned with finding a justification (such as deterrence, through law and economics) for reversing the evidential burden of proof in products liability cases, and thus ensuring a corrective remedy in every case. This approach of the EU legal system is rHGHG compared to the US Common Law approach which is rLGLG. The EU/EUMS approach is most clearly linked to the predicate in Table 73 listed under 'Welfare State'.

Table 85 Strict Liability in US and EU Legal Systems

Own table based upon arguments made in the literature set out in this section

Legal System	Nature of Strict Lib.	Purpose	Justice	Cult Ort.
US	Reversal of burden of proving breach Still requires fault No liability for unknown and unknowable latent defects	Provide a corrective remedy to claimant Side effect: deterrence Side effect: compensation	Corrective	rLGLG
EU	Producer liable even without fault Liability for unknown and unknowable latent defects	Redistribution of wealth from profiting party to injured party in compensation Side effect: deterrence	Distributive	rHGHG

The view taken of the cultural orientation of the approach to strict liability is set out above in Table 85. In the following sections I go on to consider further institutional aspects of the US

52 See Rawls, John. A theory of justice. Harvard university press, 2020 and see Cohen, Ronald L. "Distributive justice: Theory and research." Social justice research 1, no. 1 (1987): 19-40. See also Keating, Gregory C. "Distributive and corrective justice in the tort law of accidents." S. Cal. L. Rev. 74 (2000): 193 and see Posner, Richard A. "The concept of corrective justice in recent theories of tort law." The Journal of Legal Studies 10, no. 1 (1981): 187-206.

53 See Mousourakis, George. *Roman law and the origins of the civil law tradition*. Berlin: Springer, 2015.

54 Ibid.

55 See Howells and Mildred (1997).

and EU legal systems, exploring whether these are rHGHG or rLGLG and linking these institutional features to the overall regulation of product liability.

EU Legal System and EU Law

In these paragraphs I establish that elements of the institutional framework set out in Table 83 are rHGHG in their orientation. As outlined in Chapter Three, the style of EU law tends to be free from the national legal traditions of the EUMS and logical, rational, and ideologically neutral.[56] However, the substance can be expected to reflect values common to all EUMS. This explains why there is 'consumer protection' law as a body of law at the EU level whereas it is found under different names in the legal systems of the EUMS, often incorporated into the substantive law of contract, tort, property etc. Moreover, when EU lawyers draft EU law they do so in a technocratic way, they may draw upon a 'grand theory' of distributive justice – a theory of justice acceptable to the majority of the EUMS as it is sufficiently far removed (logically anterior to) any specific national legal tradition but incorporates values – those values reflecting a rHGHG cultural orientation – which are common to all or most EUMS.

The process of implementing and interpreting EU law in the EU legal system is also rHGHG. EU law is handed down from above. It comes from EU bureaucrat lawyers in the Commission and is passed through the Council (representing the EUMS inter-governmentally) and Parliament with relatively little input from the European demos when compared to the US process for law-making. It is then either directly imposed on the EUMS (Regulations) or its implementation is required by the EUMS binding in outcome (Directives) but the form of implementation is tightly policed by the Commission and the CJEU. At the CJEU, which settles all questions of EU law centrally and to which the EUMS domestic courts must send questions of interpretation when necessary to resolve cases, the Court hands down judgments reasoned deductively from the wording of primary and secondary EU law. This is a centralised organ ensuring consistency of application of the law for the whole group (of EUMS), far from the decentralised nature of US Common Law. There the focus is placed upon the availability of a remedy to the individual in individual cases, and general principles of US Common Law are reasoned inductively from the ratio in decided cases. The CJEU is known, too, for expanding the scope of its own powers through its interpretation of the Treaties, thus expanding centralised power to the detriment of decentralised domestic courts.[57]

The approach to EU law-making in the EU legal system is rHGHG compared to US Common Law which is rLGLG. The substance of EU Law – despite being presented as rational, logical, and ideologically neutral (a technocratic presentation, which itself is rHGHG) reflects the high group values which are common to all EUMS. The legal approach that those who profit from the sale of products should provide compensation to those injured by those products, even without fault, is thus evident in the PLD and the implementation of the PLD itself in accordance with that approach is made possible by the rHGHG EU process of top-down law-making. The result of this EU style of law-making is also an approach to product liability in the EU which is stable and relatively unchanging, across all EUMS. In which, too, there is little

56 See Schepel and Wesseling (1997) and Vauchez (2008).

57 See Judgment of the Court of 15 July 1964. - Flaminio Costa v E.N.E.L.. - Reference for a preliminary ruling: Giudice conciliatore di Milano - Italy. - Case 6/64 and see Judgment of the Court of 5 February 1963. NV Algemene Transport- en Expeditie Onderneming van Gend & Loos v Netherlands Inland Revenue Administration. Reference for a preliminary ruling: Tariefcommissie – Netherlands.

scope for the private incentives of EUMS judges and EU lawyers to influence the development of this body of law to suit their *own* interests.

Common Law in the US

In the rLGLG US, innovative US lawyers have focused their efforts not upon transposing grand theories of justice into whole systems of law, but rather to develop ways in which legal procedure can be adapted to ensure that individuals obtain corrective justice on the facts of every case.[58] In the EU/EUMS a fixed text code or treaty provides the basis for centralised interpretation of the law by a judicial bureaucracy, assisted (only) by a class of EU lawyers who align their interests with the court first. US lawyers, on the other hand, align their interests with those of their client first. Law is developed through inductive reasoning, which ensures first that corrective justice is done on the facts of each case. Statements of what the Common Law courts do – like the American Law Institute ('ALI') Restatements – are descriptive and not prescriptive. The US Common Law system is therefore rLGLG compared to the system of EU Law. The adversarial procedure both follow from and causes these institutional aspects of US Common Law and is similarly rLGLG. This rLGLG institutional framework also results in a process of law-making in which legal rules change back and forth over time.[59]

To the aspects of the institutional framework set out for the US Common Law in the first column of Table 83 above I can also add: the US 'costs' rule; and the permission of class-action lawsuits; the use of juries to determine damages; and the availability of punitive damages. I analyse these further below.

Jury Trials, Punitive Damages, the US 'Costs' Rule and Class Action Lawsuits

All four of these institutional features of the US Common Law lead to high expected damages for USPI in the product liability sphere[60] and so they are culturally analysed here together. Punitive damages have been argued to be consistent with corrective justice, and thus I say they disclose a rLGLG cultural orientation as an institution. Owen argues[61] that punitive damages in Common Law were originally intended as a sum awarded in recognition of nonpecuniary harm, such as insult and outrage.[62] Strong public interest arguments were identified in Chapter 3 for allowing punitive damages in product liability suits, but the unpredictability of jury awards leads to uncertainty for industry which risks stifling innovation, and this is not necessary either from the perspective of corrective justice or from deterrence and public interest theory. Therefore, an analysis of the use of juries to determine punitive damages follows below.

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58 With one eye on what effect this would have on the number of injuries caused by defective products.

59 It is due to the adversarial process and – I argue – the tendency for the private incentives of lawyers (both plaintiff and defendant) to seek substantive legal changes beneficial to them in a process. Due to the uncertainty created by the ever-changing rules, this leads to large wealth transfers to the interest group of US lawyers (as a whole) over time and thus suits this interest group as a whole, over time. Ironically, of course, as argued in the efficiency of the common law hypothesis, this process may lead to efficient outcomes in the long run. But note that this is 'productively' efficient only. These outcomes maximise the 'size of the pie' overall, whilst leaving a disparity in the distribution of the pie. Hence there is a link to the larger gap between rich and poor that is found in the overall rLGLG US than in the overall rHGHG EU.

60 Which, in turn, has moved USPI to lobby for a higher liability threshold and, in turn, makes USPI less willing to cooperate with the FDA in pharmacovigilance.

61 See Owen (1976).

62 Particularly in defamation cases see Owen (1976).

Before that, I consider why the EU/EUMS do *not* commonly use punitive damages. I argue that this is reflective in substance of rHGHG legal systems at the EUMS and the EU level.[63] Because the EU legal systems are relatively more focused upon compensation (grand theory, distributive justice) than on availability of corrective remedies, one would expect the EU/EUMS systems to accept that some forms of harm cannot be compensated and let these losses lie where they fall. Just as the US legal system is relatively preoccupied with fault as being logically anterior to correction, the EU and EUMS systems are relatively preoccupied with *compensability* as logically anterior to compensation. Take the original justifications given for punitive damages in Common Law (English and US) systems. These systems recognised that injury had been suffered in individual cases which could *not* be compensated. The defamatory insult could not be undone, nor the reputation repaired, nor the injury healed with any sum of money. Nevertheless, from the perspective of corrective justice correction is still needed because harm has been suffered and fault is identified.

Thus, an *arbitrary* sum for correction may be awarded based upon a consideration of the facts of the case, and this is called punitive damages.[64] In a rHGHG legal system such as that of most of the EUMS or that of the EU itself, there is no need to compensate in such cases. Compensation would be illogical because the harm cannot be compensated. Secondly, the type of non-compensable harm which provided the basis for correction (when coupled with fault) in the US Common law related historically to insult[65] which is a degradation of individual character and honour; and/or to an interference with personal autonomy, the person's freedom to pursue their chosen path in life without this being restricted by harm caused by another. Both interests are strongly linked to individualism. In rHGHG systems the individual identifies more with the group than as an individual, so their individual character is less in need of protection, and their freedom to live their life as they pleased was already curtailed by the many social rules present in a rHGHG society. Tangible harm, on the other hand, must be compensated, for the good of the group.[66]

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63 As has been seen, punitive damages can have very useful incentive effects in terms of lowering the overall volume of product accidents – through providing strong deterrence of intentional conduct, through incentivising swift unilateral action by producers where latent defects emerge and to overcome the rational apathy problem. Why is it then that the EUMS/EU systems have not adopted punitive damages in light of these policy arguments which would further the distributional outcomes sought under distributive justice? Wells argues that this is a result of the impermeability of the (particularly) EUMS legal systems to policy arguments. In the EUMS, as discussed above and in Chapter Three, the law is an autonomous discipline, and a rHGHG one where 'the rules' provide the answer to the question 'what are the rules?' In such legal systems there is little scope to introduce consequentialist policy-based arguments. Not finding punitive damages for consumers at the EUMS level, when designing the PLD at the EU level under the rebranded name of 'consumer protection law' the idea of punitive damages was not included. See Wells, Michael L. "A Common Lawyer's Perspective on the European Perspective on Punitive Damages." La. L. Rev. (2009): 557. Wells, Michael L. "Basic Questions of Tort Law from a Comparative Perspective." Journal of Civil Law Studies 9, no. 2 (2017): 11.

64 It may be worth noting that in English Common law punitive damages are to be distinguished from 'aggravated' and 'exemplary' damages. The latter two are tied more closely – in the case law – to the justifications set out in the public interest section in Chapter Three. See City Law School. Remedies. Oxford University Press, USA, 2014.

65 This is why, as Owen explains, punitive damages were first found available in common law systems in defamation cases. See Owen (1976).

66 Because intra-group solidarity strengthens the group as a whole. A large part of this, of course, results from the fact that in a rHGHG society the state or some other subgroup will be under an obligation to care for the injured anyway, and thus within the context of a rHGHG approach, liability rules simply coordinate who it is that

Another important reason for punitive damages in US Common Law is the need for damages awards in US courts to cover legal expenses,[67] which often amount to one third of the value of any judgment awarded to the claimant. This also follows from corrective justice – because otherwise the claimant would effectively be denied any remedy - and it thus also reflects a rLGLG approach. The causative factor – which is that in the US the costs rule is adopted such that parties usually have to pay their own legal expenses - is also a rLGLG approach to legal expenses. Treating the payment of these - or rather the risk inherent on taking on a lawyer to argue a case - as the individual responsibility of the claimant himself, and prioritising the contractual relationship between client and lawyer, both indicate that the costs rule is a rLGLG institution. By contrast, in the EUMS, state funded legal aid payments often fund litigation expenses, and thus the state provides and funds the process of justice, which is a system which exists for the good of the state (the group) as a whole. That is a rHGHG approach.

Jury determination of damages is also a rLGLG institution.[68] In the US, Vidmar argues that parties view jury determination of damages awards as fairer than expert determination or judicial determination. Expertise is rejected in rLGLG cultures relative to in rHGHG cultures, and so is judicial bureaucracy. Any discretion or quasi-discretion in the hands of experts or bureaucrats represents a threat to individual interests and so both claimants and defendants support jury determination of the quantum of punitive damages awards subject only to broad judicial oversight. The very high (and unpredictable) expected damages in US product liability cases may therefore be a by-product of individualistic preferences for jury determination.[69]

I turn finally to class action lawsuits. The procedural legal institution facilitating these follows from corrective justice, which follows from individualism. Class action lawsuits allow the risk of bringing a claim by a consumer against a firm to be spread out so that any given consumer bears relatively little risk of doing so. As the risk of doing so often effectively bars a corrective remedy (the rational apathy problem), it is natural that a rLGLG legal system would permit class action suits. Those suits also stand to benefit rLGLG lawyers who can be expected to actively seek out injured prospective claimants and present them with the chance to obtain[70]

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will do the compensating. In a rLGLG group, the key difference is that without fault no one is under an obligation to compensate or look after the injured, although studies have shown that individualistic societies have higher levels of personal responsibility for charitable giving and hence we can expect individualistic societies to rely more upon charity than upon any centralised obligation to look after the injured.

67 See Wells, Michael L. "A Common Lawyer's Perspective on the European Perspective on Punitive Damages." La. L. Rev. 70 (2009): 557. Wells Michael L. "Basic Questions of Tort Law from a Comparative Perspective." Journal of Civil Law Studies 9, no. 2 (2017): 11.

68 Vidmar, Neil, and Jeffrey Rice. "Jury-determined settlements and summary jury trials: Observations about alternative dispute resolution in an adversary culture." Fla. St. UL Rev. 19 (1991): 89.

69 To this I would add the observation made earlier, that the emotional symbolism of a group of 12 ordinary people making a very large award against a corporation, acts as an important outlet for consumer grievances towards USPI generally for high pharmaceutical product prices and for the high profits made by USPI. In a sense it is this mechanism which keeps the system in equilibrium, and where an award – even a very significant one – is determined by an expert or a judge rather than a group of ordinary people (consumers) then that emotional symbolism is lost. As such, the system itself would have to change. The system, therefore, including its use of jury determined punitive damages - whilst it leads to unpredictability for USPI - suits all actors overall. Bear in mind too, that USPI has been able to point to the unpredictability of these awards as a persuasive reason why the liability threshold for pharmaceutical products should be set relatively high.

70 Also, contingent fee arrangements are worthy of consideration here.

their corrective remedy, which also stands to benefit the laywers.[71] Again, therefore the structure of the US legal system is seen to be founded upon a rLGLG cultural orientation, both in that system and in the groups which interact in that system.

6.5.2.4 Social Norm of Litigiousness

The social norm of litigiousness in the US is shaped directly by the jurisdictional culture of the US. It is also shaped by the institutional framework provided to consumers in the adversarial common law system with all its individualistic institutional features. The lack of socialised healthcare or a strong welfare state also plays a major role. When compared to consumers in the EU/EUMS, often consumers in the US *must* use the courts to seek corrective remedies. If they do not use the courts then they will be unable to pay their medical bills. If their medical bills bankrupt them then there is a much lower level of social security to fall back upon compared to that found in most EUMS, and so it is to be expected that US consumers would be moved to litigate out of necessity more than their European counterparts. Thus, the social norm of litigiousness in the US (versus the lack thereof in the EU/EUMS) is linked to the Table 73 predicates of 'Welfare State'.

In addition, it is also linked to the predicate of 'Accountability and Blame'. Wagatsuma and Rosset have argued that in US culture often an apology is not enough to restore peace when harm has been caused by one group member to another, whereas in Japan often it is.[72] They say:

> *"Americans attach greater significance and legal consequence to the perceptions of autonomy and internal coherence, thus making apology important as an expression of self. This leads apologetic behavior to be accompanied by a justification or an emphasis on the acceptance of liability along with responsibility. The act of apology must accordingly spring from internal motivations, not from the request of external authority, and must not be weakened by mixed motives. In Western eyes, ambiguity and ambivalence detract heavily from the worth of an apology. Sincerity in an apology means internal coherence and wholeheartedness. In contrast, the Japanese concept of apology attaches primary significance to the act as an acknowledgment of group hierarchy and harmony. Less concern is expressed for paying the damages and more on repairing the injured relationship between the parties and between the offending individual and the social order that has been disturbed."*

Therefore, in a rLGLG society, an apology will arguably be less likely to suffice to settle a dispute until a tangible correction has taken place – often in a liability award.[73] When harm

71 Note that the 2020 Directive introduced in the EU is primarily concerned with representative actions for consumer protection. It does not envisage the involvement of lawyers from private firms. Again, therefore, EU law shows the rHGHG approach of protecting consumers from above without the involvement of self-serving individualistic private lawyers.

72 They are writing about Japan: Wagatsuma, Hiroshi, and Arthur Rosett. "The implications of apology: Law and culture in Japan and the United States." Law & Soc'y Rev. 20 (1986): 461.

73 See also Licht, Goldschmidt, and Schwartz (2007) *(at 2.3.1)…"In high autonomy cultures, individuals need the law as a transparent, a-contextual source of guidance. This would support societal endorsement of law-abidingness and law-based dispute resolution in courts.*

occurs, the offer of an apology on its own may be insufficient. The apology is likely to be viewed either as an attempt to avoid the corrective remedy, or as insincere because it is only given to mitigate the corrective remedy which may be imposed by the court. Yet, at the same time, where the possibility of a corrective remedy exists the offer of an apology may be taken as an admission of guilt and weaken any prospective defence to a claim. These factors combine in individualistic societies to ensure that all financial and economic aspects of a dispute must be settled before apology can operate to restore peace between victim and injurer.[74] This may help to explain the greater use of litigation by consumers (and generally) in the US relative to many other places in the world**.**

By contrast, in rHGHG societies, often there is a strong welfare state[75] including socialised healthcare, and thus less need for consumers to resort to litigation when injured. Overall, too, consumers are less accustomed to using the courts to resolve disputes with neighbours, employers etc. They prefer instead - where the counterparty is a part of the same group – to rely upon apology.[76] The prevalence of the norm of litigiousness in the US, coupled with the lack of socialised healthcare, leads to a much greater volume of product liability litigation by US consumers against US pharmaceutical firms when compared to that of EU consumers against EU pharmaceutical firms.

My conclusion for pharmacovigilance and product liability is that the groups, organisations and institution which are most proximate to the shaping of the regulatory position in each jurisdiction have a cultural orientation which - in each case – matches the preliminary cultural positioning of the jurisdiction in which they exist. As such, CT-GG has provided additional explanation to that provided by the extant theories in the case of pharmacovigilance and product liability, and that explanation – i.e., the underlying cultural orientation - is consistent across both divergences. It has also been capable of consistently explaining both the transatlantic divergences and the system divergences at the same time.

74 Note victim and injurer, rather than the group as a whole, as Wagatsuma and Rosset imply is the case in the rHGHG culture of Japan.

75 Certainly, this is the case in the EU/EUMS relative to the US.

76 That is what I have already set out regarding the PLD. Whilst it does make pharmaceutical firms strictly liable even for unknown and unknowable latent defects, often consumers will never use the system because they have no need to and there is a prevailing social norm against litigation. See Licht, Goldschmidt, and Schwartz (2007) (at 2.3.1) *"a culture that emphasizes embeddedness is less likely to promote a rule-of-law norm. Obligations and behavior are highly contextual in such societies and are not subject to rigid rules. Enforcement is more likely to be community-based (Greif, 1994). The key values in such cultures—respect for tradition, honoring elders, and obedience—encourage people to seek guidance in sources other than the law. Insistence on one's legal entitlements may be seen as a-social in such cultures"*

6.6 Sale Classification and Generic Substitution

6.6.1 Proximate Groups, Organisations, and Institutions

The most important group identified to impact upon the regulation was pharmacists in the US and the EU. The proximate organisations are the FDA in the US and the EMA/NAs in the EU/EUMS. The proximate institutions are price regulation in the EU/EUMS (versus its absence and/or supply side measures such as the Hatch-Waxman Act instead in the US) and product perceptions in the US and the EU. By product perceptions I mean consumer (and decision maker) risk perceptions concerning Nicotine Replacement Products (NRPs); consumer quality perceptions of generic/originator products; and consumer (and decision maker) efficacy perceptions of herbal remedies. I analyse these together under the heading product perceptions.

6.6.2 Culture and the Proximate Groups, Organisations, and Institutions

6.6.2.1 Pharmacists

In Chapter Four, I analysed the interest group of pharmacists in the US and in the EU. I determined that pharmacists in the US were relatively more dominated by Large Retail Pharmacy (LRP) whereas in the EU/EUMS (and particularly the SEUMS) they more often operated as Independent Pharmacy (IP). This is summarised below in Table 86.

Table 86 Pharmacists in the US and the EU

Group	Description/Objectives	Dominant In
LRP *Large Retail Pharmacy*	Commercial retail interests Maximising revenues Employing pharmacists in large numbers	**US**
IP *Independent Pharmacy*	Pharmacist owned and operated pharmacies Protecting independence/occupational task boundaries Maximising role and status as advisers and experts	**EU/EUMS** *Particularly SEUMS*

Cultural Orientation of Pharmacists in the US and the EU

I argue below that pharmacists in the jurisdictions/Clusters - faced with a trade-off between the goods which they could maximise in reward for the practice of their profession and forced to choose between those goods - followed two different paths over history. Their choice of paths reflected the underlying culture of the groups, and the culture of the jurisdiction/Cluster in which they operated. In the US pharmacists chose to focus more on the *occupational task role* of selling products for which they were rewarded with monetary payment. They followed a path marked by division of labour and vertical integration (with retail interests, to become LRP). In the SEUMS, particularly, pharmacists chose to focus more on the occupational task role of advising consumers,[1] for which they were rewarded with social status as experts. They followed a path marked by stratification: legal and social rules restricted competition and erected barriers to entry to the profession. Because of this, pharmacists in the SEUMS were able to retain both task roles of selling products and advising consumers, although in doing so their ability to specialise in sales and maximise their revenues was compromised. They were also able to maintain their independence and did not become vertically integrated with any another group such as large retail interests. The former path reflects rLGLG group cultures operating within rLGLG jurisdictional cultures. The latter reflects rHGHG group cultures operating within rHGHG jurisdictional cultures. These behaviours by the various groups are linked to the predicates in Table 73 above under the headings, 'Social Roles and Social Mobility', 'Competition and Profit', 'Innovation and Expertise' and 'Subgroups.'

I begin the argument by describing the trade-off and thus the inevitability of the need to choose. I then explain what I mean by the different goods and how these are maximised through the practice of the two different task roles. After this I describe the paths taken by pharmacists in the EU (particularly the SEUMS) and the US over history. This final part establishes the cultural positioning of the pharmacist groups (US: LRP and EU: IP), which I then adopt going forward in this section.

1 Regarding the products, their health and the interaction between the products and their health.

The Trade-Off Faced by Pharmacists

As stated at the end of Chapter Four, pharmacists face or faced a trade-off from the mid-20th Century onwards. This is shown again in Table 87.

Table 87 Trade-Off for Pharmacists in the EU and US from Mid-20th Century Onwards (2)

	Focused upon….	Maximised…	Method
US (LRP)	Occupational task role as sellers	Monetary revenues/income	Adopt larger business structures Employ pharmacists in LRP Support mandatory prescriptions **Sacrifice some expert advisory role**
EU (IP) *(particularly SEUMS)*	Occupational task role as advisors	Social status as experts	Retain ban on chain pharmacies Retain independent pharmacy Resist mandatory generic substitution **Sacrifice some revenue/income**

Here I focus on two occupational task roles which may lie either with doctors or with pharmacists. They are 1) the provision of advice to consumers ('Advice'); and 2) the sale of pharmaceutical products to consumers ('Sale').

Inevitability of Choosing: Division of Labour/Integration v Stratification

The inevitability of pharmacists choosing to focus[2] upon one task role comes down to the fact that without making a choice, pharmacists would be unable to defend either from encroachment by a 'neighbouring' profession or group such as doctors or retailers. Kronus[3] argues that over history the professions have sought to expand and/or defend their occupational task role boundaries vis a vis neighbouring profession. She gives the example of pharmacists and doctors.[4] To her insights I add the following. The reason why, without making a choice, neighbouring professions will encroach upon task roles is that productive efficiency results from specialisation and division of labour.[5] Specialisation leads to the ability to provide one 'unit' of Advice or Sale at lower cost than without specialisation, and because of this, division of labour occurs. Over time, a group of pharmacists providing both Advice and Sale will split and become two separate groups performing the two roles separately. Conversely, where pharmacists try to exercise both without specialising, another group will take one of the roles, *except* in so far as pharmacists have protected themselves from encroachment by

2 I say just focus, neither group/s totally abandon the other task role.

3 Kronus, Carol L. "The Evolution of Occupational Power: An Historical Study of Task Boundaries between Physiclans and Pharmacists." Sociology of Work and Occupations 3, no. 1 (1976): 3-37.

4 Kronus (1976) at pg. 3

5 If Pharmacist 'A' spends half of his labour hours specialising in retail skills, and the other half his labour hours specialising in advice giving skills then he will lose his Sale customers to Pharmacist 'B' who has invested 100% of her time developing her retail skills. He also loses his Advice customers to Pharmacist 'C' who has spent 100% of her time developing her advice-giving skills.

securing restrictions upon competition in the form of stratification (rules establishing barriers to entry to the profession and thus the legal permission to undertake the task roles in question). Division of labour also occurs in reverse. This is called integration. Integration can be horizontal[6] or it can be vertical.[7] Both forms of integration[8] lead to productive efficiency:[9] minimisation of unit production cost will result from allowing market forces to bring about division of labour and integration.[10] These market forces are impeded by legal regulation[11] which restricts competition or erects barriers to entry to a market or profession.[12] The opposite of the market dynamic of division of labour and integration I call here stratification. In societies that are highly stratified human beings erect[13] regulation such as this.

6 For example, between two independent pharmacies operating in the same Spanish village, neither of which has sufficient customers to stay in business and both of which are missing out on the economies of scale which could result from combining their businesses.

7 This is the case, for example, where four separate pharmacies in a rural county in a midwestern US State are each staffed by an owner-operator pharmacist. Each lacks the resources to expand their pharmacies to meet the retail demand in that county. However, each of the individual pharmacists is skilled in the sale of pharmaceutical products. An LRP operation such as Walgreens - which has sufficient capital resources to meet retail demand - employs the four pharmacists in one large retail pharmacy in the county town.

8 I argue here that vertical integration can be less clear cut than this. A profession may become vertically integrated – to some extent – with another economic actor (and interest group) through formal employment or through what I call an 'alliance' for mutual benefit, which involves repeated interactions between the members of the profession and the other actor. In the early-mid 20th century US it was efficient for the doctors' profession to vertically integrate (or ally itself) with the pharmaceutical industry to provide a distribution system for the sale of certain pharmaceutical products (the prescription system). Similarly, at the turn of the 20th Century in Germany it was efficient for certain pharmacists to vertically integrate with the new chemical/pharmaceutical industry to provide a distribution system for these products.

9 The ability to produce one until of the good: Advice or Sale (Sale can be the service of retail or the physical good itself – the product) at the lowest possible cost given the current state of technology.

10 Contrast the situation where not market forces but private incentives lead to excessive vertical or horizontal integration to obtain monopoly power in markets. In my view these are not market forces but human actions – more similar in nature to the erection of barriers to entry and restrictions upon competition through legal regulation.

11 Or by informal social regulation, such as the requirement in antiquity for doctors to be of noble birth.

12 One example is regulation which forbids chain ownership of pharmacies, thus withholding the possibility that retail will vertically integrate with pharmacists even where that would lead to greater productive efficiency.

13 In two senses: public interest theory says that market failures exist and regulators remedy these through regulation. Private interest theory says that interest groups demand regulation, which is supplied by regulators. It is the latter case which is contemplated here. Public interest theory states that regulation is enacted to remedy market failure. However, the definition of market failure will vary from culture to culture. Thus, a rHGHG culture may adopt a great deal of safety regulation – the cost of which is spread across the whole group - to save the few individuals each year who may be harmed by defective products. A rLGLG culture may be much more concerned with the regulation of markets (supply side competition regulation) to ensure that they remain free, and that individuals are free to enter, compete on, and leave them. Stratified groups with a rHGHG culture are likely to prefer much safety regulation, and professional interest groups such as pharmacists are likely to have high barriers to entry and restrictions on competition in place to protect those groups and the social status of members. Each professional group will struggle with each other over occupational occupation task boundaries, resisting vertical or horizontal integration. Groups with a rLGLG culture will prefer less safety regulation and more regulation in protection of competition, and their professional interest groups are more likely to accept vertical or horizontal integration where efficient.

Stratification also divides labour[14] but this division is likely to result in productive inefficiency.[15]

Task Roles, Rewards and Culture: Advice and Sale

The two task roles - Advice and Sale - are rewarded with different 'goods' in payment. In choosing between the task roles, pharmacists have implicitly chosen one good over another. Sale is rewarded with monetary payment. Advice[16] is rewarded with social status: advisers are experts and are esteemed by others in society for this role. Pharmacists have chosen their task roles based upon their preferred good and their preferred good reflects their group culture. A group with a rLGLG culture[17] will prefer monetary payment. Money is in theory a universal medium of exchange, but its effectiveness as such depends on the level of economic freedom in a society. In rLGLG cultures such as the US there is a high level of economic freedom.[18] Thus, it is more often possible to exchange money for whatever good/s are sought according to individual preferences.[19]

A rHGHG group will seek money relatively less. Money will not be so effective a means of exchange in a rHGHG culture because of the external prescriptions which fetter the ability to bid and bargain for the satisfaction of individual preferences.[20] Moreover, in rHGHG groups there are hierarchies,[21] and groups which are rHGHG attract hierarchical individuals who accept hierarchical structures, tending to believe that their place within those structures is fixed. Thus, rather than seek monetary payment they instead seek a good which reaffirms their place within the hierarchy and signals this to others in the hierarchy. Those who, in rHGHG cultures, become pharmacists educate themselves to achieve this reaffirmation. The return they receive on their educational investment is that reaffirmation, and their objective as professionals is not to build wealth but to continually reaffirm that status and signal it to others.[22] Advice giving is associated with expertise, which is associated with education, and

14 E.g., the regulation in England and Wales stipulating that only Barristers may speak in court but only solicitors may conduct litigation.

15 For example: stratification in the form of restrictions upon chain ownership of pharmacies permits IP to engage simultaneously in Advice and Sale but because of the productive inefficiencies which result, the reward obtained through the task role of Sale (i.e. revenue) is diminished.

16 Whilst it may receive some monetary payment in fees.

17 I am writing here about the two groups of pharmacists: EU/SEUMS pharmacists operating as IP, and US pharmacists dominated by LRP, however in the US and the EU/SEUMS these groups both operate in a wider national/jurisdictional culture which is also rLGLG or rHGHG and the culture of which constrains the culture of the subgroups. Thus, operating in a rHGHG French culture the interest group IP pharmacists in France will likely also be rHGHG.

18 Although money is still not a *perfect* medium of exchange even in a society with the highest possible level of economic freedom.

19 If a change of social position within a rLGLG society is sought by an individual, then he saves his money and buys the new position. This is not so easily done in a rHGHG society.

20 The most basic example is a regressive, redistributive tax system.

21 And these groups operate within the broader hierarchies of the rHGHG jurisdiction in which they exist.

22 For example, noble birth was once the only way to obtain a specific position within a rHGHG society. And, due to its nature, that position was fixed. As European countries became relatively less HGHG and relatively more LGLG over time, noble birth became less important as a means of ordering the social positions of individuals. Educational attainment has often led to a professional occupation which imports a certain social status. This is how the bourgeoise flourished and the middle class emerged in Europe as the industrial revolution advanced: they became educated and learned skills which not only increased their monetary payment on the labour market but gave them as status as independent professionals.

signals a high social status in a rHGHG society. Thus, pharmacists in a rHGHG society will be rHGHG as a group and will seek to protect their occupational task role of Advice. Moreover, they will trade off monetary payment to preserve that role and social status.[23]

A History: Division of Labour/Integration and Stratification and Pharmacists in the US and the EU/EUMS

Now I apply these insights to position pharmacists culturally in the US and the EU/EUMS. I do so by giving a history.[24]

In antiquity in England and throughout Europe doctors would generally be of noble birth, and entry to this profession was not possible any other way.[25] Later, toward the renaissance, international trade developed, and mercantilism emerged. Many new products with purported medicinal qualities became available across the continent. Noble doctors did not have the time to specialise in importing these products, becoming expert in, or selling them, so a new group of tradesmen emerged known (in England and in English) as apothecaries.[26] As time went on, apothecaries amassed wealth from their activities and were able to organise themselves in a guild[27] which lobbied the King successfully for monopolies on the import and sale of certain products.[28] Eventually, apothecaries in England became powerful and won

23 In rLGLG societies where hierarchies are not so strong, there is a relatively less high social status payment associated with education and the giving of advice, although there may be a strictly economic reward associated with the investment made in education which justifies the charging of high fees to give advice (as is the case with doctors) or salaries high relative to the average uneducated salary and it is likely that this is what will be sought in individualistic societies. Thus, in these societies pharmacists are likely to be more keen to protect their occupational task role of Sale, for which they receive a money payment.

24 Kronus (1976) at pg. 8 onwards. The history is taken from Kronus (1976) but the insights regarding culture, division of labour, integration, and stratification - applied to this historical story - are my own. My argument is that the US has had less stratification than Europe/the EU since its existence began, and that pharmacists in the US have been less stratified as a group and in their place within US society than their European counterparts in the EU/EUMS. The lack of stratification in the US is shown by the greater proclivity for and propensity towards integration and division of labour there relative to the EU/EUMS. This, I argue, is reflective of an underlying culture which is rLGLG.

25 Kronus (1976) at pg. 10

26 Kronus (1976) at pg. 10 The apothecaries themselves split from a pre-existing group at the time: grocers. Grocers were the forerunners of modern-day retailers. Apothecaries specialised in the import and Sale (only) of a narrower range of products than grocers. Hence division of labour occurred in the group of grocers. Being an apothecary reaffirmed a different social status than being a doctor. Apothecaries, like grocers, were tradesmen. Tradesmen were not educated or noble at this stage, nevertheless they represented the beginning of the emergence of the middle class in Europe. They were socially inferior, however, to doctors.

27 The earliest professional body representing pharmacists (as apothecaries at this time approximated) as an interest group.

28 Kronus (1976) at pg. 15. Now, apothecaries had wealth, but not yet the social status of doctors. In these still rHGHG (compared to today in the EU/EUMS) societies, money was not yet enough to purchase social status, for the reasons given above. The wealth of apothecaries grew, however, as standards of living raised across Europe over time, and a wider class of people could afford to pay for healthcare in some form. Unable still to afford the services of noble doctors, many ordinary people turned to apothecaries who at least has expert knowledge of the products which they sold. Now, apothecaries were being asked to perform Advice as well as Sale. But the barrier to entry of noble birth excluded them from the doctor's profession. Arguably the productively efficient solution at this stage was for apothecaries to advise on the specific products which they sold, whilst doctors gave general advice on health without selling products. Doctors opposed efforts by apothecaries, however, to give any advice at all.

expanded occupational task boundaries to include Advice as well as Sale.[29] Market forces caused efficient division of labour again as apothecaries came to focus mostly on Advice, later becoming modern doctors whilst the class of noble doctors disappeared.

Modern pharmacists emerged during the industrial revolution to take over the role of Sale.[30] But this group (pharmacists) behaved differently in the North of Europe than in the South. By the time the 19th Century was ending, pharmacists in Germany had become vertically integrated with the new chemical-pharmaceutical industry, providing a distribution system for these new products. In the UK, for many decades there existed both pharmacists – who provided Advice and Sale – and chemists – who focused only on Sale. Chemists[31] incorporated themselves and focused on maximising revenues. Eventually by the middle of the 20th Century the latter came to vertically integrate the former through employment, and LRP emerged. In the south of Europe, however, something different happened. Pharmacists there had erected stronger barriers to entry, which meant that they were able to retain the roles of Advice and Sale together. Quoting Barger in 1936:[32]

> *"On the Continent, pharmacy is more of a learned profession, less a matter of trade, than it is in Great Britain. Its prestige is perhaps greatest in France and in Spain, where a pharmaceutical training still often precedes an academic career in pure chemistry."*

They also defended themselves against integration in to LRP by lobbying for the bans on chain ownership of pharmacies. Subsequently, productively efficient division of labour between Sale and Advice has not happened so strongly in the SEUMS as in the NEUMS. Advice is split between doctors and pharmacists in this more stratified (rHGHG compared to the US, at least, and relatively high group vis the NEUMS) Cluster. Doctors and pharmacists there continue to fight over their occupational task boundaries.

Turning to the history in the US. In the 1600s, at the time of the original colonisation of the north-eastern American continent by northern European settlers, there was very little reason for doctors of noble birth to board a ship and join the American colonies. The established hierarchies in Europe were already to their benefit. Thus, in the early decades of European settlement of what is now New England, there were few doctors. The doctors' profession here began without stratification in the form of barriers to entry or other restrictions upon competition which might have inefficiently demarcated the occupational task boundaries between doctors and pharmacists.[33] Even when educational institutions were established, educational attainment did not become the barrier to entry which it was at the same time in

29 Kronus (1976) at pg. 15. As a result, eventually, the class of noble doctors in Europe was to disappear entirely as apothecaries completely supplanted them. Later, apothecaries in the UK were to form the British Medical Association to represent their interests and they are the forerunners of today's general practitioners, or modern-day doctors.

30 Or rather they emerged and encroached upon the apothecary task role of Sale which apothecaries could not defend simultaneously with that of Advice.

31 Like Boots Cash Chemists Ltd. from *Pharmaceutical Society of Great Britain v Boots Cash Chemists Ltd*. [1953] 1 QB 401.

32 Barger, G. Grundriss der Geschichte der deutschen Pharmazie. Nature 137, 474–475 (1936). https://doi.org/10.1038/137474a0

33 Kronus (1976) at pg. 20, in fact, it was a frontier free-for-all ruled largely by economic opportunity. Doctors thus maintained their independence and could claim to be doctors without official regulatory certification as such. The forerunners of modern American pharmacists were able make a great deal of money during the revolutionary war by importing medicines and selling these to whichever side paid the highest price.

Europe. The colleges tended to oversupply the market with doctors.[34] Market forces rules instead: good doctors would be able to retain their patients, whilst bad doctors would lose them and drop out of the market as supplier. This free market for patients, caused some doctors to thrive and these lobbied to retain this non-stratified system.[35]

The lack of stratification left both doctors and pharmacists open to opportunities for vertical integration.[36] Thus, by the mid-20th Century doctors in the US had become vertically integrated with the pharmaceutical industry in the US.[37] This, as I have set out in Chapter Four, and above, helped lead to the introduction of the compulsory prescription system in the US. Compulsory prescriptions left US pharmacists with no choice but to focus on Sale rather than Advice. As such, when modern retail emerged in the latter half of the 20th Century, US pharmacists were vertically integrated into retail to become LRP.

Vertical integration of pharmacists in the NEUMS and the US was possible because these groups were LGLG relative to pharmacists in the SEUMS Cluster. The latter operated within a stratified rHGHG society and erected stronger barriers to entry and restrictions upon competition. This enabled them to defend both task roles of Advice and Sale simultaneously, albeit at the cost of revenues due to foregone gains from productive efficiency. This also enabled them to avoid vertical integration and to remain independent. In the SEUMS Cluster pharmacists reaffirm and signal to others in that stratified society an elevated social status. Key to this is high educational attainment, which is associated with the giving of Advice. In the US and NEUMS Cluster pharmacists are content to accept monetary payment over social status and the rLGLG society in which they operate enables them to exchange money for whichever goods are individually preferred – if their preferences are for goods which can be priced in the market. The cultural orientation of pharmacists as a group in the US (LRP) and the NEUMS (IP and LRP) and SEUMS (IP) Clusters matches the preliminary cultural positioning.

6.6.2.2 Product Perceptions

Now I turn to the informal social institution of product perceptions.[38] That informal institution either is, or shapes, the individual perceptions of consumers and of decision makers in agencies. The perceptions can relate to the (safety) risks or to the benefits (efficacy) of the products. Here I discuss specifically to the following products: synthetic pharmaceutical products, NRPs, herbal remedies, and generic (versus originator) products. The proximity of this institution to the regulation in the US and the EU was set out at the end of Chapter Four. The perceptions of the various products are summarised in Table 88 below.

34 Kronus (1976) at pg. 20

35 I.e., to avoid the introduction of any more centralised system for the employment of doctors and the allocation of patients, of the type seen in European healthcare systems

36 In other ways than vertical integration with agencies or the state. Ways to which they were not opposed

37 In the sense of being allied with it.

38 I consider this an institution because it is an informal rule governing how individuals in a group *collectively* perceive 'good' and 'bad', 'safe' and 'unsafe' and 'effective' and 'ineffective' which impacts upon how individuals perceive products. An example is what is called the 'natural is better' heuristic. That heuristic itself is an informal rule of social interaction, a rule governing how individuals from the same culture discuss products. This, in turn, may shape individual risk perception.

Table 88 Product Perceptions in the US and EU

	Synthetic[39]	Herbal	NRPs	Generics v Originators
US	Relatively effective	Natural, ineffective	Addictive, risky	Brand (efficacy) value
EU	Relatively risky	Natural, effective	Synthetic, risky	Less brand (efficacy) value

The cultural orientation of these informal social institutions is linked most clearly to the predicates in Table 73 above under 'Innovation and Expertise,' but also – in the case of perceptions of generics v originator products under 'Social Roles and Social Mobility.' The aspect of the theoretical framework developed in Chapter Five which is most directly applicable in this section, however, are the sections developed regarding the 'myths of nature,' which I summarise again below. I begin by setting these out, then the following section is structured in two halves. In each half I adopt a certain cultural positioning (rHGHG/rLGLG) then - drawing upon the theory and the predicates from Table 73 - I consider what perception of each product is expected based upon that positioning, taking each of the four products in turn.

Myths of Nature, Views of the Human Body, and Product Perceptions

In Figure 25[40] below I set out again the insights explained more fully in Chapter Five regarding the myths of nature.

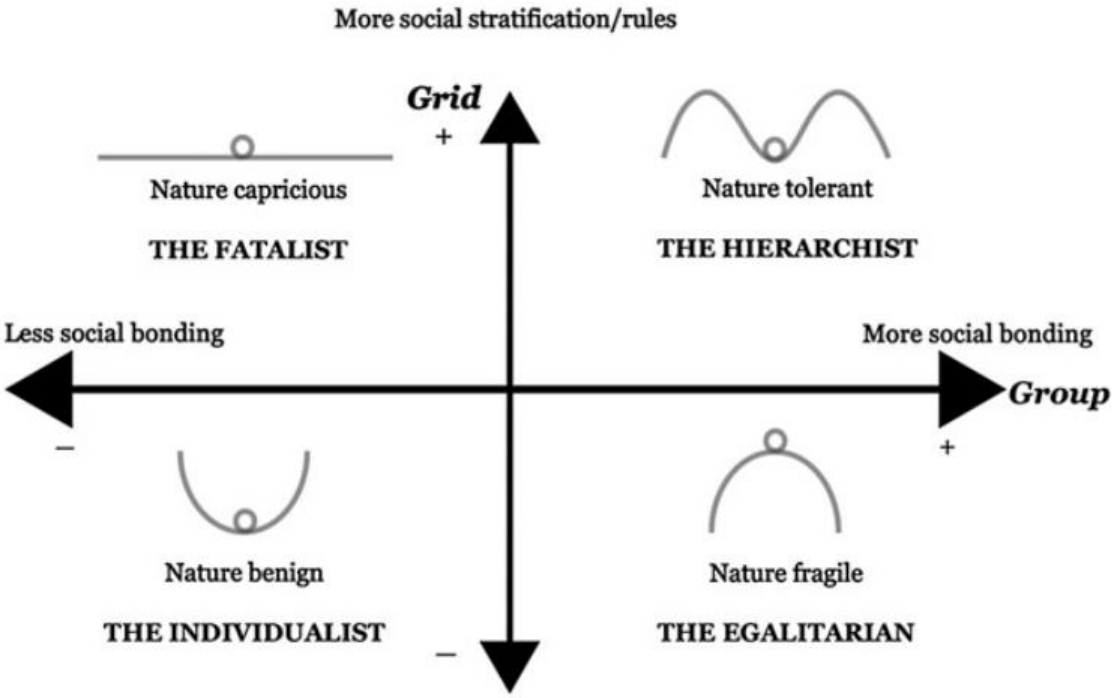

Figure 25 **Myths of Nature (2)**

Figure taken from McNeeley and Lazrus 2014

39 Versus natural, unprocessed products.

40 The figure here, is taken from McNeeley and Lazrus (2014) at 508..

To recapitulate: the myth of nature associated with egalitarianism is that *"nature is fragile and in a precarious balance with society"*[41] and egalitarians *"tend to view the relationship between humans and nature as lying in a delicate balance, prone to human influence leading to a collapse."*[42] The hierachical worldview corresponds with a myth of that nature that it is *"manageable and tolerant of some human influence and will thus accommodate human action to a point"*.[43] Individualism corresponds with a myth of nature that it is benign and that it automatically adjusts to human actions.[44] The fatalist worldview corresponds with a myth of nature that it is *"capricious and fundamentally random and unpredictable".*[45] I adopt this approach to analyse perceptions of pharmaceutical products. In doing so I consider how the myths of nature relate specifically to the human body, which is a thing of nature.

Table 89 Myths of Nature and Corresponding Views of Human Body

Own Table based upon McNeeley and Lazrus 2014 and Others[46]

Worldview	Myth of Nature	Corresponding View of Human Body
Hierarchical	Nature tolerant	Non-natural human actions in relation to the human body are inherently harmful to it. Rules are effective, up to a point, to protect the human body from this harm. Rules should govern the consumption of non-natural substances.
Egalitarian	Nature fragile	Non-natural human actions in relation to the human body are inherently harmful to it. Rules will not mitigate this risk. Humans should avoid consumption of non-natural substances.
Individualistic	Nature benign	The human body will adjust to what the human puts in it, or otherwise does to it. The human body can be changed and improved by the consumption of non-natural substances.
Fatalist	Nature capricious	The state of the human body is not determined by human actions. Consumption, abstinence and/or rules make no difference.

So – I say - to the egalitarian the human body is fragile, lying in a delicate balance with nature. Non-natural human interference with the human body: including through what humans eat, snort, smoke or inject – so far as this is unnatural - is inherently harmful to the human body. To the hierarchist, nature is tolerant up to a "*tipping point"*[47] and so there is a need to direct human actions through rules to protect nature. To protect the human body there should be

41 Jones, Michael D. "Leading the way to compromise? Cultural theory and climate change opinion." PS: Political Science and Politics 44, no. 4 (2011): 720-725. Douglas, Mary. Thought styles: critical essays on good taste. Sage, 1996.

42 McNeeley and Lazrus (2014) at 509

43 Ibid. at 508

44 See Thompson, M. "Cultural discourses. Human Choice and Climate Change, Volume 1: The societal framework. S. Rayner and EL Malone. Columbus: Ohio." (1998): 265-344. For example, in the case of climate change risks individualists are likely to believe that the climate is naturally variable and that humans cannot change this process.

45 McNeeley and Lazrus (2014) at 508

46 See the references set out in Chapter Five.

47 Ibid. at 509

rules governing the availability of non-natural substances for consumption. For both the 'high group' worldviews – egalitarian and hierarchical - nature and the human body are inherently susceptible to harm by human action. The two differ on the extent to which rules are capable and welcome as a means of mitigating that risk. By contrast, to the individualist nature is benign and automatically adjusts to human actions. Thus, the human body can be improved, strengthened, reshaped, and resized through non-natural human action including consumption. The fatalist, on the other hand, would consider that regardless of what one does or does not do to the human body, the result is unlikely to change.[48] The four cultural worldviews and myths of nature as applied to the human body are set out above in Table 89.[49]

Relatively High-Grid, High-Group

Synthetic Pharmaceutical Products

i. Expected Perception

Synthetic pharmaceutical products are non-natural products which have been processed by human action.[50] Consumption of a synthetic pharmaceutical product is a non-natural human action in relation to the human body. Therefore, the hierarchist is likely to perceive the consumption of synthetic pharmaceutical products as potentially harmful, and in need of constraint by rules regarding licensing and availability for sale etc.

ii. Evidence

Evidence from Chapter Four fits with this. Many fewer products are available in the GSALE category in the rHGHG EU/EUMS [51] than in the rLGLG US, and there is widespread use of the PSO category. Adopting a broader approach, this is also the perception of synthetic pharmaceutical products which is observed amongst consumers in the EU/EUMS. For example they consider a synthetic product - pain relief medication - to be riskier once switched to non-prescription status, [52] whilst US consumers take the opposite view.[53] Where

48 Because human action in relation to the body is rendered meaningless by external (non-human) forces which ultimately determine what will happen to the human body (e.g. disease, death etc).

49 This is my own table but it applies insights from McNeeley and Lazrus (2014) and others cited in this Chapter and Chapter Five.

50 In the case of pharmaceutical products normally in a lab to identify and extract active ingredients, combine them with other active ingredients and/or add excipients etc.

51 Barrenberg, E., and E. Garbe. "Use of over-the-counter (OTC) drugs and perceptions of OTC drug safety among German adults." European journal of clinical pharmacology 71, no. 11 (2015): 1389-1396.

52 Perceptions of synthetic products as inherently harmful – e.g., prescription medicines – are stronger among young people than among older people and this makes sense given that high group egalitarian worldviews are more common amongst younger people. See Balog-Way, Dominic HP, Darrick Evensen, and Ragnar E. Löfstedt. "Pharmaceutical benefit–risk perception and age differences in the USA and Germany." *Drug Safety* 10 (2020).

53 Hanoch, Yaniv, Konstantinos V. Katsikopoulos, Michaela Gummerum, and Eric P. Brass. "American and German students' knowledge, perceptions, and behaviors with respect to over-the-counter pain relievers [OTCPRs]." Health Psychology 26, no. 6 (2007): 802. The authors found that significantly more Americans than Germans take over the counter pain relief medications and that they also take significantly more of these. Americans exhibited less knowledge about side effects than their German counterparts. Americans were also less likely to consult a doctor when feeling pain but more likely to take OTCPRs. Finally, Americans viewed OTCPRs as

General Sale (GSALE) exists in Europe (Germany) consumers are more likely to consult a doctor before using these products than are US consumers.[54] These pieces of evidence both correspond with the expected rHGHG product risk perception: the product is only safe where its availability is constrained by rules.[55] 'Chemophobia' is prevalent in the EUMS, for example. Siegrist, who undertook a survey in Austria, France, Germany, Italy, Poland, Sweden, Switzerland, and the United Kingdom observes: *"The term, 'natural', evokes almost exclusively positive emotions... Consumers often rely on the natural-is-better heuristic, which results in a preference for natural foods and a much more negative perception of synthetic chemicals when compared with chemicals of natural origin."*[56] Particularly in the south of Europe (France, Portugal and Spain), the risks of pharmaceutical waste in the environment is considered high by both laypeople and experts.[57] Outside of pharmaceuticals, consumers in the EU/EUMS are more likely than their US counterparts to view genetically modified food as risky.[58]

Nicotine Replacement Products

i. Expected Perception

NRPs are synthetic pharmaceutical products and so the expected rHGHG perception is as set out above. Tobacco smoking is likely to be perceived – without more information - as less risky to the human body than NRPs, since tobacco is a natural, non-synthetic product.

ii. Evidence

The evidence in relation to NRPs is set out under the rLGLG section, below.[59]

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riskier after their status changed from prescription only to over the counter, whereas Germans believed they posed less risk.

54 Hanoch et al (2007).

55 This can also, of course, be linked to the fact of the high levels of consumer confidence in the FDA in the US. That, as was discussed above, results from direct-to-consumer accountability which, in turn, is liked to a rLGLG cultural orientation in the FDA.

56 He continues *"...This manner of thinking also results in a biased risk perception of cleaning products that are labelled as being 'eco'. Laypeople will typically evaluate an 'eco' drain cleaner to be much safer than a regular drain cleaner, despite the two products containing very similar ingredients and the same warning labels."* Siegrist, Michael, and Angela Bearth. "Chemophobia in Europe and reasons for biased risk perceptions." *Nature chemistry* 11, no. 12 (2019): 1071-1072.

57 Luís, Sílvia, Maria Luísa Lima, Lucía Poggio, Juan Ignacio Aragonés, Audrey Courtier, Benoit Roig, and Carole Blanchard. "Lay people and experts' risk perception of pharmaceuticals in the environment in Southwestern Europe." Regulatory Toxicology and Pharmacology 117 (2020): 104783.

58 Nelson, Carl H. *"Risk perception, behavior, and consumer response to genetically modified organisms: toward understanding American and European public reaction."* American Behavioral Scientist 44, no. 8 (2001): 1371-1388.

59 A survey undertaken in the US in 2011 found that amongst respondents taken from a demographic which is consistently shown on other surveys to be high group, egalitarian or hierarchical including female and African American respondents… (Kahan, Dan M., Donald Braman, John Gastil, Paul Slovic, and C. K. Mertz. "Culture and identity-protective cognition: Explaining the white-male effect in risk perception." Journal of Empirical Legal Studies 4, no. 3 (2007): 465-505.)… there was a great deal of concern regarding the safety risks posed by NRPs, with many believing that NRPs were at least as likely to cause cancer and heart disease as cigarette smoking. This was despite there being no strong evidence for the harmfulness of NRPs. This belief was less pronounced amongst white male Americans but many of these were opposed to NRPs on the basis that they were addictive. This is further evidence that high group cultures perceive synthetic pharmaceutical products as inherently risky. See also

Herbal Remedies

i. Expected Perception

The rHGHG efficacy perception here has two components. The first is that the products, being natural, are not inherently harmful to the body if consumed. The second relates to what healing *means* in high group (including rHGHG) cultures. The meaning of healing adopted in these cultures will affect perceptions of the efficacy of products sold for healing. Kirmayer argues that *"healing involves a basic logic of transformation from sickness to wellness that is enacted through culturally salient actions"*.[60] The culturally salient outcome of 'wellness' is matched to a culturally salient 'process' of healing. The process is key: whatever results from the culturally salient process *will be* the culturally salient outcome. The mainstream (and rHGHG) approach to healing in the US and the EU/EUMS is medical science. This accepts only changes in certain biomedical markers of body functioning as evidence for or against the effectiveness of a pharmaceutical product. The administration of certain products is the process and the change in the markers is healing. As Kirmayer points out[61] this will not mean that the person is 'well' in all cultures.[62]

Other examples of culturally salient processes are given in his paper.[63] Naturopathy is one, and this includes the use of traditional herbal remedies. Here the 'theory of affliction' is a weakened state of body, which can be strengthened through diet, cleansing, and 'natural' remedies. According to the high group cultures the body is weakened through non-natural human action and so can recover only through natural processes. This matches the high group myths of nature and corresponding view of the human body. In addition, in high group cultures tradition – longstanding use in the community - will be important. Extensive social bonding will determine individual views of the culturally salient process. Here, it may be enough that everyone in the community accepts the product and uses it for the purposes of healing. In a rLGLG culture the individualist may prefer to differentiate himself from the group

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Czoli, Christine D., Geoffrey T. Fong, Darren Mays, and David Hammond. "How do consumers perceive differences in risk across nicotine products? A review of relative risk perceptions across smokeless tobacco, e-cigarettes, nicotine replacement therapy and combustible cigarettes." Tobacco Control 26, no. e1 (2017): e49-e58. It is worth noting that smoking rates in the EU/EUMS are much higher than in the US. According to 2020 data the rate of adult smoking in the US is 12% whereas the rates in some of the EUMS from the sample are: France 22%, Spain 23%, Germany 19%, Italy 20%, Portugal 17%, Greece 27%, the Netherlands and Belgium both 18% (source: https://ourworldindata.org/smoking). This evidence supports the view that the rHGHG cultures perceive natural tobacco smoking to be less harmful than use of synthetic NRPs. Carpenter, Matthew J., Marvella E. Ford, Kathleen Cartmell, and Anthony J. Alberg. "Misperceptions of nicotine replacement therapy within racially and ethnically diverse smokers." Journal of the National Medical Association 103, no. 9-10 (2011): 885-896 at 885

60 Kirmayer, Laurence J. "The cultural diversity of healing: meaning, metaphor and mechanism." British medical bulletin 69, no. 1 (2004): at 33.

61 Kirmayer (2004) at 43.

62 Kirmayer (2004) at 43. "*Biomedicine defines physiological parameters and aspects of healthy functioning independent of the person's experience or global state of being; it is thus possible for a treatment to work (e.g. correcting blood levels) even though the person continues to be ill."* In addition, to confuse the picture, the culturally salient process may have a psychological effect on the afflicted person such that they show biomedical markers of improvement which satisfy high grid high group hierarchical scientific medical experts that healing has taken place. This is the placebo effect.

63 Kirmayer (2004) at 35. One is traditional Chinese medicine – commonly adopted across east Asia, whereby through acupuncture an imbalance in the energies or the five phases may be corrected. Homeopathy is a practice originating in northern Europe for which the theory of affliction is that life force is out of balance, and this balance can be restored by the administration of homeopathic remedies.

by seeking a newer, more expensive, more processed, or branded product.[64] In a relatively high group culture one therefore expects a perception of herbal remedies as effective. A rHGHG culture would accept rules which mitigate the risk of interactions between natural and non-natural products such as synthetic products taken at the same time as herbal remedies. Moreover, it follows from the preference of rHGHG cultures for expertise (see 'Innovation and Expertise' in Table 73 above) that doctors and pharmacists would promote safe (but only safe) use of herbal remedies, and would thus be correspondingly more willing to prescribe or recommend them to consumers.

ii. Evidence

Some evidence of this perception has been given already where discussing synthetic products. The high demand for herbal remedies in the EU/EUMS is further evidence. The acceptance of longstanding traditional use as a basis for limited efficacy claims under the Traditional Use Registration (TUR) provisions of the 2004 Directive is further evidence. The mandate for safety warnings against interactions with synthetic products also supports the view that there is a rHGHG perception of herbal remedies in the EU/EUMS.

Generic (versus Originator) Pharmaceutical Products

i. Expected Perception

The rHGHG perception institution is unlikely to attach value to originator over generic drugs or see the former as more effective. That is because for those of a rHGHG cultural orientation their use of all synthetic medications is likely to be guided by experts such as doctors and pharmacists (see the predicates in Table 73 under 'Innovation and Expertise'). They will follow the advice of the doctor or the pharmacist. The advice – including choice of medicine - is the external rule upon which reliance is placed to mitigate risk in the rHGHG perception.

ii. Evidence

This is reflected in the approach taken in the EU to patient consent in the regulation of generic substitution.[65] Additional evidence is found in surveys in the EUMS. Whilst doctors and

64 Consumers in the rHGHG EU perceive the products as effective because of their longstanding traditional use regardless of what randomised clinical controlled trials say. The original belief in the efficacy of herbal remedies has long been there in Europe and – in Germany in particular – persisted even when synthetic products began to enter the market in force. Thus, as has been explained above, herbal remedies were given their own system of regulation, first by splitting them off from sale side by side with synthetic products in Germany in 1901, and then later in the German Medicines Act and most recently in the 2004 Directive. The EU approach to herbal remedies is to 'grandfather' these products in their ability to make efficacy claims where there is a longstanding history of traditional use in the community. This regulatory approach reflects a high-group underlying culture and – because it then subjects the products to safety requirements including label warnings, it is also a high grid approach.

65 Of some significance in these EUMS is the perception which doctors and pharmacists have of generic medicines, which seems to be largely negative. Granlund finds that Swedish Doctors – particularly in private practice seem to show a relatively high degree of brand loyalty to originator medicines over generics whilst Dylst finds that physicians in France have a particularly poor view of generic drugs in terms of both efficacy and safety. Pharmacists, meanwhile, he finds to have more positive perceptions. See: Granlund, David. "Are private physicians more likely to veto generic substitution of prescribed pharmaceuticals?." Social science & medicine 69, no. 11 (2009): 1643-1650. See also: Dylst, Pieter, Arnold Vulto, and Steven Simoens. "Analysis of French generic medicines retail market: why the use of generic medicines is limited." Expert review of pharmacoeconomics & outcomes research 14, no. 6 (2014): 795-803.

pharmacists both have strong views on generics v originators in France and Sweden,[66] patients do not. Respondents to a survey in Greece were opposed to mandating generic substitution on pharmacists or generic prescribing on doctors because these respondents relied upon doctors and pharmacists to apply their expertise to choose the right product, having little basis upon which to do so themselves.[67]

Relatively Low-Grid, Low-Group

Synthetic Pharmaceutical Products

i. Expected Perception

Individualists can be expected not only to welcome synthetic products, but to also consider them as *more effective* than natural, unprocessed, products. In the rLGLG view the purpose of processing is to increase quality (effectiveness) and thus the more a product is processed, the more effective it will be for changing and improving the body. High prices signal product quality because processing requires resources and raises the cost and price of the product. Natural products require no processing and are cheaper and thus in the eyes of individualists will be less effective. The preference for innovation (i.e. processing of natural substances to produce products with new qualities) is also linked to the predicates in Table 73 under 'Innovation and Expertise'.

ii. Evidence

It was set out above and in Chapter Two how consumers in the US seek to exercise relatively more say over the prescription decision since the advent of DTCA. This is evidence of consumers seeking pharmaceutical products as a tool to change and/or improve their bodies.[68]

66 Dylst, Vulto, and Simoens (2014) at 795-803. These negative perceptions amongst doctors are probably a result of the decades long practice of pharmaceutical firm detailing which have led to strong brand loyalty on the part of doctors. Coupled with the indifference amongst consumers/patients (many of them are not paying anyway so the price aspect of the price-product choice is irrelevant to them) explains why doctors and pharmacists are targeted with coercive regulation to increase generics uptake, with the difference between which group is targeted depending upon the extent to which they view generics as unsafe or ineffective. This helps us to explain, to some extent, the lack of express consent requirements from consumers across the EU, even where pharmacists have retained discretion (to date) whether to substitute – France is the best example.

67 Yfantopoulos, John N., and Athanasios Chantzaras. "Drug policy in Greece." Value in health regional issues 16 (2018): 66-73.

68 That informal social institution of perception of synthetic medicines as both largely safe and to be used to change and improve the body has contributed to the regulation of sale classification as we see it today in the US. In the case of Prescription Only (PO) medicines, these are now advertised direct to the consumer and often the consumer/patient will go to see the doctor to request a specific medication based upon a specific result he wishes to see based upon an advertisement shown to him by the pharmaceutical firm. In the case of non-prescription medicines, the abundance of pharmaceutical products made available GSALE (compared to in the EU) and the lack of the Pharmacist Supervision Only (PSO) category is brought about in part by a public who perceive synthetic products as safe and effective generally, and desired for use to change and improve bodies. Not, as is more the case in the EU, to be taken only as a last resort and then only under the advice of the more qualified doctor and pharmacist. In the US, the patient picks the health outcome he wishes to achieve and then either buys the GSALE product direct from a retailer or seeks it from the doctor if it is a PO product. There is no need for a PSO category

Nicotine Replacement Products

i. Expected Perception

NRPs are a synthetic product, thus the individualist would perceive them as safe and effective and seek them for certain health outcomes. But there is an additional complication in the case of NRPs and individualistic cultures, and that is the issue of addiction.

Addiction is particularly salient, and troubling, in the rLGLG worldview. It is a socio-cultural concept more than it is a medical one. Room explains[69] that addiction as a concept was brought to the foreground *"by social conditions in the new American republic"* as a result of *"growing population mobility and the stretching of extended family ties and the weakening of social support networks for the nuclear family, which objectively made the fortunes of family members more dependent on the self-control of the husband/father".*[70] In rHGHG societies family and social ties are strong and rules enforced by others can be expected to act as an effective control on the behaviour of individuals. In rLGLG societies there are fewer of these social controls and thus 'self-control' became key.[71] Self-control cannot be achieved perfectly, but to be accepted by his family and his employer the individual – according to Room and, earlier, Levine[72] - needs some way of explaining those times when he prioritises his own desires. According to Alasuutari,[73] *"the phenomenon called "loss of control" is shown to be the result of a particular way of solving the cognitive dissonance between a man's will to preserve both his personal freedom and a peaceable relation to his significant others."* Therefore, in rLGLG societies where extended social ties became weaker as a means of third-party control of individuals, there would be relatively more reliance upon 'self-control' and correspondingly more instances of 'loss of control'. This phenomenon in individualistic cultures is linked to the predicates in Table 73 above under 'Accountability and Blame.' In particular, the individualistic focus on personal blame for failure and personal credit for success is relevant here.

Considering specifically the US, 'loss of control' would often be accompanied by the consumption of alcohol. It is useful to the individualist to be able to point to some *external* thing, such as a substance, which explains his behaviour because he retains the option to simply abstain from the substance and thus, he maintains his illusion of control in the long run.[74] In rLGLG societies therefore there is shared socio-cultural conception of a problem

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That system is what he wants and that is what he – either directly through interest group lobbying (e.g. the anti-smoking lobby in the case of NRPs) or speaking through mass consumption choices on the market – has brought about as the result of his perceptions.

69 Room, Robin. "The culture framing of addiction." Janus Head 6, no. 2 (2003): 221-234.

70 Room (2003) at 221.

71 Self-control is difficult particularly, according to Room, where a man feels the responsibility of supporting a family through work. In exercising self-control, individuals are required to supress the desire for personal freedom. See also Elster, Jon. 1979. Ulysses and the Sirens. Cambridge: Cambridge University Press.

72 Levine, Harry Gene. "Notes on work and drink in industrializing America." In National Institute on Alcohol Abuse and Alcoholism Research Conference on Alcohol Use and Work Environment, Belmont, Maryland, vol. 10, pp. 20-21. 1978.

73 Alasuutari, Pertti. "Alcoholism in its cultural context: the case of blue-collar men." Contemp. Drug Probs. 13 (1986): 641 at 641.

74 Levine (1978). It is no surprise then that in rLGLG societies, temperance movements emerged, which sought to blame the alcohol instead of the men and coined the concept of 'addiction'. Levine argued just this – that

'addiction' to which 'abstinence' is the solution. Thus, NRPs are particularly appealing in individualistic cultures - particularly where marketed for short term use as a stepping stone to long term abstinence from addictive tobacco smoking. They offer an opportunity to Ulysses to tie himself to the mast[75], anticipating inconsistencies in his own preferences over time. By contrast in rHGHG societies harm - as determined by medical experts - does not include addiction, but only dependence: short term symptoms associated with abrupt cessation, absent the psychological and social aspects of addiction. Risk perception of these products here will focus only on the expert medical view of harm, save that in addition culturally conditioned views of synthetic products as inherently harmful may cause some consumers and decision makers to perceive them as more risky than tobacco smoking.

ii. Evidence

Survey evidence regarding US consumer perceptions of NRPs supports the view that US consumers have concerns about addiction to these products. A study undertaken in the US by Shiffman in 2008[76] found that concerns over the safety of NRPs led to many smokers using NRPs for too short a period (even less than that indicated on the label) with the result that many tried to go 'cold turkey' from nicotine too early and ended up returning to tobacco smoking. A survey undertaken by Carpenter in 2011[77] found that concern over addictive potential of the products was prevalent amongst US respondents.

Herbal Remedies

This is the inverse of the position for the rHGHG EU/EUMS thus the evidence and theory is set out in more detail in that section above.[78]

Generic (and Originator) Pharmaceutical Products

i. Expected Perception

Individualists are expected to perceive originators as more effective than generics due to the former being branded. In market economies – the preferred mode of organisation for rLGLG cultures – firms brand products to capture a segment of the market in a market structure of monopolistic competition. This works because rLGLG individuals identify with brands and once that identification is complete brand loyalty results which makes this market structure ubiquitous. Branding becomes a valid and important part of the product and, in a sense, consumption of the brand becomes a part of the individual's branding of themselves. It becomes a way in which the individual distinguishes him or herself in the market for people.[79] To consume products which are not branded might suggest to others that one does not have

addiction concepts emerged as a phenomenon of the late modern period, particularly in the UK and in the US. The only cure for addiction, according to the temperance movement, was abstinence.

75 Elster, Jon. 1979. Ulysses and the Sirens. Cambridge: Cambridge University Press.

76 Shiffman et al (2008) at 1371-1378.

77 Carpenter et al (2011) at 885-896.

78 The expected individualistic perception of herbal remedies will follow from the expected individualistic perception of synthetic products as effective because processed and more effective with more processing. Herbal remedies are thus ineffective relative to processed synthetic medicines and seen as inferior to them. That this is the perception in the US is evidence by the lack of demand for herbal remedies, i.e., they cannot command a higher price by virtue of being natural nor by virtue of being in traditional use (both at least are the case vis a vis the demand levels in Germany and other parts of Europe).

79 This has implications for employment, for marriage etc.

individual value. This process is much less important in rHGHG cultures, where one identifies more with the group and less as an individual. Moreover, one's place in the market for people is generally a fixed place within a hierarchy, which cannot be bought and sold. This explains why many US consumers, despite knowing that generics are bioequivalent to originators, and that they are as safe and as effective as originators, nevertheless have a willingness to pay to consumer originators. In addition, the market-oriented individualist takes investment in a product branding[80] and subsequent rise in product cost/price as a signal of the quality of the product. Together these help to explain why the placebo effect may operate so that rLGLG consumers consuming branded originators sometimes experience better biomedical outcomes than those consuming originators. The former consumer pays more for the product and believes that price signals quality. This belief is strong enough to prompt a somatic effect. This expected perception also arises from the predicates in Table 73, in particular 'Social Roles and Social Mobility,' and 'Regulation of Transactions.'

ii. Evidence

Survey evidence confirm that many US consumers – in addition to around 23% of doctors who consider originators to be more effective than generics[81] - many consumers hold this view. A 2009 survey by Shrank et al[82] undertook a survey in the US which investigated consumer perceptions of generic and originator products. It found that:[83] 94% of consumers believed generics were less expensive than branded originators; 10% believed that generics caused more side effects than originators; and 70% agreed that generics were *"better value"* than originators. However, when asked if they *"would rather take generics than branded medications"* only 37.6% agreed while 26.1% disagreed. Respondents more strongly agreed with the statement that Americans, in general, should use generic drugs, than with the statement that they, as individuals, should take generics. This evidence indicates that many Americans have a willingness to pay for brands and that consumption of branded originators distinguishes them as individuals.

6.6.2.3 Price Regulation

Price regulation is a rHGHG institution whilst supply side competition measures such as the Hatch-Waxman Act of 1985 are the corresponding rLGLG institution. Price regulation ensures affordable access to pharmaceutical products for all by limiting the rewards that the pharmaceutical industry can obtain for developing these.[84] By seeking to ensure a high level of competition in the market, supply side competition measures preserve economic freedom. Socialised medicine is also rHGHG, and the corresponding rLGLG approach is private

80 Branding is, in a sense, a form of processing.

81 Shrank, William H., Joshua N. Liberman, Michael A. Fischer, Charmaine Girdish, Troyen A. Brennan, and Niteesh K. Choudhry. "Physician perceptions about generic drugs." Annals of Pharmacotherapy 45, no. 1 (2011): 31-38 at 35.

82 Shrank, William H., Emily R. Cox, Michael A. Fischer, Jyotsna Mehta, and Niteesh K. Choudhry. "Patients' perceptions of generic medications." Health affairs 28, no. 2 (2009): 546-556.

83 Shrank et al (2009) at 546-556.

84 This means that in the long-term access to pharmaceutical products for all is limited because innovation is stifled.

insurance. The former treats healthcare as a collective concern, the costs of which are to be shared by the whole group according to ability to pay. The latter treats healthcare as an individual concern, expense on which is to be borne by the individual according to willingness to pay.[85] These insights are linked to the predicates in Table 73 above under, 'Regulation of Transactions,' 'Competition and Profit,' and 'Welfare State'.

My conclusion for sale classification and generic substitution is that the groups, organisations and institution which are most proximate to the shaping of the regulatory position in each jurisdiction have a cultural orientation which - in each case – matches the preliminary cultural positioning of the jurisdiction in which they exist. As such, CT-GG has provided additional explanation to that provided by the extant theories in the case of sale classification and generic substitution, and that explanation – i.e., the underlying cultural orientation - is consistent across both divergences. It has also been capable of explaining both transatlantic divergence and intra-EU divergences.

85 This combination of (mostly) private insurance, supply side competition measures and a lack of direct price regulation is inherently individualistic, accepting a certain amount of inequality to ensure faster progress. The opposite is the high group (hierarchical) combination of social insurance (socialised medicine) and price regulation which ensures all within the group have access to the best pharmaceutical products today, but which rapidly becomes unaffordable for the societies which adopt this system.

6.7 Conclusions

In this Chapter, I made use of CT-GG (as operationalised for this task through the predicates adopted in Table 73 and the theory set out across Chapter Five) to culturally analyse the groups, organisations and institutions which had been identified in Chapters Two through Four to shape the regulatory positions/divergences scrutinised in this work. I began by assigning the jurisdictions of the US and the EU a preliminary cultural positioning which was rLGLG and rHGHG respectively. Then, I took the proximate groups, organisations, and institutions in the case of each pair of divergences and analysed these culturally using CT-GG. In each case, using the pairs of predicates arrived at in Chapter Five as guidance, I found that there was a match between the cultural orientation of those proximate groups, organisations, and institutions and the preliminary cultural positioning of the jurisdictions. This, therefore, vindicated the preliminary cultural positioning of the jurisdictions. Therefore, I found within-jurisdiction cultural consistency, and consistent between-jurisdiction cultural differences, across all divergences. This is summarised below in Table 90.

Table 90 Jurisdictions, Organisations, Groups, and Institutions after Analysis using CT-GG

Cult. Orient.	JURISDICTIONS		Cult. Orient.
RLGLG	United States	European Union *NEUMS Cluster* *SEUMS Cluster*	RHGHG *R. Low Group* *R. High Group*
	ORGANISATIONS		
RLGLG	FDA	EMA	RHGHG
		NAs	RHGHG
	GROUPS		
RLGLG	US Doctors	EU Doctors	RHGHG
RLGLG	US Consumers	EU Consumers	RHGHG
RLGLG	US Pharmaceutical Industry	EU Pharmaceutical Industry	RHGHG
RLGLG	US Lawyers	EU Lawyers	RHGHG
RLGLG	US Pharmacists (dominated by LRP)	EU Pharmacists (more IP)	RHGHG
	INSTITUTIONS		
RLGLG	US Free Speech Protections	EU Free Speech Protections	RHGHG
RLGLG	Private Healthcare	Socialised Healthcare	RHGHG
RLGLG	US Common Law	EU Legal System	RHGHG
RLGLG	No Price Regulation	Price Regulation	RHGHG
RLGLG	Norm of Litigiousness	Norm against Litigiousness	RHGHG
RLGLG	US Product Perceptions	EU Product Perceptions	RHGHG

That Table 90 shows a perfectly consistent picture is not surprising. As stated in the introduction, this was intended to be and has been a positive analysis. Culture, by definition, must be affecting regulatory divergence, since regulation itself, being an institution, is a part of culture and – according to the pyramid in Figure 16 in Chapter Five – must be derived from the basic underlying institution or institutional logic of culture. What Table 90 **Jurisdictions, Organisations, Groups, and Institutions after Analysis using CT-GG** does provide positive evidence for, is the existence of observable cultural diversity between these two jurisdictions. Relative to each other, the US and the EU/EUMS have (even slightly) different underlying basic institutions or institutional logics of culture. Here, I have adopted the CT-GG orientations of hierarchism and individualism, and in doing so I have shown observable cultural diversity across all groups, organisations, and institutions. This is a positive, scientific finding, albeit within the limits imposed by my selection of the CT-GG orientations for this task.

In the case of licensing and DTCA the addition of cultural analysis was able to consistently explain the regulatory position taken across each of the divergences (the transatlantic divergences). That is because the underlying cultural orientation remained consistent across both divergences. This was the case, too, for pharmacovigilance and product liability, and for sale classification and generic substitution. In the case of pharmacovigilance and product liability, the addition of culture was also able to consistently explain the system divergences (from the SPI system). Finally, in the case of sale classification and generic substitution, the addition of culture was able to consistently explain the intra-EU divergences.

My conclusion, therefore, is that some support for the research hypothesis has been found. I.e., that cultural theory can add some further explanation to the extant theories of public interest, private interest, and institutional analysis, in the case of transatlantic regulatory

divergence in the pharmaceutical sector. The explanation added is *supplementary* only, and not alternative to the explanation provided by the extant theories of public interest, private interest and institutional analysis. This is because the effects of culture have only been revealed through application of those theories *first*. However, once culture has also been applied, a consistent picture emerges, anchored in the cultural orientations of individualism (US) and hierarchism (EU/EUMS).

Again, this is the case only *relative* to each other. The US and the EU share much in common and it is quite possible that both would be considered highly individualistic or hierarchical when collectively compared, in a similar fashion to this work, to another jurisdiction such as China, Russia or Japan. As such, this work has been a *positive* analysis of the relationship between culture and regulatory divergence, which has revealed *how* culture impacts upon regulatory divergence, it additionally confirms that culture does have an effect of some sort, and it evidences a *relative* cultural positioning between the US and the EU/EUMS which is individualistic, and hierarchical, respectively. All of this is limited, of course, by the limited range and number of divergences, groups, institutions, and organisations considered, and my justification for these choices was set out in the Introduction to this work.

In Chapter Seven – the concluding Chapter – I develop this point by culturally analysing the regulatory positions themselves. In doing so I show how it was only through first considering public interest, private interest, and institutional analysis, that the effects of culture are observed. This is demonstrated by showing that if one were merely to consider the regulatory positions themselves against the predicates of hierarchism and individualism set out in Table 73 above, then inconsistencies would emerge in many places between the preliminary cultural positioning of the jurisdictions and the regulatory positions in divergence.

In Chapter Seven I show how these inconsistencies are resolved only upon cultural analysis of the groups, organisations, and institutions. In doing so, I show that the regulatory positions ultimately adopted in each jurisdiction result from a complex interaction between the public interest motivations for regulating, the private interest elements which affect the choices made between public and private interests, and the impact of jurisdiction-wide institutions which expand or constrain the choices available to those private actors (including regulators). Uniting all, underneath, is consistent jurisdictional culture.

In Chapter Seven, therefore, I both provide evidence of the accuracy of my approach to culture (the institutional approach adopted in Chapter Five) and I find vindication for the overall methodology in this work, in which I applied public interest, private interest and institutional analysis, in addition to culture, in order to seek explanation for regulatory divergence. I then set out some implications of this finding for the question of to what extent international regulatory harmonisation in the field of pharmaceuticals is desirable or feasible.

Chapter Seven: Conclusions and Implications

7.1 Supplementary, but not Alternative, Explanation

This work has been a positive analysis of the relationship between culture and transatlantic regulatory divergence in pharmaceuticals. By the end of Chapter Six my research question: 'Can cultural theory add further explanation to the extant theories in the case of regulatory divergence in the pharmaceuticals sector?' was answered in the affirmative. The explanation provided by culture added something to that already provided by the extant theories because it was able to provide a consistent explanation across all six divergences considered.[1] The explanation provided was *supplementary* and not *alternative* to that provided by the extant theories, and in Section 7.1.1 below I demonstrate this by showing how public interest, private interest and institutional analysis were indispensable to arriving at the overall explanation for the regulatory divergences across all cases. In Section 7.1.2 I explain how and why this vindicates the methodology chosen for this work, and the approach I have adopted to culture. In Section 7.1.3 I summarise my overall results up to this stage. In Section 7.2 I discuss the implications of these results for the question of international regulatory harmonisation in the pharmaceuticals sector. Following from this, in Section 7.3 I state my final seven conclusions from this work.

7.1.1 Cultural Analysis of the Regulations versus Jurisdictional Culture

Now I directly assess the cultural orientations of the formal legal institutions which are the twelve regulatory positions: the six pairs which form the six divergences considered in this work. I assess the cultural orientations of these against the (now confirmed) cultural orientations of the jurisdictions. In each case I find that there are some inconsistencies. However, the inconsistencies are explained and thus resolved by reference to the: public interest explanations, private interest explanations, and institutions which have been considered in Chapters One, Two, Three, Four, and Six. This shows that cultural theory does not provide *alternative* explanation, nor *superior* explanation to the extant theories. It only provides *supplementary* explanation, which discloses a consistent underlying cultural orientation on each side of the Atlantic. The methodology adopted in this work, in applying both the extant theories, and then cultural theory, is thereby vindicated.

1 What is added by cultural analysis is the consistent underlying within-jurisdiction cultural orientation and the consistent underlying between-jurisdiction difference in cultural orientations.

7.1.1.1 Licensing and Direct to Consumer Advertising

Direct Cultural Analysis of the Regulation

I begin with a cultural analysis of the regulation itself in each jurisdiction. The regulatory positions are set out below again in Table 91 below.

Table 91 Transatlantic Divergence in Licensing (TTAs and PSMs) and DTCA (2)

Jurisdiction	Licensing (TTAs and PSMs)	DTCA
US	More Cautious	Permitted
EU	Less Cautious	Banned

A relatively Low-Grid Low-Group (rLGLG) jurisdiction is expected to license relatively less cautiously than a relatively High-Grid High-Group (rHGHG) jurisdiction. Rules which restrict economic freedom – such as the requirement to obtain a market-access license – are likely to be rejected by rLGLG cultures. This is linked to the predicates in Table 73 of Chapter Six under 'Regulation of Transactions' and 'Innovation and Expertise.' RLGLG cultures would be expected to allow individuals – rather than a regulatory agency – to make their own consumption decisions. As such, based on the cultural orientation of the United States (US) as rLGLG, one would expect it to be relatively less cautious in licensing. Overall, I have concluded in Chapter Two, that the approach of the US Food and Drug Administration (FDA) is more cautious relative to that of the European Union (EU) European Medicines Agency (EMA) and the EU Member States (EUMS) National Agencies (NAs). It seems the approach of the US to licensing is not consistent with the cultural orientation of the US.[2] A rHGHG culture is expected to license relatively more cautiously than a rLGLG jurisdiction. Rules which restrict individual economic freedom in the interests of the safety of the group are welcome in these cultures, as indicated by the same two pairs of predicates in Table 73 of Chapter Six. Thus, rHGHG cultures are expected to exhibit relative caution in licensing. That is not the case for the EMA/NAs. There is thus an inconsistency between the regulatory position and the cultural orientation of the EU.

A rLGLG culture is likely to favour direct consumer access to information because information empowers individual consumers to make economic choices. A rLGLG culture is thus expected to regulate direct to consumer advertising (DTCA) permissively compared to a rHGHG culture. In a rLGLG culture individual (not group) preferences are considered most important and vice versa for a rHGHG culture. Thus, in a rHGHG culture the provision of information about products direct to consumers should be less important. More reliance should be placed on the group's preference for consumption – as expressed through expert medical consensus in the form of doctor matching, or the licensing decision of an agency. This reflects the predicates in Table 73 of Chapter Six under 'Regulation of Transactions' and 'Innovation and Expertise.' The regulatory positions on DTCA therefore match the cultural orientations of the US and the EU.

2 They would be expected to prioritise the provision of information to consumers so that their individual consumption choices are fully informed.

Table 92 Inconsistency: Licensing Regulation – Jurisdictional Cultural Orientation

	Expected	Actual
rLGLG US	Licensing: Less Cautious DTCA: Less Cautious	**Licensing: More Cautious** DTCA: Less Cautious
rHGHG EU	Licensing: More Cautious DTCA: More Cautious	**Licensing: Less Cautious** DTCA: More Cautious

There is, thus a partial inconsistency between the cultural orientation of the regulatory positions and the cultural orientation of the jurisdictions. This is summarised above in Table 92.[3]

Licensing Inconsistency Resolved by Cultural Analysis of Groups, Organisations, and Institutions

Chapter Two showed that the licensing and DTCA positions are the product of private interest factors driving interest groups and organisations, constrained by jurisdiction-wide institutions, and constrained by a need to serve the public interest which itself may be determined by collective (shared) preferences underpinned by group culture.[4] Therefore, in Chapter Six I culturally analysed the proximate groups, institutions and organisations and the result of this is that this inconsistency is resolved. Culture is having an effect *indirectly* through the organisations, groups, and institutions.

In the US, the fact of rLGLG consumers and a rLGLG FDA mean that the FDA is responsive to activist consumers. However, despite the strength of rLGLG doctors (who are opposed to DTCA) in the US, the FDA is unable to ban or heavily restrict DTCA because it is constrained by the rLGLG US institution of constitutional free speech protections. Moreover, the FDA cannot rely on rLGLG doctors, who must accommodate rLGLG US consumers, to act as safety gatekeepers. As such, it is forced to be cautious on licensing. Whilst on the face of it the US position on licensing is not rLGLG, this analysis of the proximate groups, organisations, and institutions has clarified the picture.

The underlying cultural orientation of the jurisdiction, which has shaped the cultural orientation of the groups, institutions, and organisations, has caused the US system to be configured towards more caution in licensing and less caution in DTCA regulation. In the case of the EU, the rHGHG EMA/NAs do not have direct-to-consumer accountability and rHGHG passive EU/EUMS consumers do not hassle these agencies. Therefore, the EMA/NAs can be

3 Here, again, I show the 'private interest puzzle' set out in Chapter Two, except this time it is the other way around. In Chapter Two I concluded that the extended reputation model explained the approach of both jurisdictions to licensing but failed to explain the approach of both jurisdictions to DTCA. Now, I say that culture explains the approaches taken to DTCA, but not the approach taken to licensing. This illustrates clearly how the regulatory positions adopted in both polities are the result of an interaction between public interest, private interest, institutions, and culture. My argument is, however, that culture sits underneath both private interest and institutions, affecting how organisations and groups will act to maximise their own interests whilst vying with the requirements of the public interest. The public interest, too, relies upon culture as it will reflect the collective (shared) preferences of the consumer public.

4 Consumers also being an interest group.

relatively less cautious (and accommodate industry) when licensing new products. That lack of caution is accounted for in part by the fact it can rely on rHGHG EU/EUMS doctors to act as safety gatekeepers in relation to consumption of these products. However, the Commission cannot accommodate industry on DTCA because the rHGHG institution of socialised healthcare means that the EUMS governments are opposed to this from a budgetary perspective. The regulatory positions are the product of public and private interest factors, and institutional constraints. Underneath the private interest and institutional factors lies a consistently rLGLG cultural orientation in the US and a consistently rHGHG cultural orientation in the EU/EUMS.

7.1.1.2 Pharmacovigilance and Product Liability

Direct Cultural Analysis of the Regulation

I begin with a cultural analysis of the regulation itself in each jurisdiction. I do this from the perspective of both the transatlantic divergence and the system divergence. These divergences are set out below again in Table 93 and Table 94 respectively.

Table 93 Transatlantic Divergence Pharmacovigilance and Product Liability (2)

	TRANSATLANTIC DIVERGENCE	
	Pharmacovigilance	**Product Liability**
US	FDA led and funded 'Unitary' system with licensing Relatively poor industry compliance	Relatively high liability threshold No liability for unknown and unknowable design defects Relatively high expected damages
EU	EMA collaborative with industry 'Plural' system with licensing Relatively good industry compliance	Relatively low liability threshold Potential liability for unknown and unknowable design defects Relatively low expected damages

Table 94 System Divergence (Pharmacovigilance + Product Liability) US, EU and SPI (2)

	SYSTEM DIVERGENCE	
	System = Pharmacovigilance + Product Liability	
	Pharmacovigilance	**Product Liability**
SPI	**Broad pharmacovigilance** Integrated with licensing	Limited application
US	**Narrow pharmacovigilance** Not fully integrated with licensing	Full application
EU	**Narrow pharmacovigilance** Not fully integrated with licensing	Full application

I now assess the cultural orientation of the regulation and the systems which leads to the transatlantic and the system divergences. I am assessing the cultural orientation of the regulation against the preliminary cultural positioning adopted for each jurisdiction above.

Transatlantic Divergence: Pharmacovigilance

Because now I consider the transatlantic divergence only, I consider pharmacovigilance in isolation, before then considering product liability in isolation. In the case of the US one would not expect a rLGLG jurisdiction to adopt a centralised approach which hands significant power to one agency. Moreover, within the agency one would expect separation of executive authority between committees. This follows from the predicates in Table 73 of Chapter Six under 'Regulation of Transactions'. rLGLG cultures should prefer responsibility and freedoms to lie with smaller units (individual committees or devolved to the United States Pharmaceutical Industry (USPI) for example) rather than the actions of individuals (even corporate or committee) actors being directed by prescriptions handed down from above, which is a rHGHG approach. Yet, in the case of the US there is a unitary committee system and pharmacovigilance is FDA led and funded as shown in Table 95 below. For the EU, the opposite is the picture, the EMA hands much responsibility and freedom to the EU Pharmaceutical Industry (EUPI) and also divides executive authority between its committees. That is the expected rLGLG approach, not the expected rHGHG approach. Clearly, therefore the US and EU approaches to pharmacovigilance – when considered in isolation from both product liability and from any cultural analysis of groups, organisations, and jurisdiction-wide institutions - does not match the cultural orientation of either jurisdiction, in fact it is the opposite of what one would expect. I argue below that the transatlantic divergence in approaches to pharmacovigilance are more fully explained when culture is applied to analyse the groups, organisations, and institutions themselves. This, too, helps to explain the system divergence.

Table 95 Inconsistency Pharmacovigilance Regulation – Jurisdictional Cultural Orientation

	Pharmacovigilance Expected	Pharmacovigilance Actual
rLGLG US	Plural committee system Devolved to industry	Unitary committee system Agency led and funded
rHGHG EU	Unitary committee system Agency led and funded	Plural committee system Devolved to industry

Transatlantic Divergence: Product Liability

On product liability, a rLGLG culture is expected to condition liability upon fault. This means a rLGLG culture would reject liability upon a firm for unknown and unknowable design defects. That is because rules, in a rLGLG system, are only accepted in so far as they perform a coordinating function,[5] not a distributive one. In rLGLG cultures rules – according to Raz's conception of the rule of law as based on autonomy, for example[6] – should enable individuals to plan their lives and their conduct according to their individual preferences.[7] Thus the rules are designed such that all individuals are able to maximise their utility without interfering with the ability of any other individual to maximise their utility. This, and its link to the predicates set out in Table 73 of Chapter Six, has been set out in Chapter Six where I discuss corrective and distributive justice in the context of strict liability. This matches the US position on liability. In the case of rHGHG cultures one would expect these to be more welcoming of liability for unknown and unknowable defects. This is because rules also further a redistributive purpose, ensuring the welfare of the whole group. Thus, I argue, even without fault and even without the possibility that an actor could plan his life to avoid causing the harm, a rHGHG jurisdiction is expected to be more likely to impose liability to redistribute the gains of the injurer to the victim. This follows from the predicates in Table 73 of Chapter Six above under 'Regulation of Transactions,' 'Competition and Profit,' 'Accountability and Blame' and 'Welfare State'.

In relation to expected damages, one would expect that this point would follow the approach taken to liability. I.e., where there is a low threshold for liability there would be high expected

5 Licht, Amir N., Chanan Goldschmidt, and Shalom H. Schwartz. "Culture rules: The foundations of the rule of law and other norms of governance." *Journal of comparative economics* 35, no. 4 (2007): 659-688. *(at 2.3.1)…"In high autonomy cultures, individuals need the law as a transparent, a-contextual source of guidance. This would support societal endorsement of law-abidingness and law-based dispute resolution in courts. In contrast, a culture that emphasizes embeddedness is less likely to promote a rule-of-law norm. Obligations and behavior are highly contextual in such societies and are not subject to rigid rules. Enforcement is more likely to be community-based (Greif, 1994). The key values in such cultures—respect for tradition, honoring elders, and obedience—encourage people to seek guidance in sources other than the law. Insistence on one's legal entitlements may be seen as a-social in such cultures"*

6 Raz, Joseph. *The authority of law: essays on law and morality*. Oxford University Press on Demand, 2009. See also Fuller, Lon L. "The morality of law." (1964).

7 See Licht, Goldschmidt, and Schwartz (2007): 659-688 *(at 2.3.1)… "The logical consequence of cultural emphases on autonomy is to promote the rule of law as an overarching norm. Cultural autonomy defines people as bounded entities who should be encouraged to cultivate their unique ideas and feelings."*

damages and vice versa, simply because firms should expect more damages awards to be made against them where the liability threshold is relatively low.

The expected damages position, therefore, is inconsistent with the preliminary cultural positioning – as shown below in Table 96. It has already been argued in Chapter Three to some extent that differences in features which bring about the differences in expected damages are due partly to private interest mechanisms. Because the liability threshold is relatively low in the EU, relevant interest groups (EUPI) have had a strong and successful argument to cap overall damages awards, and vice versa for the position in the US. I argue below that the US and EU approaches to product liability (both liability and damages) are more fully explained when culture is applied to analyse the groups, organisations, and institutions. This, too, helps to explain the system divergence.

Table 96 Inconsistency Product Liability (Damages) Regulation – Jurisdictional Cultural Orientation

	Liability Expected	Damages Expected	Liability Actual	Damages Actual
rLGLG US	Relatively high threshold: not for unknown and unknowable design defects.	Relatively low expected damages	Relatively high threshold: not for unknown and unknowable design defects.	Relatively high expected damages
rHGHG EU	Relatively low threshold: possible for unknown and unknowable design defects.	Relatively high expected damages	Relatively low threshold: possible for unknown and unknowable design defects.	Relatively low expected damages

System Divergence

My starting point is that without the influence of culture acting through private interest mechanisms – including the demands of consumers, who I treat as an interest group too - then the system adopted by the US and the EU would be the Suggested Public Interest (SPI) system. This is not the case, as set out in Chapter Three. I now consider what *system* would be expected based upon the cultural orientation of the jurisdictions in each case.

rHGHG cultures base social interaction upon external prescriptions which constrain individual freedom, and in regulation they are likely to prioritise the common good over individual freedoms. As such, rHGHG cultures are expected to have strict regulation in the interests of the safety of the whole group. This follows from the predicates in Table 73 of Chapter Six under 'Regulation of Transactions,' 'Innovation and Expertise' and 'Welfare State.' One would therefore expect a rHGHG jurisdiction to adopt broad pharmacovigilance. Broad pharmacovigilance involves a large degree of power being placed with a regulatory agency to interfere in the market over the entire life cycle of the product, and in the interests of ensuring public safety. By contrast the rLGLG jurisdiction would be expected to rely upon the enforcement actions of private individuals with liability rules incentivising private actions by firms. That follows from the same sets of predicates, but the rLGLG one of each pair in this case. There is an inconsistency, therefore, in the fact that the EU does not use broad

pharmacovigilance (with a limited role for product liability) but has the Product Liability Directive 1985 (PLD), and the fact that US invests so much in pharmacovigilance. Therefore, not only do both the US and the EU systems diverge from the SPI system, but they appear to do so uniformly, and not along cultural lines. As shown below in Table 97.

Table 97 Inconsistency Pharmacovigilance/Product Liability Systems – Jurisdictional Cultural Orientation

	Expected System	Actual System
rLGLG US	Pharmacovigilance (-) Product liability (+)	Pharmacovigilance (+/-) Product liability (+)
rHGHG EU	Pharmacovigilance (+) Product liability (-)	Pharmacovigilance (+/-) Product liability (+)

In Chapter Six I analysed the proximate groups, organisations, and institutions to see whether culture could add further explanation to the extant theories, and whether such explanation was capable of explaining both the transatlantic divergence and the system divergence. Now I ask whether the three inconsistencies identified here are also resolved.

Pharmacovigilance and Product Liability: both Transatlantic and System Inconsistencies Resolved with the Cultural Analysis of Groups, Organisations, and Institutions

Transatlantic Divergence Inconsistency: Pharmacovigilance

Cultural analysis of the proximate groups, organisations and institutions has assisted in resolving the inconsistency in the transatlantic divergence concerning pharmacovigilance (see Table 97 above). This is shown to reflect a consistent underlying cultural orientation shared by the jurisdictions, groups, organisations, and institutions. In this case, it is the context in which the rLGLG US FDA operates, and the relationships it necessarily has with the other actors in the system, which cause it to have a unitary committee system between pharmacovigilance and licensing, and to take the lead and fund pharmacovigilance. The converse is true in the case of the EU's EMA.

The FDA is a rLGLG organisation. However, the behaviour and organisation of the FDA in pharmacovigilance is necessitated by its tendency to protect its reputation for consumer protection. That is because – as outlined in Chapter Three – by adopting a plural committee system, the FDA would risk contradicting itself in the eyes of consumers. The mission statement (i.e., the reputation to protect) which the FDA has, is shaped in turn by the rLGLG actors in the system of pharmaceutical regulation in the US, and the rLGLG adversarial way in which they have interacted. USPI, being rLGLG as a group, is relatively innovative and competitive. As such, it does not primarily self-regulate when it comes to consumer safety but rather has its boundaries set by the rLGLG US Common Law and by the FDA, both of whom mediate its relationships with rLGLG US consumers. Product liability rules can only provide deterrent incentives, and not prevent harm in the first place, so the 'gatekeeping' function remains with the FDA. Gatekeeping lies more with the FDA than with rLGLG US doctors or rLGLG US pharmacists. That is because, due to the permission of rLGLG DTCA and a rLGLG

patient-doctor relationship, doctors came to be in a relatively weak gatekeeping role vis a vis consumers compared to that which they occupy in the EU/EUMS. Left with the gatekeeping role entirely on its shoulders, the FDA would prefer to exercise that role perfectly in its licensing function, and thus best preserve its reputation for consumer protection. However, it cannot, due to the underlying information problem: the uncertain benefit-risk profile of pharmaceutical products.

What can the FDA do, then, about unknown defects? It cannot rely on USPI to find these because USPI is disincentivised from doing so by the product liability system, the rLGLG social norm of litigiousness, and the adversarial relationships it has with consumers, the FDA and intra-industry. Neither does the FDA want USPI to take credit for discovering a product defect, which may reflect poorly on the FDA in its licensing role. The FDA is happier with the situation in which consumers, through the courts, hold USPI to account for defects, yet the institutional constraints of the rLGLG Common Law and its commitment to rLGLG corrective justice will not permit holding USPI liable without fault: where the defect was unknown and unknowable. Out of necessity therefore - because consumers will inevitably blame the FDA in the absence of a salient court judgment against an USPI firm where an unknown and unknowable design defect caused harm[8] - the FDA undertakes pharmacovigilance. But, in so far as possible, it makes this a part of licensing, hence the unitary committee system. And, it keeps tight control over the process and provides the funding. The FDA approach to pharmacovigilance is borne out of its desire to protect its reputation, which developed out of its initial role as a rLGLG organisation mediating the other rLGLG actors in an adversarial system.

In the rHGHG EU, the rHGHG EMA/NAs can adopt a plural committee system and devolve pharmacovigilance activities to rHGHG EUPI, precisely because these organisations are rHGHG. They do not have strong individual personalities nor any strong reputation to protect in the eyes of the general public (as opposed to the scientific community), and so are more able to contradict themselves without consequences. They collaborate with other actors in the system in a corporatist network of relationships in which they mediate a relationship between the EU/the EUMS governments and EUPI which is also regulated by reciprocity between EUMS-imposed rHGHG price regulation (limitation of returns on capital to EUPI) and EUMS-provided rHGHG socialised healthcare (bulk purchasing of products from EUPI). As such, the EMA/NAs can reasonably expect EUPI to cooperate in pharmacovigilance and are able to devolve pharmacovigilance to EUPI.

Transatlantic Divergence Inconsistency: Product Liability (Damages)

The inconsistency between the cultural orientation of the jurisdictions and the transatlantic divergence in product liability relates to the level of expected damages. The individual regulatory positions on damages were shown in Chapter Six to be further explicable by reference to institutions and institutional features of the legal systems. The permission of punitive damages awards in the rLGLG US was shown to be rLGLG and the size of those awards was argued to be due to the rLGLG preference for use of juries, the rLGLG permission/use of class action suits, and the rLGLG US costs rule. The opposite was true in the rHGHG EU/EUMS. In addition, the position taken on liability in the jurisdictions affects the position which was likely to be taken on damages. In the US where a rLGLG approach requiring fault for liability limits the likelihood of USPI facing very widespread liability which it could not afford, the

8 The precise situation – Thalidomide – upon which the FDA founded its reputation for consumer protection.

argument is strengthened that high damages awards should be permitted when fault is found. It was also argued that this punitive damage mechanism assists in mediating the relationship between rLGLG consumers and rLGLG USPI in the rLGLG adversarial network of relationships which exists in the US. In the EU, where rHGHG EUPI acts as one ultimate insurer of rHGHG consumers there is a need for the rHGHG jurisdiction to preserve EUPI as a subgroup within the larger group in order to protect that position – as well as the other benefits that EUPI brings to the whole jurisdiction. There is seen therefore, in the PLD and in institutional features of the EUMS/EU legal systems a reluctance to permit unlimited liability upon EUPI or any one firm within EUPI.

System Divergence Inconsistency (Pharmacovigilance and Product Liability)

Finally, I turn to show how a closer consideration of the groups, organisations and institutions has assisted in explaining the apparent inconsistency between the cultural orientation of the jurisdictions and the system divergence. I have already identified that the institutions, groups, and organisations are culturally consistent as rLGLG or rHGHG in the US and the EU respectively. Just as was the case for the pharmacovigilance inconsistency – discussed above - I say it is the interaction between the groups, organisations and institutions which explains the system divergence, without undermining the cultural positioning of the jurisdiction as a whole. That form of interaction is necessitated by (consistent) underlying culture. In the rLGLG US, where rLGLG consumers[9] and rLGLG lawyers prefer the rLGLG institution of liability (over ex ante regulation) to seek rLGLG corrective justice when harmed, this removes the incentives of rLGLG USPI to self-regulate except to avoid liability. That necessitated the emergence of a strong and rLGLG organisation – the FDA – to act as gatekeeper to prevent massive harm occurring to consumers. Because the groups and organisations are all rLGLG they interact adversarially through rLGLG institutions. This leads to a situation where pharmacovigilance and product liability sit side by side in the US system. In the rHGHG EU rHGHG consumers – relying more for their safety upon rHGHG doctors and for security upon the rHGHG institution of socialised healthcare - are less inclined towards the rLGLG institution of liability. This enables rHGHG EUPI to cooperate relatively easily with the rHGHG EMA and the rHGHG bureaucrat lawyers staffing the EU organs. Because the groups, organisations, and proximate institutions are all rHGHG the groups and organisations interact cooperatively, which results in the existence of the PLD in addition to pharmacovigilance as a way for the EMA, the NAs, the EU/ EUMS governments, EU consumers and EUPI to share the risks and benefits posed by pharmaceutical products.

9 Able to rely relatively less upon their rLGLG doctors for safety.

7.1.1.3 Sale Classification and Generic Substitution

Direct Cultural Analysis of the Regulation

I begin with a cultural analysis of the regulation itself in each jurisdiction/Cluster. The regulatory divergences are set out below again in Table 98.

Table 98 Key Transatlantic and NEUMS-SEUMS Divergences Sale Classification and Generic Substitution (2)

	Sale Classification			**Generic Substitution**
	General	**NRPs**	**Herbal Remedies**	
US	**Two categories:** (PO) and (GSALE) **Less switching**	**Wide availability (GSALE)** **Narrow indications**	**Dietary supplements (U)** No efficacy claims or safety warnings allowed	**Permissive-express** Pharmacist discretion and express consumer consent
EU	**Three categories:** (PO), (GSALE), (PSO) **SEUMS:** (GSALE) uncommon **NEUMS:** (GSALE) common **More switching**	**Narrow availability** **SEUMS** (PSO), (PO) **NEUMS** (PSO), (GSALE) **Wide indications**	**Medicinal products TUR (PSO) and (GSALE)** Limited efficacy claims allowed, and safety warnings required	**SEUMS:** More often pharmacist discretion. Less often express consumer consent. **NEUMS:** Less often pharmacist discretion. More often express consumer consent.

Sale Classification General

RHGHG cultures will be marked by strict regulation in the interests of the safety of the whole group. This clearly follows from the predicates in Table 73. It is therefore expected that there would be (relatively) extensive use of Precription-Only (PO) or Pharmacist-Supervision-Only (PSO) status and less use of General Sale (GSALE) or Unlicensed (U), and little switching out of the PO or PSO category to lower categories. The corresponding rLGLG approach would be to make all pharmaceutical products widely available but with information provision through price signals[10] or product labelling. This enables individual consumers to make free consumption choices according to their individual preferences. Extensive use of GSALE would therefore reflect rLGLG cultures. Applying this to the US and the EU/EUMS there is a partial fit with the cultural orientations in each case. More products are available on GSALE in the US than across the EUMS. The EUMS have the PSO category which puts in place additional rules for many products found in the US in the GSALE category. However, because of the two-category system and the relatively low amount of switching out of PO to GSALE the US has an abundance of products in the PO category. That contravenes the LGLG expected position, and this is the first inconsistency identified vis a vis the cultural orientation of the jurisdiction of the US. This is shown below in Table 99.

Table 99 Sale Classification (General) Inconsistency with Cultural Orientation of Jurisdiction

Jurisdiction	*Cult. Orient.*	*Expected Regulation*	*Actual Regulation*
US	rLGLG	**Little use of PO.**	**Extensive use of PO**
EU	rHGHG	Little use of GSALE/U	Little use of GSALE/U

Nicotine Replacement Products

The puzzle reached at the end of Chapter Four is set out in Table 100 below.

Table 100 Puzzling Regulation of Sale Classification NRPs US and EU (2)

	Availability	**Use**
Expert View/Public Interest	**Wide**	**Wide**
United States	Wide	Restricted
European Union	Restricted	Wide

In terms of availability, the expected regulatory position for Nicotine Replacement Products (NRPs) for rHGHG and rLGLG respectively is the same as for general sale classification above, and this follows from the same predicates in Table 73 of Chapter Six. The US approach is to make them widely available (GSALE). This matches the expected LGLG approach. In the EU/EUMS availability is restricted, which matches the expected HGHG approach. This explains

10 E.g., low prices imply high product safety risks and/or low efficacy.

the departure in both cases from the public interest approach based on a medical expert view. Taking in to account the above, however the approach to use types requires further explanation. Why does the rLGLG US restrict *use*, and why *doesn't* the rHGHG EU/EUMS restrict this? This is the second inconsistency, and it is shown in Table 101 below.

Table 101 NRPs Inconsistency Cultural Orientation Jurisdictions/Regulations

Jurisdiction	*Cult. Orient.*	*Expected Regulation*	*Actual Regulation*
US	rLGLG	**No use restrictions**	**Use restrictions**
EU	rHGHG	**Use restrictions**	**No use restrictions**

Herbal Remedies

The puzzle presented at the end of Chapter Four is set out in Table 102 below.

Table 102 Puzzling Regulation of Sale Classification Herbal Remedies US and EU (2)

	Safety (warnings)	**Efficacy (claims)**
Expert View/Public Interest	**Label warnings**	**No efficacy claims**
United States	No warnings	No efficacy claims
European Union	Label warnings	Limited efficacy claims

In relation to safety warnings, for rLGLG wide availability (U or GSALE) is expected with information provision. For rHGHG one would expect restricted availability and/or wide availability with safety warnings. These statements follow from the observations already made above and the same predicates from Table 73 of Chapter Six. The latter is what the EU/EUMS have by classifying Traditional Use Registration (TUR) herbal remedies GSALE or PSO and in both cases mandating safety warnings. The US historically did not allow safety warnings on herbal remedies where these are sold as dietary supplements: this, as I have set out, is the corollary of the fact that efficacy claims are not allowed. On efficacy claims, the expected rHGHG approach is to allow these after efficacy has been proven according to rules set by medical experts, because rHGHG cultures place trust in expertise. This is not the case: under the 2004 Directive, efficacy may be proven through history of traditional use. The expected rLGLG approach is to allow any claim to be made and to allow the marketplace of ideas to sort 'true' claims from 'false' claims.[11] Yet, the US does not allow these at all. This is the third inconsistency with the initial cultural positioning: why does the rHGHG EU allow limited efficacy claims despite a lack of medical expert evidence, and why does the rLGLG US disallow efficacy claims?[12] This is shown in Table 103 below.

11 See above the discussion of free speech and advertising in relation to licensing and direct-to-consumer advertising.

12 I assume if this question is answered then this also indirectly furnishes the answer to why the US did/does not permit safety warning too.

Table 103 Herbal Remedies Inconsistency - Cultural Orientation Jurisdictions/Regulations

Jurisdiction	*Cult. Orient.*	*Expected Regulation*	*Actual Regulation*
US	rLGLG	**Allow efficacy claims**	**Forbid efficacy claims**
EU	rHGHG	**Permit efficacy claims (expert[13])**	**Permit efficacy claims (tradition[14])**

Generic Substitution

The expected rLGLG approach is permissive-express. That is a market-oriented approach which preserves first party ordering of preferences, even if it entails that those who cannot afford to buy branded originator products must settle for generic products.[15] That clearly follows from the predicates in Table 73 of Chapter Six under 'Regulation of Transactions.' The rLGLG US adopts permissive-express regulation of generic substitution and this matches its cultural orientation. The expected rHGHG approach is to ensure that products remain affordable and available to all in the group by greater use of mandatory-implied substitution. That follows from the predicates in Table 73 of Chapter Six under 'Regulation of Transactions' and 'Welfare State.' This is the case *overall* in the EU versus the US, however as between the EUMS it is expected that the Southern EUMS (SEUMS) Cluster would adopt mandatory-implied substitution because it is culturally positioned as higher group than the Northern EUMS (NEUMS) Cluster. Yet the regulatory positions are reversed.[16] This is the fourth inconsistency, set out in Table 104.

Table 104 Generic Substitution - Inconsistency Cultural Orientation NEUMS/SEUMS Clusters-Regulations

Cluster	*Preliminary Positioning*	*Expected Regulation*	*Actual Regulation*
SEUMS	rHGrp	**Mandatory**	**Permissive**

I conclude that there is some match between the initial cultural positioning of the jurisdictions/Clusters and the regulations. However, there are also inconsistencies, which require further explanation.

13 Scientifically verifiable by medical experts.
14 Limited efficacy claims permitted on the basis of longstanding traditional use.
15 Cultures which are rLGLG prefer allocation by free markets over equality of outcomes in the distribution of wealth and income. Thus, one would expect a relatively wide gap between the richest and poorest because there are fewer centralised measures redistributing wealth from rich to poor.
16 Or, at least, the SEUMS took longer/are taking longer to introduce mandatory generic substitution.

Sale Classification and Generic Substitution: both Transatlantic and Intra-EU Inconsistencies Resolved with the Cultural Analysis of Groups, Organisations and Institutions

The four inconsistencies are resolved as follows.

The first is that for sale classification (general), the rLGLG US makes extensive use of PO when greater use of GSALE plus information provision is expected. This is explained by the alliance (vertical integration) between doctors and the pharmaceutical industry which led to the prescription system. The reason for the alliance/integration was the independence of doctors and strength of the pharmaceutical sector, both of which are linked to the rLGLG orientation of these groups operating within the rLGLG US. The extensive use of PO is thus indirectly explained by individualism operating through the private interest pathway of doctor and pharmaceutical industry lobbying and interacting with each other.[17]

The second relates to NRPs: that the rLGLG US restricts acceptable uses of NRPs but the rHGHG EU/EUMS do not. The rLGLG risk perception of NRPs in the US as addictive and therefore harmful explains the restriction on indications and uses. The rLGLG FDA and its tendency to bow to consumer pressure also provides explanation. In the case of the EUMS, rHGHG consumer perception of NRPs which is not so preoccupied with addiction explains the choice of the NAs not to restrict indications too heavily. Consistency is found, therefore, when culture is taken into account, acting through the pathways of the perception institutions and the behaviour of the FDA.

The third concerns herbal remedies: the rLGLG US disallows efficacy claims whereas the rHGHG EU allows limited efficacy claims not based upon expert evidence. In the US this is the result of lobbying by the strong pharmaceutical industry. The strength of the pharmaceutical industry vis a vis the herbal remedies industry is attributable to rLGLG culture in the US. In the EU, limited efficacy claims not based on expert medical views are explained by consumer perceptions of herbal remedies as effective, which reflects relatively high group culture in the EUMS. The abundance of rules surrounding those efficacy claims and safety warnings, found in the 2004 Directive, are an embodiment of rHGHG culture.

The fourth and final inconsistency relates to generic substitution, and to the intra-EU divergence rather than to the transatlantic divergence. The relatively low group NEUMS Cluster was quicker to permit mandatory substitution than the relatively high group SEUMS Cluster. This has been explained by the fact that the rHGHG pharmacists in the SEUMS have focused on Advice and sought to maintain their independence whereas rLGLG pharmacists in the NEUMS have focused on Sale. The SEUMS pharmacists have consequently resisted government interference with their task role of Advice. Meanwhile the healthcare budget pressure experienced across all EUMS has moved the NEUMS to introduce mandatory substitution, and would have similarly moved the SEUMS save for the resistance of the rHGHG SEUMS pharmacists. Again, culture has indirectly influenced the regulation through the

17 Also, individualistic litigiousness and products liability law meant that to obviate their risk of liability the pharmaceutical industry sought to share the liability risk with doctors, and doctors sought the rewards offered by the pharmaceutical industry, as well as a monopoly on the power to prescribe certain products.

private interest pathway of interest group lobbying, and when the cultural orientation of all groups, institutions and organisations is considered, cultural consistency is found.

7.1.2 The Methodology and Approach to Culture Vindicated

The preceding section vindicates the methodology used in this work, and the institutional approach to culture which was adopted in Chapter Five. What sections 7.1.1.1 to 7.1.1.3 show is that regulatory provisions, looked at *in isolation*, cannot easily be meaningfully explained by culture. Recall Figure 16 from Chapter Five.

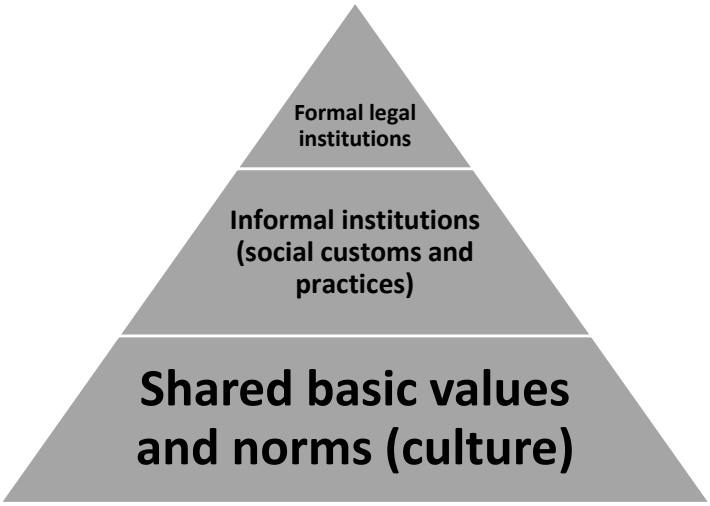

Figure 26 **Culture as the Basic Institution in a Group or Subgroup (2)**

Regulatory provisions (or practices etc.) are formal legal institutions, or based upon them. Such institutions are found at the very top of the pyramid. Not only this, but regulations are some of the most easily changed of all institutions. Based upon this pyramid in Figure 26 one would expect to have to look further than the regulatory provisions or practices, in order to be able to observe the effects of underlying culture, the most basic institution.

A hypothetical alternative methodology for me to have adopted in this work would have been as follows:

1. Develop the set of predicates of hierarchism v individualism shown in Table 73 from Chapter Six.
2. Taken all regulatory provisions and practices related to the pharmaceutical sector in the US, the EU and the EUMS and sorted them in to coupled pairs (covering the same aims or areas).
3. Coded each of these according to the guidance provided by the predicates.
4. Analysed the results in relation to which of the jurisdictions that the provisions and practices were drawn from.

5. From this, drawn conclusions regarding the cultural orientation of the jurisdictions and the predictive power of these cultural orientations for outcomes in the field of pharmaceuticals regulation.

Such a methodology would have glossed over the very rich texture implied by the institutional approach to culture. It will have forgotten to take into account the *shape* of the pyramid itself. Certain institutions are more entrenched than others. Constitutional legal provisions may be merely formal legal institutions but – like free speech protections – because they are constitutional, they are a fundamental institution binding together the whole group which is the jurisdiction. These are much better evidence of what the basic institution/institutional logic (or culture) of the jurisdiction is, even than the sum of *many* discrete but transitory regulatory provisions related to the technical aspects of pharmaceutical sector regulation.

Moreover, such an approach will have neglected the extant theories of public interest and private interest explanations for regulation. These theories cannot be ignored. They clearly provide explanation for regulation and for regulatory divergence. Adopting the approach that consumers themselves are an interest group, with diverse preferences conditioned by the culture of their group, and thus that the public interest theory of regulation can therefore be seen as a special branch of private interest theories of regulation. Then, groups become of fundamental importance to explaining regulatory divergence. The alternative methodology outlined in 1)-5) above will have failed to illustrate the importance of groups. In fact, the methodology suggested there, if it had produced some evidence of a link between the cultural orientations of the jurisdictions and the regulatory positions for pharmaceuticals regulation (which, due to its deficiencies, I suspect would have been unlikely) may then have suggested that *only* culture matters in determining regulatory outcomes. This is not the case, it is clear that the private interests of groups and organisations matter in determining regulatory outcomes, and that the demands of consumers (regardless of how consumer preferences are shaped) are highly relevant to the regulatory positions adopted by regulators in these cases.

It was made clear from the outset that this work was a positive analysis. Culture must affect regulatory outcomes (and thus regulatory divergence) because regulation itself, by any definition of culture, is one aspect of culture. What is called culture, in common parlance, just refers to differences between things including e.g., regulations. I am most interested, in applying cultural theory, to see whether these differences are systematic, and consistent between different places and different groups. Here, I have shown, in the case of six regulatory divergences that there are consistent, systematic between-jurisdiction cultural differences. Moreover, I have shown that these cultural differences have found themselves manifest in divergent regulatory positions *through* the theoretically extant mechanisms of regulators (private actors) acting in response to the public interest (consumer demands, culturally conditioned), and the lobbying efforts of groups sharing private objectives and bound together by institutions of behaviour, and the effects of jurisdiction-wide institutions. The institutional approach to culture, and the methodology adopted here – considering the extant theories in addition to applying cultural theory – has been able to show *how* underlying culture has found its way into regulatory positions, and thus shaped regulatory divergence.

My research question is thus answered in the affirmative. Although, perhaps not for the reasons anticipated at the outset. There were no real surprises here. I did not show that the extant theories are wrong – although my approach has necessitated a modified

understanding of the boundary between public and private interest theory, in order to treat consumers as an interest group themselves. Instead, I confirmed – in the case of these six divergences – that all of the extant theories have explanatory power. However, further explanation has been added by culture, because a consistent underlying cultural orientation is shown – in these six cases - to take effect on the regulatory divergences via the medium of groups, organisations, and institutions. This was, therefore, a positive analysis. The results show *how* culture has an effect. That is the nature of the supplementary explanation which has been shown here. The methodology and the approach to culture here has been vindicated by what is demonstrated.

7.1.3 Results

As set out in the introduction and above, this work has been a positive analysis of *how* culture shapes regulatory divergence. It has been shown that this occurs through jurisdictional culture shaping collective (shared) preferences which in turn inform the regulator what lies in the 'public interest'. In addition, all subgroups within a jurisdiction possess a cultural orientation which is evidenced in the cultural orientation of the institutions which bind together those groups. Those institutions (and thus the cultural orientation) affect the objectives and behaviour of those groups. Those groups – as per classic private interest analysis of regulation – then demand (interest groups) or supply (organisations) regulation accordingly. On top of this, jurisdictions are bound together by institutions which define them as groups, and these jurisdiction-wide institutions may constrain or widen the choices available to interest groups and regulatory organisations demanding, and supplying, regulation, respectively. Cultural analysis adds to the extant theories of public interest, private interest, and institutional analysis because – through the institutional approach to culture adopted here – it can provide a consistent underlying cultural explanation across multiple divergences working, as this does, through the intermediation of interest groups (including consumers and the public interest), organisations, and jurisdiction-wide institutions. As such my original research question has been answered in the affirmative in relation to the six divergences considered here.

In addition, I have adopted in this work a specific approach to culture – the institutional approach to culture. A secondary result of this research therefore, includes some evidence in support of the veracity of the institutional approach to culture: i.e., that culture is the basic institution within a group, mutually co-produced and mutually reinforcing with other formal and informal institutions as per the pyramid in Figure 26; that culture as the basic institution is the slowest to change within a group, but that change in underlying culture is possible, and does happen, but only slowly and gradually; that cultural diversity does exist because there are a limited number of compatible combinations of cultural 'types' and other institutions, and that once a group or jurisdiction has begun upon a path towards one of these equilibria it becomes path dependent upon this. Finally, that the origins of cultural diversity may be due to small initial (exogeneous and accidental) differences in the conditions faced by different groups in different places at different times.

Finally, I adopted a specific typology of culture based upon the Cultural Theory of Risk and Group-Grid (CT-GG) and developed some predicates of hierarchism and individualism drawn from the CT-GG literature. I systematically applied these predicates to analyse the behaviour of groups in the US and the EU (and directly to jurisdiction-wide institutions) by considering the behaviours of those groups or organisations, deducing institutions from those behaviours, and working out the cultural orientation of the institutions with the assistance of the predicates set out in Table 73 of Chapter Six. Therefore, I also have some tertiary results from this research, which are even more specific than those listed in the two preceding paragraphs. These are: some evidence that (according to the CT-GG typology) the US as a jurisdiction is individualistic relative to the EU which is a hierarchical jurisdiction relative to the US.

7.2 Implications for International Regulatory Harmonisation in Pharmaceuticals

All three results have policy implications in the case of proposed regulatory harmonisation. The secondary and tertiary results show evidence that cultural diversity exists between jurisdictions, and that because culture is the slowest of all a group's institutions to change, institutional shock brought about by regulatory reform (in response to harmonisation efforts) may be an exercise which is ineffective and costly. This, I submit, is the major weakness of the gold-standard approach to regulatory assessment – i.e., regulatory impact analysis, a cousin of cost benefit analysis. To perform such an analysis, monetary values must be assigned to the benefits and disbenefits attendant to regulatory changes. Then, the (presumably positive) expected monetary gains as a result of increased trade that results from the abolition of a non-tariff barrier to trade (for example a regulatory divergence) must be weighed against the costs of making the regulatory reform in one or both (or multiple) jurisdictions.[18] Yet, the secondary and tertiary results here have shown evidence that the public being regulated in either or both or all cases is likely to have heterogeneous preferences due to cultural diversity.[19] As the monetary values attached to the benefits and costs of regulatory reform are contingent upon the preferences of consumers at large, then cultural diversity between jurisdictions is, for starters, likely to make any meaningful cost benefit analysis of regulatory impact analysis impossible or at least very difficult to undertake.[20]

The secondary and tertiary results here provide evidence in support of the proposition that there is no such thing as a 'public interest' approach to regulation which can be applied globally. It can only ever be applied contingent upon the specific preferences of the public

18 See also Wiener, Jonathan B., Brendon Swedlow, James K. Hammitt, Michael D. Rogers, and Peter H. Sand. "Better Ways to Study Regulatory Elephants." *European Journal of Risk Regulation*4, no. 2 (2013): 311-319.

19 See Howlett, Michael. "Policy instruments, policy styles, and policy implementation: National approaches to theories of instrument choice." *Policy studies journal* 19, no. 2 (1991): 1-21.

20 Related to this, see Wiener, Jonathan B. "The diffusion of regulatory oversight." *The Globalization of Cost-Benefit Analysis in Environmental Policy* (2013): 123-41.

being regulated.[21] The primary results here – showing some evidence that culture will have an effect on shaping regulatory outcomes through the actions of interest groups and constrained or facilitated by pre-existing jurisdiction-wide institutions, suggest that attempts at regulatory reform (aimed at regulatory harmonisation) will likely face many obstacles.[22] This is a problem which Rieff, for example, has considered specifically in the context of the economics of federalism.[23] It is not a problem limited only to pharmaceuticals regulation/regulatory harmonisation.[24] And it has already been recognised at the level of the World Trade Organisation that greater attention needs to be paid both to heterogeneity of preferences, and the presence of certain interest groups strongly interested in particular regulatory positions within the negotiating states.[25] This has been recognised also within the context of other major trade negotiations such as the Transatlantic Trade and Investment Partnership.[26] The secondary results, that culture as the basic institution is the slowest of all institutions in a group to change, indicates that attempts to reform whole systems of regulation in order to encourage cross border trade will simply be ineffective, where the regulatory reforms introduced are too greatly incongruous with the basic underlying institution of culture in one or both (or multiple) jurisdictions.[27] This is why calls have repeatedly been made to study carefully the individual jurisdictions locked in trade negotiations before seeking to enact regulatory harmonisation[28] Indeed, the primary, secondary and tertiary results found in this work[29] may go some way towards explaining one

21 See e.g. Burgess, Adam. "Missing the Wood for the Trees?." European Journal of Risk Regulation 4, no. 2 (2013): 287-291.

22 See e.g. Thijs Van de Graaf, Tim Haesebrouck & Peter Debaere (2017): Fractured politics? The comparative regulation of shale gas in Europe, Journal of European Public Policy

23 Rieff, Joé. "National Identities and Common Policies: A case study of the European Union." (2021).

24 See e.g. Bernauer, Thomas, and Erika Meins. "Technological revolution meets policy and the market: Explaining cross-national differences in agricultural biotechnology regulation." *European Journal of Political Research* 42, no. 5 (2003): 643-683. See also Engeli, Isabelle, and Christine Rothmayr Allison. "Diverging against all odds? Regulatory paths in embryonic stem cell research across Western Europe." Journal of European Public Policy 20, no. 3 (2013): 407-424. See also Goldthau, Andreas, and Michael LaBelle. "The power of policy regimes: explaining shale gas policy divergence in Bulgaria and Poland." *Review of Policy Research* 33, no. 6 (2016): 603-622.

25 Thomas J. Bollyky and Petros C. Mavroidis RSCAS 2016/47 Robert Schuman Centre for Advanced Studies Global Governance Programme-231 Trade, Social Preferences and Regulatory Cooperation The New WTO-Think. See also Vogel, David. "Ships passing in the night: The changing politics of risk regulation in Europe and the United States." (2001). See also Grossman, M.R. (2018) Agricultural Biotechnology: Regulation in the United States and the European Union. In: Bremmers H., Purnhagen K. (eds) Regulating and Managing Food Safety in the EU. Economic Analysis of Law in European Legal Scholarship, vol 6. Springer.

26 Alemanno, Alberto. "The Regulatory Cooperation Chapter of the Transatlantic Trade and Investment Partnership: institutional structures and democratic consequences." Journal of International Economic Law 18, no. 3 (2015): 625-640.

27 See Wiener, Jonathan. "Convergence, divergence, and complexity." Green Giants (2002).

28 See Wiener, Jonathan B., and Alberto Alemanno. "The future of international regulatory cooperation: TTIP as a learning process toward a global policy laboratory." Law & Contemp. Probs. 78 (2015): 103.

29 See Rose-Ackerman, Susan. "Precaution, proportionality, and cost/benefit analysis: false analogies." European Journal of Risk Regulation 4, no. 2 (2013): 281-286. Rose-Ackerman refers to the cultural theory of risk when critiquing the work of Vogel and Wiener in explaining transatlantic regulatory divergence.

very major difference between US and EU approaches to regulation of many areas:[30] including the EU insistence on adherence to the 'precautionary principle'.[31]

I turn first to the putative benefits of regulatory harmonisation. It is trite theory in the analysis of international trade that regulatory divergences represent non-tariff barriers to trade. And, that they can amount to national protection of domestic industries in disguise. By requiring – for the entire domestic market – compliance with a regulatory requirement which domestic firms already comply with but potential foreign competitors do not, the domestic regulator raises – for foreign firms – the costs of doing business in the domestic market and thus favours its domestic industries.[32] Indeed, this reasoning is the basis for much of EU law which prohibits, between member states, measures having an equivalent effect to a quantitative restriction upon imports and exports. And, strictly limiting the legally justifiable bases upon which a regulatory requirement may be imposed by EUMS - setting them instead at the EU-wide level and inevitably imposing a competitive disadvantage on non-EU firms seeking to enter the EU market.[33] The wider the trading 'bloc' the larger the potential gains from increased trade due to reduced non-tariff barriers. A 2009 report from Ecorys[34] estimated that by 2018 50% of non-tariff measures and regulatory divergence between the EU and the US could be eliminated. They stated,[35] *"the ambitious scenario could push EU GDP to be 0.7 percent higher in 2018 compared to the baseline scenario (i.e. do nothing), which represents an annual potential gain of €122 billion ($158 billion). For the US GDP the same operation yields a 0.3 percent gain per year in 2018 (compared to the baseline), which represents an annual potential gain of €41 billion ($53 billion)."* With projections like these being made it is no surprise that there are repeated attempts, particularly by the largest economic powers, to bring about regulatory convergence.[36] In relation to the pharmaceutical sector specifically, Ecorys (in the same report) projected as follows in Table 105,[37] indicating major benefits for

30 See Lofstedt, Ragnar E., and David Vogel. "The changing character of regulation: A comparison of Europe and the United States." *Risk Analysis* 21, no. 3 (2001): 399-416.

31 See Wiener, Jonathan B., and Michael D. Rogers. "Comparing precaution in the United States and Europe." Journal of risk research 5, no. 4 (2002): 317-349. See also Wiener, Jonathan B. "The real pattern of precaution." *The reality of precaution: comparing risk regulation in the United States and Europe* (2011): 519-565.

32 See e.g. Bremmers H., Purnhagen K. (eds) Regulating and Managing Food Safety in the EU. Economic Analysis of Law in European Legal Scholarship, vol 6. Springer, Cham. 2018

33 See e.g. Why are US and EU policies towards GMOs so different? Anderson and Jackson. AgBioForum, 6(3): 95-100. '2003 AgBioForum.

34 Berden, G. K., Joseph Francois, M. Thelle, P. Wymenga, and S. Tamminen. "Non-Tari Measures in EU-US Trade and Investment–An Economic Analysis." *Rotterdam, ECORYS Nederland BV* (2009).

35 Ibid. at page 9.

36 See GLOBALIZATION, COERCION, AND COMPETITION: The different pathways to policy convergence Daniel W. Drezner February 2004

37 Berden et al. ECORYS Nederland BV (2009) at pg. 21

the pharmaceutical sector were non-tariff measures such as regulatory divergences to be removed.

Projections such as those made by Ecorys are, despite being based upon sound theory from economics and international trade, paying too little attention to the texture within each of the jurisdictions, and the feasibility or desirability of harmonising regulatory provisions (and/or practices) in the first place.

Table 105 Potential Cost Savings from Abolition of Regulatory Divergences etc (Ecorys 2009)

Sector	Additional percentage increase in costs due to NTMs (flows from EU to US)	Additional percentage increase in costs remaining after alignment of actionable NTMs (flows from EU to US)	Additional percentage increase in costs due to NTMs (flows from US to EU)	Additional percentage increase in cost remaining after alignment of actionable NTMs (flows from US to EU)
Chemicals	21.0%	9.1%	23.9%	8.9%
Pharmaceuticals	9.5%	4.8%	15.3%	8.9%
Cosmetics	32.4%	15.1%	34.6%	14.6%

7.2.1 The Economics of Federalism

A great deal has been written in law and economics regarding the desirability and/or feasibility of regulatory harmonisation between jurisdictions. Particularly in the case of the European Union and the internal market. This body of literature has often been referred to as, 'the Economics of Federalism'.[38] The starting point in many of these papers is the observation of Tiebout[39] that legal (regulatory) diversity may be welcomed rather than seen as a hindrance to trade. In Tiebout's view, because there are divergent preferences amongst (e.g.) consumers as to the goals of law, the co-existence of different legal orders and systems of regulation may lead people to 'vote with their feet' moving towards those jurisdictions or areas with legal orders which are best aligned with their own values and norms. Moreover, diverse systems of legal rules lead to the potential for learning effects between legal orders.[40] On heterogeneity of preferences regarding the goals of law and regulation, Van den Bergh[41] gives the example of those who see the purpose of tort law as that of preventing accidents

38 See, most significantly, Van den Bergh, R. J. (1998). Subsidiarity as an economic demarcation principle and the emergence of European private law. Maastricht Journal of European and Comparative Law, 5, 129–152. See more recently Visscher, L., and M. Faure. "A Law and Economics Perspective on the EU Directive on Representative Actions." *Journal of Consumer Policy* (2021): 1-28. Also Van den Bergh, R. J. (2000). Toward an institutional legal framework for regulatory competition in Europe. Kyklos, 53, 435–466. Faure, Michael. "The economics of harmonization of food law in the EU." In *Regulating and Managing Food Safety in the EU*, pp. 263-290. Springer, Cham, 2018. Van den Bergh, R. J., & Visscher, L. T. (2006). The principles of European tort law: The right path to harmonization? European Review of Private Law, 14, 511–543. See also Faure, Michael G. "Product liability and product safety in europe: Harmonization or differentitation." *Kyklos* 53, no. 4 (2000): 467-508.

39 Tiebout, Charles M. "A pure theory of local expenditures." *Journal of political economy* 64, no. 5 (1956): 416-424.

40 See Ogus, Anthony. "Competition between national legal systems: a contribution of economic analysis to comparative law." *International & Comparative Law Quarterly* 48, no. 2 (1999): 405-418 at pgs. 415-416.

41 Van den Bergh (1998) at 129.

occurring in the first place, versus those who see the purpose of tort law as compensating those who have been injured by accidents.[42] Van den Bergh points out that, due to the heterogeneity in these preferences as well as to many other aspects of heterogeneity between EUMS, there are only a few, limited bases upon which economics would justify the harmonisation of regulations or laws. One is the potential for transaction costs savings from regulatory harmonisation.[43] Another is the potential for a 'race to the bottom' in regulatory approaches amongst jurisdictions whereby, locked in a hypothetical prisoner's dilemma, they each lower their standards of regulation as far as possible in order to attract competition and investment. Although empirical evidence of this occurring seems to be weak at best[44] and many economists have argued that in such circumstances a race to the top is more likely.[45]

An argument more closely related to the scenario envisaged in the Ecorys report relates to 'levelling the playing field' for industry so that it finds it easier to do business in multiple jurisdictions: this, presumably, is what leads to projected increases in trade and investment between the transatlantic partners. Whilt it is arguable that the removal of trade restrictions, and thus the lowering of transaction costs, may increase trade efficiencies, it has been argued that harmonisation of laws and regulations wholesale often goes well beyond what is necessary to encourage trade and investment between jurisdictions. These scholars argue that in fact, 'levelling the playing field' does not constitute an economic argument for harmonisation.[46] This line of literature does, however, stress the relevance of the possibility of cross-border externalities as a potential economic argument in favour of regulatory harmonisation.[47] In the case of the regulation of pharmaceutical products, and particularly licensing of pharmaceutical products, this seems to be the strongest argument in favour of regulatory harmonisation. The problem envisaged is that a regulator in one jurisdiction (say, the EU) sets standards of safety and efficacy for new pharmaceutical product licenses very low. The product is then exported around the world, and the negative externalities are imposed upon consumers in other jurisdictions including the US, China etc. Although, Professor Faure has argued that even this problem is not necessarily sufficient to justify the harmonisation of laws and regulations. He says, *"the mere fact that different states would hold different preferences with respect to product liability and product safety and that therefore different regimes would exist, can… hardly be considered as an argument for centralisation as long as states are not capable of externalising harm to victims in third countries."*[48] Which could not be the case because the courts in the third countries would hold the manufacturer or importer liable for the harm caused by the product, and in doing so would normally apply the domestic law of the jurisdiction where the harm occurred.

42 The reader may recall how this links to my discussion in Chapter Six regarding distributive versus corrective justice.

43 Van den Bergh & Visscher (2006).

44 Revesz, Richard L. "Rehabilitating interstate competition: Rethinking the race-to-the-bottom rationale for federal environmental regulation." *NYUL Rev.* 67 (1992): 1210.

45 Prakash, Aseem, and Kelly L. Kollman. "Biopolitics in the EU and the US: A Race to the Bottom or Convergence to the Top?." *International Studies Quarterly* 47, no. 4 (2003): 617-641.

46 See Visscher, Louis. "A law and economics view on harmonisation of procedural law." In *Civil Litigation in a Globalising World*, pp. 65-91. TMC Asser Press, 2012.

47 See Faure (2000) at 476.

48 See Faure (2000) at 478.

This problem has not prompted international harmonisation of all aspects of pharmaceutical regulation, but it has undoubtedly led to the fact of numerous different agencies in numerous different jurisdictions and the need for a license to be obtained from each one – greatly increasing transaction costs. The centralised and decentralised systems of pharmaceutical licensing orchestrated by the EMA are an attempt to strike the correct balance between minimising the costs of marketing pharmaceutical products across European borders whilst respecting the diversity of product safety preferences which may exist according to the diverse cultures of the EUMS (as I have argued, this in effect comes down to presenting all EMA decision making as based purely on science). Stepping outside of Europe towards the global stage, a similar movement can be seen in the International Council for Harmonisation – again, an attempt to ease trade frictions by harmonising certain aspects of regulation, but equally eager to convince the onlooker that this is being done on the basis of neutral and rational science. It will be clear to the reader by now that such a 'scientific-expertise' approach is not culturally neutral but is instead very much hierarchical in cultural terms. I return to this momentarily.[49]

Before I move on, I make a couple of observations regarding the 'economics of federalism' literature. The first is that it, like my results in this work, endorse a key observation, which is that preferences of consumers are heterogeneous. The economics literature often notes this and does not seek to explain it, instead focusing on how best to approach (e.g.) legal reform given heterogeneity of preferences. In this work I have actively sought to explain the heterogeneity of preferences. With respect to (for example) preferences for specific pharmaceutical products; to the goals of legal systems; to the roles of doctors and pharmacists. I have said that these reflect culture and I have explained how this process occurs (in Chapter Five). My analysis, and my results here support the arguments in the economics of federalism literature, by further strengthening the first postulate upon which those arguments are based – the postulate that preferences are heterogeneous. I say not only are they heterogeneous, but that they are not likely to change quickly because, moving from the individual to the group, what these individual preferences really represent are the group institutions of culture.

7.2.2 The International Council For Harmonisation

What exists at the global level, on the question of international regulatory harmonisation in pharmaceuticals, is the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ('ICH'). This grew out of coordination between the US, Europe, and Japan from 1989 onwards. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (as it was then called) was created in Brussels in 1990, and from 2015 it moved to Switzerland. It is a collaboration between regulatory agencies in each of the (now 18) members and *"concerned industry organisations"*. According to its website[50] the purpose of the ICH is, *"to achieve*

49 This cultural explanation may also explain why the lessons from the economics of federalism (which largely come from the US) were in fact never taken over at the policy level in the EU. There, it was often argued that harmonisation is simply not only based on economic arguments. This is a point for future research.
50 https://www.ich.org/

greater harmonisation worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards." The ICH focuses heavily upon technical and scientific aspects of pharmaceutical product development and registration.[51]

The main argument of the economics of federalism scholars against further EU legal harmonisation is based upon the diversity of consumer preferences. These same scholars (albeit often grudgingly) accept the potential for transboundary externalities as a justification for centralisation and regulatory harmonisation. The work of the ICH may, therefore, be difficult for those scholars to attack. After all, what is being harmonised is merely the technical and scientific aspects of (in particular) licensing procedures including clinical trials. And yet, the arguments made in this work, and the results found here, should provide those scholars with a basis for critiquing the work of the ICH too.

Recall the arguments made in Chapters One and Two, and the characteristics of the EMA and the NA's: 'Science Excludes Politics' which leads to a lack of 'Direct to Consumer Accountability' and thus 'Insulation' for ministers. This is precisely what is happening at the ICH. Now, on the global level rather than 'merely' the European level. Recall too, that trust in expertise and the ability of experts to control innovation is a predicate of Hierarchism according to the CT-GG literature. The ICH and its work is hierarchical. Then, also recall the diversity of approaches between the US and the EU/EUMS agencies. There is a (culturally engendered) preference amongst US consumers and the FDA for transparency and public participation, for consumer activism and responsiveness to consumer activism, in order to maintain popularity with consumers. The greater the share of US and EU regulation of pharmaceuticals which is derived from the behind-closed-doors scientifical-technical negotiations between experts and industry leaders at the ICH, the further the US regulatory system for pharmaceuticals will depart from its current cultural form. This is likely to be much more acceptable to Europeans than it will be to Americans, based upon the results found in this work.

Perhaps then, when President Trump signed in to law the 21st Century Cures Act,[52] which many commentators saw as a departure from the scientific gold standard of randomised controlled clinical trials for pharmaceutical product licensing, observers should neither have been surprised nor necessarily very critical. If activist US consumers want 'cures' now, then what good reason is there, given US jurisdictional culture, for pleading delays due to science, such an argument would hold a high-grid, high-group, cultural orientation. Is the US (and the FDA) under Biden more likely to cooperate more closely with the other members of the ICH? That may seem likely to be the case, but there is surely a limit, and a time will come where US consumers will want to be able to influence the regulation of the pharmaceuticals sector directly and will not be interested in accepting inaccessible science. The basis for this is the same basis that the economics of federalism scholars have for their arguments – that the preferences of humans are heterogeneous in very many respects, and here I have argued that these heterogeneous preferences are shaped by culture.

51https://en.wikipedia.org/wiki/International_Council_for_Harmonisation_of_Technical_Requirements_for_Pharmaceuticals_for_Human_Use

52 See Chapter One

I cannot and will not conclude one way or the other. Neither that the world should place the regulation of the pharmaceutical sector in the hands of experts alone and find the world regulatory system harmonised that way, nor that all efforts at harmonisation of regulation should be abandoned despite the potential macroeconomic benefits from trade. The two approaches to the problem represent two different cultural orientations: the ICH is hierarchical, and the economics of federalism scholars are individualistic. Wildavsky posits the interdependence condition amongst the cultural orientations. Hierarchism and individualism cannot survive without each other. Recall that without individualism there would be no negotiated transactions to enforce, but without hierarchism no negotiated transactions would be enforceable. The same applies to the regulation of pharmaceuticals, and the two (as well as the egalitarian view that innovation and expertise are to be rejected) will continue to struggle against each other, on a global scale, in a constant state of disequilibrium. That is as far as I will go in this work towards a normative conclusion. I do believe, however, that to understand this to be this the case, is very useful for all involved in the global regulatory system of pharmaceuticals.

7.3 Seven Conclusions

My research question asked whether cultural theory can add some further explanation for regulatory divergence in the pharmaceutical sector. By definition, culture includes regulation, so the answer had to be yes. My hypothesis was that it can, because it can furnish a *consistent* explanation for regulatory divergence across all divergences considered. Additional significance and value of this research and these results, therefore, are in showing 1) evidence for the existence of consistent cultural diversity between the two jurisdictions; and 2) showing *how* culture affects regulatory divergence.

After my research has been completed, therefore, I arrive at the following seven conclusions:

1. Adopting an institutional approach to culture, as set out in Chapter Five, and adopting the typology of culture offered by CT-GG as operationalised via the predicates set out in Table 73 of Chapter Six, examination and analysis of: four jurisdictions/cultures; three regulatory organisations; ten interest groups; and twelve jurisdiction-wide institutions, have shown a consistent within-jurisdiction cultural consistency.

2. The same has shown a consistent between-jurisdiction cultural difference.

3. In the case of the jurisdiction of the US this has been relatively low-grid, low-group or individualistic; and, in the case of the EU/EUMS this has been relatively high-grid, high-group or hierarchical.

4. This cultural analysis has provided further explanation for regulatory divergence across the six aspects of pharmaceuticals regulation considered in this work but *only* in combination with the extant theories of public interest (albeit modified, see conclusion 5) below), private interest and institutional analysis, because the cultural consistency is only found by looking first beyond the regulatory positions, to the public interest explanations, the private interest explanations and the jurisdiction-wide institutions which constrain or widen the choices of the various actors.

5. There is no 'universal' public interest approach to regulation of the pharmaceutical sector, because, what lies in the interests of the regulated public depends upon their collective (shared) preferences which come from their underlying cultural orientation as a group.

6. The institutional approach to culture set out in Chapter Five (Figure 16 **Culture as the Basic Institution in a Group or Subgroup**), whereby a bi-directional relationship between culture and other institutions is posited, is vindicated by the findings of this research: regulations are easy to change and may take surprising forms in light of the cultural orientation of the jurisdictions however, ultimately, these regulatory positions will be linked to underlying culture, and given sufficient time, repeated changes to regulatory and other formal institutions will eventually lead to a change in the underlying basic institution of culture.

7. As such, from a normative standpoint, because cultural diversity is observed, and thus collective preferences are likely shaped by the shared element of culture, efforts to harmonise pharmaceutical sector regulation internationally should be cognisant of this cultural diversity. Opposition to harmonisation of pharmaceutical regulation is likely to result from an underlying individualistic culture, and preference for harmonisation of scientific and technical standards is likely to result from an underlying hierarchical culture. Both cultural orientations rely upon each other for their viability, thus neither 'no harmonisation' nor 'full harmonisation' can be the 'correct' answer.

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Summary

Recent decades have witnessed efforts towards frictionless trade between the world's most developed economies. In addition to the impact of tariffs and quantitative measures lie the effects of divergent regulatory frameworks for products, also impeding trade. One sector of particular importance to the European Union and the United States – given their global predominance – is pharmaceuticals. And, given the COVID-19 pandemic and subsequent race to develop and approve safe and effective vaccines, the spotlight has been placed in the past two years upon the regulatory systems for pharmaceuticals in both.

Major divergences exist between these two jurisdictions regarding the regulation of pharmaceutical products, including everything from the rules regarding direct-to-consumer advertising of prescription-only products, to the level of caution and thus speed applied to consideration of a market license. This work considers the problem of transatlantic regulatory divergence in the pharmaceutical sector and analyses these divergences from: a law and economics perspective (public interest); a political science perspective (private interest); and, an institutional perspective. The application of these theories all assists to some extent in explaining regulatory divergence, however what is lacking – this work finds – is some account for how collective preferences within each jurisdiction are shaped. The latter make all the difference to how choices are made regarding the regulation of pharmaceutical products. These collective preferences are manifest through both the private interest pathways – the objectives of interest groups (including consumers), and regulatory organisations in each jurisdiction – as well as through the effects of jurisdiction-wide institutions which constrain or widen the choices available to regulators and interest groups.

In this work, therefore, cultural theory is also applied to analyse the problem of regulatory divergence to shed further light upon collective preferences in each jurisdiction, and how these affect the regulatory positions ultimately taken. To do so, an institutional approach to culture is adopted which ties together the literature from economic theory, from institutional theory and from cultural theory. Dimensions of culture are taken from the cultural theory of risk, and a relative cultural positioning of the United States and the European Union is developed in which the United States is, as a jurisdiction, 'individualistic' relative to the 'hierarchical' European Union. In addition to this, a relative cultural positioning for a cluster

of northern and southern EU Member States, respectively, is also developed. Operationalising the dimensions of risk and culture theory using a set of predicates taken from that body of literature; the regulatory organisations, interest groups and institutions in each jurisdiction are analysed culturally and it is identified that a consistent underlying cultural orientation is persistent in each jurisdiction and/or cluster.

By combining the approach of law and economics, and political science, with an institutional approach to culture - which can explain differences between the preferences of groups regarding product regulation - this work presents a positive analysis showing *how* underlying culture ultimately helps to shape regulatory divergence. Because, in this case, the underlying variable of relative cultural positioning remains constant in each jurisdiction across multiple divergences, this work presents some evidence that culture can add further explanation to that provided by public interest and private interest theory, for transatlantic (and, intra-EU) regulatory divergence in the pharmaceutical sector.

This has implications for the efforts made to encourage frictionless cross-border trade, where such frictions result from regulatory divergence. And, as such, this work lends support to the starting observation of the economics of federalism. Preferences differ from group to group and place to place and they do so legitimately, because of cultural differences. Regulatory harmonisation is not necessary in every case, and regulatory diversity may better satisfy preferences globally. Even where international regulatory harmonisation is based only upon scientific and technical standards this does not immunise those efforts against that insight. The decision to place reliance upon scientific expertise to regulate the fruits of innovation in this, and any, sector is itself to take a culturally specific position. That position may not be in harmony with the collective preferences found in every jurisdiction concerned.

Samenvatting

Er bestaan grote verschillen tussen de Europese Unie en de Verenigde Staten met betrekking tot de regulering van farmaceutische producten, inclusief alles van de regels met betrekking tot direct-to-consumer-reclame voor receptplichtige producten, tot het niveau van behoedzaamheid en dus snelheid toegepast bij het overwegen van een markt licentie. Dit stelling beschouwt het probleem van transatlantische verschillen in regelgeving in de farmaceutische sector en analyseert deze verschillen vanuit: een juridisch en economisch perspectief (algemeen belang); een politicologisch perspectief (eigen belang); en een institutioneel perspectief. De toepassing van deze theorieën helpt tot op zekere hoogte bij het verklaren van verschillen in regelgeving, maar wat ontbreekt - zo vindt dit werk - is een verklaring voor hoe collectieve voorkeuren binnen elk rechtsgebied worden gevormd. Die laatsten maken het verschil voor de manier waarop keuzes worden gemaakt met betrekking tot de regulering van farmaceutische producten. Deze collectieve voorkeuren komen zowel tot uiting in de particuliere belangentrajecten – de doelstellingen van belangengroepen (waaronder consumenten) en regelgevende organisaties in elk rechtsgebied – als in de effecten van rechtsgebiedbrede instituties die de keuzemogelijkheden van regelgevende instanties of belangengroepen beperken of verbreden.

In dit werk wordt de culturele theorie daarom ook toegepast om het probleem van verschillen in regelgeving te analyseren om meer licht te werpen op collectieve voorkeuren in elk rechtsgebied, en hoe deze de uiteindelijk ingenomen regelgevingsposities beïnvloeden. Hiervoor wordt een institutionele benadering van cultuur gehanteerd die de literatuur uit de economische theorie, de institutionele theorie en de cultuurtheorie met elkaar verbindt. Cultuurdimensies worden ontleend aan de culturele risicotheorie en er wordt een relatieve culturele positionering van de Verenigde Staten en de Europese Unie ontwikkeld waarin de Verenigde Staten als jurisdictie 'individualistisch' zijn, ten opzichte van de 'hiërarchische' Europese Unie. Daarnaast wordt ook een relatieve culturele positionering voor een cluster van respectievelijk noordelijke en zuidelijke EU-lidstaten ontwikkeld. Operationaliseren van de dimensies van risico- en cultuurtheorie met behulp van een reeks benamingen uit die literatuur; de regelgevende organisaties, belangengroepen en instellingen in elke jurisdictie

worden cultureel geanalyseerd en vastgesteld wordt, dat een consistente onderliggende culturele oriëntatie aanhoudend is in elke jurisdictie en/of cluster.

Door de benadering van recht en economie, en politicologie, te combineren met een institutionele benadering van cultuur - die verschillen tussen de voorkeuren van groepen met betrekking tot productregulering kan verklaren - presenteert dit werk een positieve analyse die laat zien hoe onderliggende cultuur uiteindelijk helpt om verschillen in regelgeving vorm te geven. Omdat in dit geval de onderliggende variabele van relatieve culturele positionering constant blijft in elke jurisdictie over meerdere divergenties heen, presenteert dit werk enig bewijs dat cultuur een verdere verklaring kan toevoegen aan die van de theorie van openbaar belang en privébelang, voor transatlantische (en intra-) -EU) verschillen in regelgeving in de farmaceutische sector.

En als zodanig ondersteunt dit werk de beginnende observatie van de economie van het federalisme. Voorkeuren verschillen van groep tot groep en van plaats tot plaats, en dit is legitiem vanwege culturele verschillen. Harmonisatie van regelgeving is niet in alle gevallen nodig, en diversiteit in regelgeving kan beter voldoen aan de wereldwijde voorkeuren.

Curriculum Vitae

Liam Wells LLM, Barrister

liam.wells@emle.eu

Short Bio

Liam Wells holds a BA in Jurisprudence (with European law studies) from Merton College, University of Oxford. He also holds an LLM in International Business Law from the University of London (King's College) and an LLM in the Economic Analysis of Law from Erasmus Universiteit Rotterdam. He was called to the Bar of England and Wales in 2014, and successfully completed Pupillage in 2017: specialising in Public Law. He has appeared before the High Court, as well as County Courts throughout England and Wales. Liam has published academic articles in the Economic Analysis of Public Law, and in Behavioural Law and Economics. He is currently completing his PhD Thesis in the European Doctorate in Law and Economics programme.

Education

LLM Law and Economics with distinction 8.97/10 (joint award) Aix-Marseille Université Erasmus Universiteit Rotterdam *Visiting Research Scholar University of California at Berkeley*	2016
LLM International Business Law King's College, University of London	2015
BPTC Bar Professional Training Course BPP University/Middle Temple	2013
BA Jurisprudence with European Law Studies Merton College, University of Oxford *Erasmus Exchange at Leiden University (2009-2010)*	2011

Work Experience

October 2016-Present: Pupil Barrister/Tenant Barrister Fraser Chambers, London (Tenant 2022-Present) Goldsmith Chambers, London (Door Tenant 2017-2018) Cornerstone Barristers, London (Pupil 2016-2017/Tenant 2017)	2016-Present
Managing/Series Editor 'Elements in Law, Economics and Politics' Cambridge University Press	2020-2022
Research Assistant (part time employed position) Prof. Dr. Elena Kantorowicz-Reznichenko	2020-2021
PhD Candidate (full time employed position) Erasmus School of Law (Erasmus Universiteit Rotterdam)	2017-2022
Solicitor Intern (paid internships) Clifford Chance LLP/ Shearman and Sterling LLP/Ashurst LLP	2010-2012

Prizes/Awards	
Harmsworth Scholar Middle Temple	2014
Exhibition Scholarship/Postmaster Scholarship Merton College, University of Oxford	2009-2011
Publications	
Reznichenko, Elena, Jarowslaw Kantorowicz & Liam Wells "Can Vaccination Intention against COVID-19 be Nudged?" Journal of Behavioural Public Policy (2022) https://doi.org/10.1017/bpp.2022.20	2022
Wells, Liam & Kantorowicz-Reznichenko, Elena. (2021). "Nudging Compliance." In B. van Rooij and D. Sokol (Eds.). The Cambridge Handbook of Compliance.	2021
Wells, Liam. "Planning for Problems with Short-term Lets? A Comparative Economic Analysis of the use of Town Planning Versus Private Law Systems to Tackle Spill-over Effects." European Journal of Risk Regulation 10, no. 1 (2019): 60-79. https://doi.org/10.1017/err.2019.21	2019
Underwood, Dean & Liam Wells. "Case note: Poplar Housing and Regeneration Community Association Ltd v (1) Begum (2) Rohim". Journal of Housing Law. J.H.L.2017, 20(6), 137-141	2017
Others	
Called to the Bar of England and Wales Middle Temple, London	2014
Member of the Honourable Society of the Middle Temple Middle Temple, London	2011

EDLE PhD Portfolio	
Name PhD Student	: Liam Wells
PhD Period	: 2017-2023
Promoters	: Prof. Michael Faure, Prof. Elena Kantorowicz-Reznichenko & Prof. Luigi Franzoni

PhD Training	
Bologna Courses (2017-2018)	
Introduction to Statistics	Oct-Nov 2017
Modelling Private Law	Nov-Dec 2017
Experimental Economics	Nov-Dec 2017
Environmental Economics	Nov-Dec 2017
Game Theory, Behaviour, and the Law	Jan-Feb 2018
Law and Economics of Property Rights	Feb 2018
Behavioral Law, Econ and Enforcement	Mar 2018
Hamburg Courses (2018)	
Introduction to Stata	May 2018
Introduction to German Law	June 2018
Topics in Corruption Research	June 2018
International Law and International Relations	June 2018
Use of Economics for Understanding Law	July 2018
Rotterdam Courses (2018-2019)	
Academic Writing	Sept 2018
Dutch for Beginners	Oct-Dec 2018
Advanced Empirical Legal Studies	March 2019
Advanced Empirical Legal Methods	March 2019
Academic Integrity and Responsible Research	Sept-Oct 2019
Managing Your PhD	Oct-Nov 2019
Basic Didactics	Jan-Feb 2020
Grant Application Writing Workshop	July 2020

Seminars and Workshops (Attendance)	
DIGOV Seminar 'Roundabouts of Digital Governance' (EUR)	Jan 2020
Climate Change Roundtable: Soc. for Risk Analysis (Washington DC)	Dec 2019
EDLE 3rd year Seminar (U. Bologna)	Nov 2019
Advancing Gender Equality (DIO, Erasmus Universiteit Rotterdam)	Nov 2019
Guest Lecture by Cass Sunstein (Erasmus Universiteit Rotterdam)	Jun 2019
EDLE Third Year Joint Seminar (Erasmus Universiteit Rotterdam)	Mar 2019
Keynote Presentation Daniel Makowitz (SIDE, Lecce)	Dec 2018
Seminar 'Experimental Law & Economics' (Erasmus U. Rotterdam)	Nov 2018
Seminar 'Joint Liability in Competition Law' (EU. Rotterdam)	Nov 2018
BACT Seminar 'Organisation Culture' (Erasmus U. Rotterdam)	Oct 2018
Valedictory Lecture Roger Van den Bergh (Erasmus U. Rotterdam)	Sept 2018
Publication Strategy Seminar (Erasmus Universiteit Rotterdam)	Sept 2018
BACT Introduction Seminar (Erasmus Universiteit Rotterdam)	Sept 2018
EDLE Seminars (Erasmus Universiteit Rotterdam)	Sept 2018-2021
EDLE Thesis Defences (Erasmus Universiteit Rotterdam)	Sept 2018-2021
SABE/IAREP Workshop: Experiments (U. Salento, Soleto)	July 2018
Seminar: Thomas Miceli (U. Hamburg)	July 2018
Seminar: Barry Weingast. (U. Bologna)	Mar 2018
Seminar: Romano Prodi and Joseph Stiglitz (U. Bologna)	Dec 2017
EDLE 3rd year Seminar (U. Bologna)	Nov 2017
Presentation of Own Research at Conferences/Seminars	
EDLE Zoom Seminar (Erasmus Universiteit Rotterdam)	Dec 2020
EDLE Joint Seminar (Erasmus Universiteit Rotterdam)	May 2020
Annual Meeting Society for Risk Analysis (Arlington, Virginia)	Dec 2019
EDLE Seminar (Erasmus Universiteit Rotterdam)	Nov 2019
Spanish Law & Econ. Association Conference (Catholic U. Porto)	June 2019
10th Economic Analysis of Litigation Workshop (U. Granada)	June 2019
Polish Law & Econ. Assoc. Conference (Warsaw School of Econ.)	May 2019
Soc. for Risk Analysis Benelux Conference (U. Luxembourg)	Mar 2019

EDLE Seminar Series (Erasmus Universiteit Rotterdam)	Mar 2019
Italian Law & Econ. Association Conference (SIDE, Lecce)	Dec 2018
EDLE Seminar Series (Erasmus Universiteit Rotterdam)	Dec 2018
EDLE First Year Hamburg Conference (U. Hamburg)	Jun 2018
Early Years Career Scholars Conference (Erasmus U. Rotterdam)	Apr 2018
EDLE First Year Bologna Conference (U. Bologna)	Mar 2018
Attendance at Conferences	
37th Conference European Assoc. of Law and Econ. (Paris)	Sept 2020
EDLE First Year Conference (U. Hamburg)	Jul 2020
EMLE Midterm Conference (Erasmus Universiteit Rotterdam)	Feb 2020
EMLE Midterm Conference (U. Hamburg)	Feb 2019
EMLE Midterm Conference (Erasmus Universiteit Rotterdam)	Feb 2018
Italian Law & Econ. Association Conference (SIDE, Rome)	Dec 2017
35th Conference European Assoc. of Law and Econ. (London)	Sept 2018
Teaching	
Senior Lecturer 'Economic Analysis of Public Law' EMLE Programme: University of Haifa	Dec 2021-Jan 2022
Guest Lecturer 'Public Law and Economics' EMLE Programme: Erasmus Universiteit Rotterdam	Dec 2018
Assistant Lecturer 'Introduction to Law' EMLE Programme: Erasmus Universiteit Rotterdam	Nov-Dec 2018
Other	
Host, Producer and Editor 'Law Out Loud' Podcast (EGSL)	2020-2021
Erasmus Pride LGBT+ Society: Board Membership	2019-2020
Host EMLE Mid-Term Meeting Careers Event	2018-2021
PHD in Law Association of Rotterdam: Board Membership	2018-2020
Summer School: Law & Logic: EUI, Fiesola	July 2019
SABE/IAREP Summer School: Experiments, U. Salento, Soleto	July 2018