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Free Trade Agreements and patterns of risk regulation in the EU and the US

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STUDY

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ABSTRACT

Transatlantic regulatory patterns overall, and in four key sectors: food, automobiles, chemicals, and pharmaceuticals, indicate that EU risk regulation is not always or generally more stringent than US regulation. The reality is a complex mix of parity and particularity. While there is overall EU-US similarity, there is also variation. In some risk matters, across and within sectors, the European regulation is more stringent, whereas in others it is the US. Even if they are unusual, such transatlantic regulatory differences can pose barriers to trade. Still regulatory variation can also be the basis for learning to improve future regulatory design, both by comparing outcomes across regulations in different jurisdictions, and by planning adaptive regulation over time. International regulatory cooperation is not limited to adopting the current standard of one side or the other: it can also involve collaboration to review existing regulations and design new approaches that improve outcomes for all.

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Executive Summary

As international trade negotiators or regulatory bodies consider options to reconcile regulatory standards to reduce barriers to trade, concerns may arise that such efforts at harmonization, mutual recognition or other modes of regulatory cooperation might weaken regulatory protections. In this context, one viewpoint is that European regulatory standards have become more protective – more stringent and precautionary – than US regulatory standards, so that converging might weaken European standards (although "harmonizing up" to higher standards is also possible). But the real pattern of regulation is more complex. Precautionary policies have been pursued on both sides of the Atlantic, in both directions (sometimes greater European precaution, sometimes greater US precaution), and cost-benefit analysis of regulation has been employed on both sides as well. A key problem in claims of greater precaution is sample selection bias: citing prominent examples that draw media attention but that do not actually represent a general pattern or trend.

This report summarizes the literature, and offers a descriptive transatlantic comparison of regulatory standards in four key sectors.

Food

In some cases, European regulations are more stringent or precautionary. This is the case for genetically modified (GMO) foods, hormones in beef, and antibiotics in animal production. In other cases, US regulations are more stringent or precautionary, such as for mad cow disease (BSE/vCJD) in beef and especially in blood, trans fats (especially in labelling and broad phase-out), unpasteurised dairy products, and choking hazards. Some cases reflect simultaneous precaution against conflicting risks but different methods, such as in poultry, where the US allows chlorine-washed chicken to reduce salmonella, while the EU restricts chlorine washing and imposes salmonella detection at source. And in still other cases, US and European regulations have converged through international regulatory cooperation, such as for organic food and possibly for pesticides.

Automobiles

The comparative safety of motor vehicles in Europe and the United States is a topic of growing importance, in part because global automakers are seeking to offer the same (or similar) products to consumers throughout the world. Vehicle safety regulations in Europe and the US are different, and it is difficult to make a technical case that European vehicles are safer than American vehicles (or vice versa). Meanwhile, US standards for automobile air pollution emissions (especially NOx and PM2.5) are more stringent, and enforced more vigorously, than in Europe. The emergence of automated and autonomous vehicles provides a new opportunity for US-EU regulatory cooperation.

Chemicals

At first glance the US approach to chemical regulation appears to be "risk-based" and the European approach "precautionary". Under the Toxics Substances Control Act (TSCA) of 1976, the US EPA considers three important policy goals in setting standards to "prevent unreasonable risk" (especially from new chemicals): the effects of chemicals on human health and the environment; the benefits of use and the availability of substitutes; and the effects on the economy and innovation. Structural features of the US law-making system tend to encourage precautionary action, such as the threat of tort liability and the expansive authority of US agencies to interpret existing statutes to deal with new problems. The new Lautenberg Chemical Safety Act (LCSA) of 2016 will, among other changes, amend TSCA to increase the testing of existing chemicals. On the European side, the REACH policy (since 2006) emphasizes testing and prioritization of existing as well as new chemicals, and setting regulatory standards to promote safer substitutes. Both regions still face problems with lack of data, high uncertainties of risk assessment, the burden of proof, the high cost of testing and low incentives for substitution of hazardous chemicals.

Pharmaceuticals

The EU and the US have been converging in their approaches to drug licensing, which is based on an assessment of safety and efficacy. Both regions aim to accelerate the licencing of pharmaceutical products thanks to adaptive approaches, with a view to enabling early access to drugs when there are unmet needs, and then using the data from monitoring such early access to evaluate whether broader access is warranted. Contrary to conventional wisdom, there do not appear to be differences in attitude to risk on a population level, despite some differences in regulation on a case by case basis. There are differences between the EU and the US in the structure of reimbursement (payment for medications by governments and insurers). Present trends suggest continuing convergence. In both the US and EU, we can expect to see greater patient involvement in defining meaningful benefit and willingness to accept risks, with lifecycle approaches to the management of risks of products, and with integrated assessments of benefits as well as risks.

Learning from regulatory variation, and international regulatory cooperation

Industry may respond to regulatory differences by producing different products to meet different standards in different jurisdictions, or by producing a single product that meets the most stringent standard. This choice is highly sensitive to the costs of each production process, and there does not seem to be a common pattern.

The variation that we observe across risk regulations in the US and Europe can be a source of learning to inform better future choices. Harmonizing standards or other modes of regulatory cooperation (to reduce barriers to trade) begs the question of which standard to converge on; studying observed regulatory variation, and even experimentation, can seek to identify differences in outcomes, better choices among current standards, and new approaches not yet adopted by either side. Both the US and Europe could benefit from such policy learning – to increase benefits, lower costs and avoid ancillary harms. Learning from regulatory variation requires careful analysis and international regulatory cooperation -- to collect data, to structure comparisons, and to evaluate results through retrospective impact assessments. The EU and US have already engaged in significant regulatory cooperation, including on specific regulations and on their regulatory impact assessment systems.

Toward Planned Adaptive Regulation

Further, trade agreements and other efforts at international regulatory cooperation could promote planned adaptive regulation (PAR) – an approach in which each regulation is not only reviewed retrospectively, but is designed from its initiation to collect data on performance, to learn from experience and to update over time. PAR is based on the premise that, in the face of uncertain evidence that was used to underpin a rule, regulators should plan for both monitoring (and revision of the risk assessment), and scheduled adaptive improvement of the rule (future review and revision within pre-established boundaries). PAR enables governments to take into account evolving evidence on the actual effects of their existing rules. PAR can be another key mechanism for policy learning – not only from regulatory variation across countries, but also from the ongoing accumulation of knowledge over time – to improve regulatory designs and outcomes.

Conclusion

The reality of transatlantic regulation is not a simple dichotomy of a European approach versus an American approach. It is not EU precaution versus US reaction, or ex-ante versus ex-post legal systems, or civil law versus common law, or uncertainty-based versus evidence-based regulatory systems. Rather, the reality is overall EU-US similarity as well as the selective application of precaution on both sides of the Atlantic. This includes both cases of greater European precaution and cases of greater US precaution. The

EU and US can learn from this variation, and from evolving understanding, to improve regulatory standards through monitoring, evaluation, impact assessment, and planned adaptive regulation.

1 Introduction and Overview

1.1 Regulatory Variation and Trade

The European Union (EU) and the United States (US) have each developed systems of risk regulation that have enabled significant improvements in health, safety, environmental quality, security, and overall risk management on both sides of the Atlantic. These regulatory frameworks include an array of institutions, laws, policies, and regulatory instruments to prevent and manage risks that might threaten the environment, public health, safety and security of the public.

Across the regulatory standards in the EU and the US, there are both similarities and differences. Even if two jurisdictions have broadly similar regulatory policies, the differences that do occur may give rise to trade disputes. 'Unnecessary regulatory differences between countries persist as lingering barriers to trade even as traditional barriers are declining' (Perez and Dudley 2016: 1). As tariffs on trade between the EU and the US have diminished, regulatory differences have become a focus of efforts to reduce barriers to expanding transatlantic trade, notably through the negotiation of a mega-regional Transatlantic Trade and Investment Partnership (TTIP) as well as through other modes of international regulatory cooperation outside TTIP (Bull et al. 2015).

Negotiating a trade agreement, or other modes of international regulatory cooperation, in order to reduce unnecessary regulatory barriers to trade raises questions about how the regulatory standards of the participating jurisdictions compare with each other, how these regulatory standards might change under the trade agreement, and what consequences such changes might entail. Some may hold the view that harmonizing regulatory standards into a single standard, or mutual recognition of each other's differing standards, will enhance trade for mutual benefit. Others may hold the view that these steps will enhance trade but lead to less protective regulatory standards if they adopt the less restrictive regulation. This report aims to help inform these discussions by examining actual regulatory similarities and differences between the EU and the US.

1.2 Perceptions of EU and US Regulation

A frequently expressed viewpoint is that European regulatory standards have become more protective – more stringent and precautionary (acting earlier and more stringently in the face of anticipated risk) – than US regulatory standards (e.g. Christoforou 2004; Cone 2005; Selin and VanDeveer 2006; Morag-Levine 2011; Vogel 2012; Bradford 2012; see the literature survey in Wiener 2011a). In support of this view, adherents cite the adoption of the precautionary principle in European law (notably in the 1992 Maastricht Treaty), coupled with the rise of EU institutions, which are said to foster more stringent and proactive EU regulation in anticipation of possible future harm, yielding a reversal from the 1970s-80s (when US regulation was seen as having been more protective than European regulation) to the era post-1990 (when European regulation is seen as having become more protective) (Vogel 2012). Adherents of this view also point to elements of the US system – such as the use of cost-benefit analysis (CBA) to review proposed regulations, and the role of ex post civil tort liability to address risks that were not fully regulated ex-ante – to argue that the US approach is more reactive, waiting for evidence of harm before acting (Woolcock et al. 2015; Vogel 2012; Christoforou 2004).

To bolster this viewpoint, examples cited of greater US precaution in the 1970s-80s include the phaseouts of CFCs and of lead (Pb) in gasoline (petrol); examples cited of greater precaution in EU regulation after 1990 include food safety policies such as regarding hormones in beef and genetically modified foods, and environmental policies such as regarding toxic chemicals and climate change (Vogel 2012). The propensity for more protective EU regulations to be emulated in other countries has been dubbed the 'Brussels Effect'

(Bradford 2012), suggesting that decisions taken in Brussels for the EU have a wider influence on policies and products around the world. This descriptive view of greater European regulatory precaution is evidently held by those who disagree on its normative merits, including both advocates and critics of such regulation (Wiener 2011a).

1.3 The Reality of EU and US Regulation

But this descriptive view of more protective European policies is not accurate. The real pattern of regulation is more complex: actual regulatory policies are more similar across the Atlantic, and, where they diverge, they point in both directions.

Seen from a global context, the EU and the US are very similar in their levels of economic development, regulatory stringency, public health, and environmental quality, and both benefit from transatlantic trade; the strong contrasts that some observers and protagonists draw reflect a kind of 'narcissism of minor differences' (Baldwin 2009). Precautionary policies have been pursued on both sides of the Atlantic, both before 1990 and after: although the EU has formally adopted the precautionary principle, the US also adopted precaution in several key statutes (including on air pollution and endangered species) (Wiener 2007; Wiener et al. 2011). And cost-benefit analysis (CBA) of regulation has been employed on both sides as well. In the US, economic analysis of the costs and benefits of regulation has been undertaken through Regulatory Impact Assessments required by executive order under every President since the 1970s. In the EU, analysis of costs and benefits is called for in the same article of the 1992 Maastricht Treaty that invokes the precautionary principle (now TFEU article 191), as well as in the European Commission's Communication on the Precautionary Principle (2000), the principle of "proportionality" in EU law, and the EU Impact Assessment system established since the early 2000s (Wiener and Ribeiro 2016). This combination of precaution with analysis of costs, benefits and countervailing risks, in real-world applications on both sides of the Atlantic, tends to produce more nuanced and varied policies than would either regulatory posture alone or in the abstract (Wiener 2002).

Overgeneralisations about wholesale differences between EU and US regulation may be based on heuristic errors (Wiener 2011b; Wiener et al. 2013). A key problem is sample selection bias: citing prominent examples (case studies) does not necessarily demonstrate a general pattern or trend, because the examples or cases may not be an unbiased or representative sample of the full set of policies (Wiener et al. 2013). Candidly, Kagan and Axelrad (2000: 18) remarked of their own volume of case studies that it 'cannot support unqualified generalisations about any of the national legal systems as a whole or about the across-the-board impact of national styles of law and regulation.' Selective attention to unrepresentative samples of unusual policies may be more misleading than informative -- it may only reflect the 'availability heuristic' in which observers give undue extra weight to recent salient examples, rather than to broader patterns and trends (Kuran and Sunstein 1999).

There are better ways to study the real patterns of EU and US regulation (Wiener et al. 2013). Rather than citing cases that are selected because they are prominent or salient, cases can be selected and data compared via more careful sampling approaches (Lieberman 2005). Indeed, an analysis of a more broadly representative array of regulatory standards – drawn from a random sample of all European and US risk regulation – indicates that over the past four decades, the EU and the US have actually been fairly similar, on average, in their degree of relative precaution, with only a slight increase in relative European precaution, not a significant shift (Hammitt et al. 2005; Swedlow et al. 2009; Wiener et al. 2013). This research found that the degree of precaution in US and European risk regulations has been, on average, about the same from 1970-present, with only a slight (less than 6%) increase in an index of relative European precaution since 1990 – not a wholesale shift to greater European precaution (Hammitt et al. 2005; Swedlow et al. 2009). This analysis also found that, within the sample, although several policies were

shifting toward greater EU precaution over time, other policies were shifting toward greater US precaution over time, while most remained in parity.

Beyond this overall similarity, there are some divergences between European and American regulatory policies. But they do not all lean toward greater protection in Europe. An extensive study involving both European and American experts to assess specific regulatory standards (Wiener et al. 2011) revealed that the divergences in US and European precaution – which can yield discord and trade barriers and news media attention –go in both directions: sometimes greater EU precaution, but sometimes greater US precaution. For example, sometimes European regulation is more precautionary, such as regarding hormones in beef, genetically modified (GM) foods, toxic chemicals, and climate change; but sometimes US regulation is more precautionary, such as regarding Mad Cow disease (BSE/vCJD) in beef and in blood donations, air pollution (especially fine particulate matter, PM2.5), tobacco, counterterrorism measures, and others (Wiener et al. 2011).

This research indicates that the reality of precaution has not been principle, it has been particularity: selective application of precaution to specific risks, on both sides of the Atlantic. On both sides, regulation has often been spurred by reaction to crises (van Asselt et al. 2014; Balleisen et al. 2017), which contributes to a shifting pattern of selective precautionary policies against future risks and hence potential trade conflicts. There is also variation in risk regulation within the US and within Europe – both across the member states of each, and across different ministries regulating different topical domains (Sand 2000; Zander 2010; Hamilton and Pelkmans 2015).

In the present report, we update this analysis of case studies by examining regulatory similarities and differences across four key sectors, noted below. Our detailed findings are presented in Chapter 2, and are summarised in Chapter 4. They show considerable variation in relative precaution and stringency across the EU and US.

Thus, the reality is not a European approach versus an American approach. It is not EU precaution versus US reaction, or ex-ante versus ex-post legal systems, or civil law versus common law, or uncertainty-based versus evidence-based regulatory systems. Rather, the reality is parity and particularity: both overall EU-US similarity, and also the selective application of precaution on both sides of the Atlantic, including cases of both greater European precaution and cases of greater US precaution.

To be sure, the cases examined in the present study were not selected in a random or representative sample, and so they may not support broader generalisations. But at least they show that the claimed generalisation of greater EU precaution is not accurate. The cases studied here were selected to assess some of the key sectors currently under negotiation between the US and EU. Across and within the four sectors studied here, there are differences not only in the regulatory standards but also in the relative impact of the regulations on the economy, on social well-being, and on innovation. And a full comparison of regulatory standards must be undertaken and characterised with care, to ensure attention not only to the official standards, but also to implementation, and to the surrounding institutional context, including other policies that also may affect outcomes (Wiener 2011b; Wiener et al. 2013).

Meanwhile, there have been extensive efforts at EU-US regulatory cooperation, even before the negotiations on TTIP. The US and EU have given mutual support in the creation of their horizontal systems of impact assessment and regulatory oversight, through the US Office of Information and Regulatory Affairs (OIRA) and its counterparts at the EU Impact Assessment Board (IAB) and now Regulatory Scrutiny Board (RSB) (Graham 2014; Wiener and Ribeiro 2016). In 2012, President Obama issued Executive Order 13,609, encouraging US federal agencies to undertake regulatory cooperation with their counterparts in Europe, Canada and elsewhere (Bull et al. 2015). In Europe, regulatory cooperation has similarly been promoted by the Barroso and Juncker Commissions. Furthermore, it is important to note the efforts of the OECD, as a forum for sharing information and experiences on regulatory performance and effectiveness,

organising regulatory collaboration on matters of economic and societal importance for OECD countries, and helping to spread shared approaches to regulatory quality, impact assessment and oversight (De Francesco 2013). Thus, in fundamental ways, the EU and US regulatory systems have actually become more similar and mutually constructive over time.

1.4 Implications for Trade Agreements and Regulatory Cooperation

The transatlantic regulatory differences that exist, even if they are unusual deviations from typical parity, and even if they go in both directions, can still pose barriers to trade. Regulatory differences can complicate trade both for large enterprises and perhaps especially for small and medium-sized enterprises (SMEs). Harmonizing regulatory standards, mutual recognition, or other forms of international regulatory cooperation, could potentially reduce such barriers and enhance trade for mutual benefit.

At the same time, converging regulatory standards to reduce barriers to trade may raise a concern that doing so might entail relaxing regulatory protections on one side or even both sides. For those who hold the descriptive comparative viewpoint discussed above – the view that European regulatory standards are always or generally more protective than US regulatory standards – the normative concern may be that reducing regulatory barriers to trade would entail weakening European regulatory protections. This concern has been expressed as a criticism of TTIP, and could also arise regarding other modes of international regulatory cooperation.

But even if this descriptive comparative viewpoint were accurate (which it is not, as discussed above), it would not necessarily follow that harmonizing standards requires weakening European regulatory protections, because the trade agreement could 'harmonise up' to more stringent standards, rather than 'harmonise down' to less stringent standards. This is an issue of negotiation.

The reality, as described above, is a more complex array of EU-US parity and particularity, going in both directions (sometimes more stringent European protections, sometimes more stringent US protections). Our study of 4 key sectors in this report adds further evidence to this complex reality.

In this situation, harmonizing transatlantic regulations, or other modes of international regulatory cooperation, could entail a mix of changes that makes (some) protections more stringent on each side of the Atlantic. And even if regulatory convergence is not attained or sought, there can still be benefits from international regulatory cooperation, such as from sharing information on tests, inspections, clinical trials, and impact assessments (both prospective and retrospective). International regulatory cooperation can take advantage of regulatory differences to study their consequences and learn how to design even better policies (Wiener and Alemanno 2015). We discuss these opportunities further in chapter 4 below.

1.5 Outline of this Report

Thus, there is a need to examine the evidence on actual regulatory similarities and differences across the Atlantic, and the implications for trade agreements such as TTIP. In order to help clarify the similarities and differences in EU and US regulation, Chapter 2 of this report offers a descriptive transatlantic comparison of regulatory standards in four key sectors:

- food safety
- automobiles
- chemicals
- pharmaceuticals

These sectors were selected because of their prominence in transatlantic economic activity and in the TTIP negotiations; they are not a representative sample of all regulated sectors. In each sector, the report illustrates the variation in regulatory approaches (this report focuses on risk regulatory systems at the EU level and the US federal level, with some attention to policies in the EU member states and the US states). In some cases, the report identifies current or potential opportunities for regulatory cooperation, in order to shed light on how transatlantic trade could be facilitated while sustaining high levels of protection.

Chapter 3 then attempts to assess how industry responds to these regulatory differences, such as by producing different products to meet different regulatory standards in different jurisdictions, or by producing a single product that meets the most stringent standard.

Chapter 4 of this report summarises our findings across the four sectors. It then highlights that such regulatory variation can offer opportunities for international regulatory cooperation to invest in learning to improve future regulatory design. Regulatory learning can be gained both by comparing outcomes across regulations in different jurisdictions, and by planning adaptive regulation over time.

2 Sectoral Cases

2.1 Food Safety Risk Regulation in the EU and US

Food safety regulation includes a variety of subtopics. In this section, we review 10 cases of food safety regulation. These ten cases, selected by their prominence and diversity (not as a random or representative sample of all food safety policies), suggest that the relative degree of stringency or protection in US and European policies is not uniform but varies among these subtopics. Thus, claims that European food safety standards are generally more stringent or precautionary than US food safety standards do not appear to be accurate. In some cases, European regulations are more stringent, such as for genetically modified (GMO) foods, hormones in beef, and antibiotics in animal production. In other cases, US regulations are more stringent, such as for mad cow disease (BSE/vCJD) in beef and especially in blood, trans fats, unpasteurised dairy products, and choking hazards. Some cases reflect simultaneous precaution against conflicting risks, such as chlorine-washed chicken to reduce salmonella. And in still other cases, US and European regulations have converged through international regulatory cooperation, such as for organic food and possibly for pesticides.

2.1.1 Genetically Modified Organisms (GMOs)

Genetically Modified Plants

Regulations may address genetically modified (GM) foods as they reach the consumer, the cultivation of GM crops by farmers, or both. The European Union generally takes a more precautionary approach to GM plants than the United States (Law Library of Congress 2014). USDA reported in 2014 that about 90 percent of all US corn (maize), cotton, and soy fields were planted with GM varieties (Fernandez-Cornejo et al. 2014). In contrast, by 2015 only one GM cultivar (MON810, a corn plant) had been approved in the EU, although other GM products are being imported as feed, and new varieties are pending approval through the regulatory process (Valeeva et al. 2015). Worldwide, about 12 percent of all cropland is planted with GM crops, and of all GM crops, about 40% are grown in the United States (US NAS 2016).

European Union

Under its multi-tiered decision process for authorizing GMOs, both EU-level and member state approvals are needed for GM plants to be authorised: the EU-level institutions may allow the marketing and import of GM products for food and animal feed, but the individual member states may opt out, and the member states may also restrict the cultivation of GM plants. This decision process was set forth in a Communication from the Commission on 22 April 2015 (European Commission 2015d; for flow charts and updated materials, see European Commission 2016e). Over the last two decades, the EU has developed a series of legislative enactments on GM food and crops, including Regulation No. 1829/2003 on Genetically Modified Food and Feed (European Commission 2003), Directive 2001/18/EC on the Deliberate Release into the Environment of Genetically Modified Organisms (European Commission 2001)—later amended by Directive 2008/27/EC (European Commission 2008)—and Directive (EU) 2015/412 (March 2015), which allows the individual Member States more autonomy to restrict the use of GM crops in their territory (European Commission 2015c), even if the European Food Safety Authority (EFSA) and the European Commission have authorised them. (Such discretion for each member state implies that international regulatory cooperation efforts by the US federal government may need to engage each member state rather than or in addition to the EU level institutions.)

United States

The United States, by contrast, operates under the 1986 Coordinated Framework (OSTP 1986), regulating GM products under the statutes applicable to each product or application. The US does not have federal

legislation to regulate genetic modification as a process or technique, but rather takes a risk-based approach to regulation of the products of biotechnology and other processes for breeding plants (OSTP 1992). The White House announced a review of the Coordinated Framework in 2015 (Holdren et al. 2015). In May 2016, the US National Academy of Sciences released a report finding that there is a diverse array of breeding and modification techniques rather than a simple dichotomy between GM and non-GM plants, and that risks and benefits depend on specific product characteristics rather than on the process or technique used to modify the plant (US NAS 2016). For example, it found that one modification, growing GM crops with pesticidal properties encoded in the plant (such as Bt-corn), has led to reduced spraying of chemical pesticides, while a different modification, growing GM crops that are herbicide-resistant, has led to increased spraying of herbicides (such as Roundup, containing glyphosate) (NAS 2016). The US Food and Drug Administration (FDA) regulates GMOs based on its authority to determine the safety of 'food additives' under the FFDCA (21 USC. §§ 301–399f 2012) and in a 1992 policy statement (US FDA 1992) the FDA decided that GM foods would be classified as Generally Recognized As Safe (GRAS) unless they are significantly different from other food in structure and form. FDA has approved several GM foods, both to benefit farming and to benefit consumers, such as the Simplot potato designed to reduce acrylamides.

Vermont became the first US state to pass a law requiring the labelling of GMO organisms in food in 2014 (General Assembly of the State of Vermont 2014). Proposed legislation is pending in the US Congress to replace state labelling laws with a national labelling standard (US Congress 2014). Some local governments of the US also have passed legislation to prohibit the cultivation of GMOs, such as Marin County in California.

Studies find that the increase in GM crops in the US has been associated with reduced use of chemical pesticides (replaced by pesticidal properties engineered into plant crops) and increased use of chemical herbicides (applied to plant crops engineered to be herbicide-tolerant) (Klumper and Qaim 2014).

Genetically Engineered Fish

European Union

Currently, no GM animals (such as fish) or derived products are on the EU market, nor have any applications for GM animals been received in the EU. The European Commission asked the European Food Safety Authority (EFSA) to develop comprehensive risk assessment guidelines to evaluate the possible risks of GM animals for food and feed safety, which were published in 2012 (EFSA 2012). The risk assessment guidelines compare GM animals and derived food and feed with conventional counterparts, and recommend post-market monitoring to identify unintended effects of GM after the product has been authorised (EFSA 2012). EFSA risk assessments would also consider human health risks from pathogens carried by fish, and allergic responses to operators from contact (EFSA 2012). EFSA does not itself set regulatory standards, which remain the role of the European Commission (primarily DG Santé).

United States

On November 19, 2015, the FDA approved the sale of AquAdvantage salmon to US consumers (Dunham 2015), marking the first genetically engineered (GE) animal product approved for human consumption. FDA reviewed the GE salmon under its authority for 'new animal drugs' (US FDA 2015b1, 2015b2). This approval came almost twenty years after AquaBounty's first submission of data to the FDA (Naik 2010). The approval is strictly applicable to sterile females grown by AquaBounty in one on-land breeding facility in Canada and one grow-out facility in Panama, with consideration for environmental and food safety guidelines (Dunham 2015; US FDA 2015b3). FDA did not yet approve any GE salmon to be grown in the US.

The FDA assessed the food safety of GE salmon by comparing it to non-genetically engineered farmed Atlantic salmon, finding that eating the same quantity of both salmon products is equally safe and equally nutritious and the two products are not 'materially' different (US FDA 2015b1, US FDA 2015b2, Smith et al.

2010). FDA used both AquaBounty's research and peer-reviewed literature to ascertain safety of the product. FDA requires on-going self-reporting of safety and environmental impact.

At this time, there has not yet been a sale of GM salmon in the US. The 2016 federal spending bill enacted by Congress stipulated that GM salmon may not be sold until the FDA publishes labelling guidelines for consumer use (which FDA is currently considering). In early 2016, the FDA banned imports of GE salmon until the agency publishes guidelines for how the product should be labelled (Dennis 2016). The approval of AquAdvantage salmon initially had no stipulations for product labelling when sold to consumers, but had requirements for labelling the eggs when they are transported.

2.1.2 Hormones in Beef and Dairy

EU regulation of hormones in beef and dairy has been more stringent than US regulation. The US FDA regulates the use of hormones in beef and dairy cows, focusing on the safety of the end consumer product. The EU, however, banned imports of hormone-treated beef from the US, citing public concern, animal welfare, and the unnaturalness of hormonally altering animals to grow and produce at accelerated rates (Gray et al. 2011). The US and Canada protested the EU's beef ban to the World Trade Organization in 1997, which ruled that the EU measure, lacking a risk assessment, violated the Agreement on the Application of Sanitary and Phytosanitary Measures (the SPS agreement). The WTO panel, affirmed by its appellate body in 1998, ruled that under the SPS agreement such a measure must be based on relevant assessment of the risks to human health, which had yet to be substantiated. The WTO then authorized the US and Canada to impose added tariffs on EU food products. After continuing disputes over the science and the tariffs, the US and EU signed a memorandum of understanding in May 2009 that seeks to phase in changes – to allow market access in Europe for some US beef raised without growth promoting hormones, and to limit higher US tariffs on European foods – but leaving a full resolution to be addressed in the TTIP negotiations or further talks (Johnson 2015b). Meanwhile, despite differing regulatory stances on the use of recombinant bovine somatotropin (rBST), which US federal regulations allow but EU rules prohibit, US-produced butter, lactose, milk albumins, concentrated milk proteins, and milk powders circulate within the EU market and European dairy products are sold in the US (US FDA 2015, WHO 2014a, Sechen 2013, European Commission 2016, European Association of Dairy Trade 2011).

2.1.3 Mad Cow Disease (BSE/vCJD)

Bovine spongiform encephalopathy (BSE) (commonly known as mad cow disease) is a type of transmissible spongiform encephalopathy (TSE) that is transmitted primarily when an animal ingests high-infectivity tissues, principally from the central nervous system (brain, spine and related tissues), of a TSE-infected animal (Anderson et al. 1996; Gray et al. 2011). An epidemic of BSE occurred in the late 1980s, predominantly in the United Kingdom, when rendered animal protein including infectious tissues from BSE-infected cattle and scrapie-infected sheep was used as a protein supplement in cattle feed (Wilesmith et al. 1991).The epidemic probably started in the UK between 1981-1982 (Wilesmith et al. 1991) with the peak in January 1993 (US FDA 1997). On March 20, 1996, the UK reported the appearance of a new variant form of Creutzfeldt-Jakob disease (vCJD), a TSE of humans that usually appears in older people but which was now appearing in younger people, raising the inference that this vCJD may have come from humans eating BSE-infected beef (Gray et al. 2011; US FDA 2010, updated 2016). According to the FDA, through May 2015, 228 patients, including 177 in the U.K., 27 in France and 25 in ten other countries (including four in the US and two in Canada), had been diagnosed with clinical vCJD, with deaths in the UK appearing to peak in the year 2000, although future cases may appear years after exposure (US FDA 2010, updated 2016, p.5).

As detailed below, US regulation has been more precautionary than EU regulation regarding BSE in imported beef, and in blood donations; European regulation has been tighter on testing of cows at slaughter; and both sides have adopted bans on animal feed. As to imported beef from places with BSE

(mainly the UK), the US adopted its import ban earlier than did the EU, and maintained this import ban for much longer. As to blood, the US adopted earlier and more stringent measures than did the EU to safeguard the blood supply against the risk of vCJD. Meanwhile, the EU adopted a policy on testing all beef at slaughter (later relaxed), while the US tested those cattle exhibiting signs of illness. As to animal feed, the EU acted formally to ban rendered animal products in animal feed earlier than the US (the EU adopted its ban in 1994 and the US in 1997, although a ban had been voluntarily applied in the US since 1990), but the US adopted its feed ban before BSE was detected in US cows, while the EU adopted its feed ban after BSE had been detected in European cows.

United States

The US Animal and Plant Health Inspection Service (APHIS) of USDA banned the import of UK ruminants and some cattle products in 1989, and in 1991 (USDA 1991) further restricted importation of ruminant meat, meat products and by-products from all countries with confirmed cases of BSE (Gray et al. 2011). In 1997, APHIS broadened the import ban to include all beef imports from all EU countries (USDA 2000; Gray et al. 2011). After the first BSE case was found in the US, APHIS adopted new domestic regulations limiting nervous system tissues and ruminant blood in feed. The US ban on UK beef is still in place. In March 2014, the US lifted the 15-year ban on beef from the EU and in January 2015 Ireland was the first EU country approved to export beef to the US (McFarren 2015). *[Need to add here re: USDA testing of cows and problems in testing methods; Japan and South Korea limiting imports of US beef.]*

In 2003 Japan suspended imports of US beef after a single case of BSE was observed in the US, and in July 2006 Japan lifted the ban on imports of US beef from cattle 20 months of age and younger (Strom and Tabuchi 2013). Lacking a test to detect BSE in a live animal, USDA's BSE surveillance program sampled approximately 40,000 animals each year for BSE and targeted cattle populations where the disease is most likely to be found, including cattle exhibiting signs of central nervous disorders, emaciation or injury (USDA 2000). In 2013, the World Organization for Animal Health (OIE) granted the US negligible risk status for BSE (USDA 2013).

In 1999, the US FDA also adopted 'precautionary measures' to restrict blood donors who had spent over 6 months in the UK or 5 years in Europe during the BSE outbreak, despite the uncertain nature of human-to-human transmission of vCJD via blood (Gray et al., 2011), but based on the 'theoretical possibility' of such transmission (US FDA 2010, updated 2016). In 2002 the FDA went further, deferring any blood donor who had spent 3 months or more in the UK or 5 years or more anywhere in Europe in 1980-1996 or anyone who had received a blood transfusion in the U.K. from 1980-2001 (US FDA 2002; Gray et al. 2011). FDA estimated that the new policy might lead to a loss of 4.6% to 5.3% of blood donors with a 72% reduction in existing vCJD risk, for a total reduction of 90% relative to the risk that had existed prior to implementation of the 1999 recommendations (US FDA 2010, updated 2016). The FDA continues to maintain these policies deferring blood donors (US FDA 2014; US FDA 2010, updated 2016).

European Union

Individual countries, including France, West Germany, Italy and Russia, banned the import of British beef in the early 1990's and lifted the bans in 1994 when the EU agreed to tighten regulations and adopt a feed ban to prevent the spread of BSE (Gray et al., 2011). One week after the 1996 UK report of vCJD was issued, the European Commission banned all exports of beef, live cattle and beef products from the UK on March 27, 1996 (European Commission 1996). In November 1998, the EC lifted the export ban and required EU Member States to lift their import bans on British beef; France maintained its ban (Council of the European Union 1998), and the EU sued France to force it to lift its ban (European Court of Justice 2003; Gray et al. 2011). In 2000, the EU applied strict regulations on the use of animal protein in all animal feeds (Council of the European Union 2000). In 2001, the European Council started requiring testing for all slaughtered cattle over the age of thirty months (Freeman 2002; EC 2010), while the US has only tested cattle exhibiting signs

of illness. In 2013, the EU Standing Committee on the Food Chain and Animal Health discontinued mandatory BSE testing of healthy slaughtered animals, but some individual member states continue to implement mandatory testing.

The EU adopted no EU-wide restriction on blood donation regarding BSE, but some individual EU member states did adopt such restrictions: for example, since 2000, France, Austria, Finland, Germany and Ireland (and also Switzerland) adopted restrictions on blood donated by people who had lived in the UK for longer than 6 or 12 months between 1980 and 1996 (O'Neill 2003) (Gray et al. 2011)[1].

2.1.4 Antibiotics in Animal Production

The European Union has taken a more protective and whole-systems approach than the US on the issue of antibiotic use among food animals. By a decision taken in 2005, the EU banned the use of antibiotics for growth promotion in 2006 (European Commission 2005). In March 2016 the European Commission and European Parliament adopted the 'Animal Health Law' to reduce the use of antimicrobial medicines by promoting better overall health of animal populations (European Commission 2016c). The EU has also banned specific antibiotics from being used in animals that the United States Department of Agriculture has not yet banned—for example, avoparcin in 2006. Denmark has adopted one of the most stringent policies to limit antibiotic use in animals (Wielinga and Schlundt 2012). In March 2015, the US adopted a "National Action Plan for Combating Antibiotic-Resistant Bacteria," which included (among several other measures) a goal of eliminating the use of medically-important antibiotics for growth promotion in food-producing animals by the year 2020, and the establishment of a common U.S.-European Union (EU) system for sharing and analyzing bacterial resistance patterns for priority pathogen.

There have been several attempts at international coordination on policies regarding antimicrobial resistance and antibiotics used in animal farming. One example is the EU/USA Transatlantic Task Force on AMR (2009) (see http://www.cdc.gov/drugresistance/tatfar/). WHO provided guidance in its Global Principles for the Containment of Antimicrobial Resistance in Animals Intended for Food (WHO 2000), and in its series of Critically Important Antimicrobial reports (WHO 2012), which ranked antibiotics as 'critically important, highly important, and important' and supplemented the Codex Alimentarius guidelines established by the WHO and FAO.

2.1.5 Pesticides

The US generally has adopted more stringent limits on exposure to pesticides in food than has the EU. In the EU, Member States and the European Food Safety Authority determine maximum residue levels (MRLs) for pesticides in food on a case-by-case basis, whereas the US Environmental Protection Agency (EPA) uses a cumulative risk assessment approach for all pesticides that yields a more conservative Acceptable Daily Intake (ADI) level for individuals (Barlow et al. 2015). US EPA ADIs have typically been more stringent than WHO recommended ADIs (Brock et al. 2003).

In the US, the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) gives EPA authority to regulate pesticides (7 USC. § 136a (a)), while FDA and USDA supervise pesticide residues in food. For example, regarding the herbicide Roundup (containing glyphosate), EPA registered the herbicide for use, and in 2016 FDA began monitoring for glyphosate residues on food (Gillam 2016). In the EU, Regulation (EC) No 1107/2009 gives the European Food Safety Authority, the European Commission, and Member States the power to assess and authorise 'plant protection products' (European Commission 2009). (See also the section of this report on Chemicals)

[1] See www.dondusang.net/rewrite/article/2436/dons-de-sang/les-contre-indications-au-don-de-sang/les-principales-conditions-a-respecter-pour-un-don-de-sang.htm?idRubrique=980 . For links to blood donor policies in each European member state, see http://ec.europa.eu/health/blood_tissues_organs/blood/become_blood_donor/index_en.htm.

Of course, in particular cases, EU standards may be more stringent than US standards: for example, the European Commission implemented a 2-year ban on neonicotinoid pesticides (due to concerns about impacts on pollinator insects) starting in 2013 (Gross 2013), while in the US, the federal EPA has not issued such a ban (though it is now reviewing all neonicotinoid pesticides, see https://www.epa.gov/pollinator-protection), and in May 2016, one state, Maryland, passed a bill banning the use of neonicotinoids by consumers, beginning in 2018 (Maryland General Assembly 2016; Springuel 2016).

2.1.6 Organic Food

In the United States, the US Department of Agriculture sets standards for organic foods under the 1990 Organic Food Production Act (7 US Code Chapter 94). The European Council of Agricultural Ministers passed a 2007 regulation (Council Regulation (EC) No. 834/2007 (European Commission 2007, European Commission 2014). Although a greater percentage of farmland in the EU is certified organic than in the US, the US produces more organic products for the market (Dimitri and Oberholtzer 2005); in 2010 the US surpassed the EU as the largest organic market in the world (Dias et al. 2015).

Despite some regulatory differences, the US and EU reached an agreement in 2012 on common standards that enable organic products from each jurisdiction to be marketed in the other (European Commission 2015). This agreement is an example of US-EU cooperation and convergence on regulatory standards for food safety.

2.1.7 Chlorine-Washed Poultry

In the early 1990s, salmonella could be found in up to 60 percent of fresh chickens sold in the US (Burros 1992). By 2013, Consumer Reports found this bacterium on just 11 percent of supermarket chicken samples (Andrews 2014). Chickens in European stores appear to have lower rates of salmonella (Andrews 2014). The US Centers for Disease Control (CDC) estimates that 1 million cases of salmonella-related illness occur each year in the US, with around 380 deaths (CDC 2015). The European Food Safety Authority says that more than 100,000 salmonella cases are reported annually in the EU (EFSA 2014), but these reports understate the true number of cases: 'At the EU-level, the under-ascertainment ratio of clinical illness is expected to range between 5 and 100 in different [member states]. This would imply that in the EU27 … the approximately 130,000 verified of human salmonellosis cases would translate into not less than 1 million and possibly as high as 15 million cases of clinical salmonellosis per year' (EFSA 2010: 8).

The US allows pathogen reduction treatments (PRTs) in poultry, such as 'chlorine-washed chicken,' to mitigate the threat of salmonella and other microbes entering the consumer food supply (US FDA 2016a). US FDA regulations permit chlorine dioxide levels up to 3 ppm for poultry washing (US FDA 2016a). The EU approach seeks to remove infected birds and contaminated meat at each stage of the production process (EFSA 2010). Since 1997, the EU has banned imports of US poultry because of PRTs (e.g. chlorine-washed chicken). The US has initiated proceedings in the WTO to challenge the EU's ban of chlorine-washed chicken.

Controversy continues on the issue of chlorine-washed chicken (Capelouto 2014, Friends of the Earth Europe 2015, Faiola 2014, Johnson 2015a, APPPT 2015, European Union 2002, European Commission 2016). But rather than demonstrating that US regulatory standards are less stringent, this example is better seen as reflecting simultaneous precaution in the US and EU against two conflicting risks: the risk of chlorine residue on food or in water, and the risk of salmonella or campylobacter on food that the chlorine washing is intended to reduce. Salmonella is a concern for both the US and EU, with each taking a different approach to mitigating disease risks. Complicating this comparison are the differing amounts of poultry production in the US and EU, differing poultry production methods, and differing methods of reducing poultry-borne pathogen risks.

2.1.8 Trans Fats in Food

US federal regulation is more stringent than EU level regulation regarding trans fats in food, notably from partially hydrogenated oils (PHOs). But there are notably protective policies in some EU member states.

By the late 1990s and early 2000s, studies showed a strong association between trans fat intake and cardiovascular disease risk, with estimates rising to perhaps 100,000 deaths per year in the US (Zaloga et al. 2006; Mozaffarian et al. 2006). On July 11, 2003, US FDA issued a rule requiring the quantity of trans fat content to be listed in the Nutrition Facts label on packaged foods by the year 2006 (68 Fed. Reg. 41434) (see US FDA 2003). This national labeling requirement led many food companies to reduce their trans fat content to zero.

Also in 2003, Denmark adopted a policy limiting trans fat content to no more than 2 g per 100 g of total fat, leading to about a 90% reduction in consumer intake (WHO 2014b). Other European countries that have since adopted similar near-bans on trans fats include Austria, Hungary, Iceland, Norway and Switzerland. "Despite this progress, the lack of policies or bans in many parts of the European Region remains a serious concern. … consumption remains high where no policies are in place. For example, a recent study revealed that people could consume as much as 30 g trans fat per day in some eastern countries in the Region. This is a concern, as consumption of only 5 g per day is associated with a 23% increase in the risk of coronary heart disease. Even in European Union countries, high levels of trans fats can still be found in some food categories, and there is some evidence of higher consumption in low socioeconomic groups." (WHO 2014b).

In 2013, US FDA announced a preliminary determination that PHOs would no longer be generally recognised as safe (GRAS), which was made final on June 16, 2015 (US FDA 2015a; US FDA 2016b). FDA says that 'This action is expected to reduce coronary heart disease and prevent thousands of fatal heart attacks each year in the United States' (US FDA 2016b). FDA's central estimates of the costs and benefits of this regulation over 20 years are $6 billion and $140 billion, respectively (US FDA 2015d: part VII). Food companies have a three-year period from 2015 to 2018 to eliminate PHOs, or otherwise seek an exemption from the FDA (US FDA 2015a; US FDA 2016b).

The EU level has moved more slowly than the US federal government to regulate trans fats. Although EFSA released a report on the cardiovascular risks of trans fat consumption in 2004 (EFSA 2004), the European Commission has not yet adopted a regulation banning trans fats from the food supply across Europe. The Commission adopted a report in December 2015 outlining the health effects of trans fatty acids in the European diet (European Commission 2015). Although Denmark and some other EU member states have adopted stringent policies, as noted above, the UK, Germany, France and other European countries have not, instead relying on consumer pressure rather than on government regulation to convince companies to self-regulate to remove trans fats from their recipes (Coombes 2011; WHO 2014b). In late 2016, the EU released an initial Impact Assessment on its potential future regulation of trans fat intake (European Commission 2016f).

2.1.9 Unpasteurised Dairy Products

The United States generally has more stringent standards related to pasteurisation of dairy products than the European Union, limiting the import of some European cheeses into the US, in order to prevent exposure to microbial pathogens such as Campylobacter, Salmonella, E. coli, and Listeria (CDC 2016). FDA prohibits the import or interstate sale of raw milk for human consumption, and of products of raw milk for human consumption such as cheese, yogurt and butter (NCSL 2015). Thus the US requires pasteurisation more stringently, and some popular European cheeses such as traditional French reblochon are therefore not available in the US.

US FDA's Pasteurised Milk Ordinance (PMO) is a model rule for the production, processing, packaging and sale of raw milk and dairy products in the United States; an early version of the PMO was issued in 1924 (US FDA 2015c). The FDA regularly revises the ordinance, which defines 'Grade A' dairy products, with input from the National Conference on Interstate Milk Shipments (NCIMS), a voluntary cooperative body of state and federal industry and government representatives that meets biennially (US FDA 2015c). Based on the federal PMO, 46 out of 50 states have adopted the PMO to regulate sales of raw milk within their states (California, Maryland, New York and Pennsylvania have not adopted the PMO, but have their enacted their own strict milk safety laws) (NCSL 2015).

By contrast, the sale, marketing, and distribution of raw milk are legal in the EU, with some provisions on production and labelling of the product (Corrigendum to Regulation (EC) No 853 2004). The EU does, however, regulate the somatic cell count (SCC) and bacterial standard plate count (SPC) for raw cow's milk imports and domestic products: ≤ 400,000 per ml and ≤ 100,000 per ml, respectively, according to a 2004 EU regulation (Corrigendum to Regulation (EC) No 853 2004). Under current regulations, the US has a maximum SCC of ≤ 750,000 per ml and bacterial SPC of ≤ 100,000 per ml (USDA AMS 2012). These requirements apply at the farm level for EU products and imports, whereas they apply to the processing or distribution level in the US. In 2012, the USDA Agricultural Marketing Service established a voluntary EU Health Certificate program for US producers to become certified to export dairy products into the EU (USDA AMS 2012).

(Another strategy for killing microbial contamination in food – irradiation – is allowed in the US for a wide variety of foods, notably meats, whereas in the EU it is limited to the category of dried aromatic herbs, spices and vegetable seasonings, plus additional categories designated individually by each member state. In both the US and EU, irradiated foods must be labelled. Consumer acceptance of food irradiation has been slow. For summaries of current policies, see US FDA (June 28, 2016), http://www.fda.gov/Food/ResourcesForYou/Consumers/ucm261680.htm, EU (December 16, 2016), http://ec.europa.eu/food/safety/biosafety/irradiation_en, UK FSA (April 26, 2012), https://www.food.gov.uk/science/irradfoodqa, and IFST (June 2015), http://www.ifst.org/knowledge-centre/information-statements/food-irradiation)

2.1.10 Choking Hazards

US regulation is more stringent than EU regulation regarding choking hazards in food. Food items may contain objects, such as toys, on which people may choke, especially young children whose airways are smaller and whose teeth and judgment are not fully developed (Tarkan 2010). For example, Kinder Surprise Eggs have a chocolate coating that covers a plastic capsule which contains a toy. In January 2016, a three-year-old French girl choked to death on the contents of a Kinder Surprise Egg, and in earlier years at least three children in the UK have similarly choked to death (Horton 2016). Kinder Surprise Eggs are widely available and 'immensely popular among small children' in Europe, but '[b]ecause of their choking hazard, the eggs are banned in the United States' (Horton 2016).

United States

US law restricts concealed objects in food, including Kinder Surprise Eggs. The US Federal Food Drug and Cosmetic Act (FFDCA) of 1938 bans embedded objects in food unless the FDA determines that the object has nutritive or functional value. US FDA adopted Import Alert 34-02 on March 01, 2012 regarding the plastic eggs inside the chocolate coating of Kinder Surprise Eggs that 'may pose a public health risk as the consumer may unknowingly choke on the object.' The FDA banned Kinder Eggs from US import or domestic sale because of this hazard and created a Red List of similar products that are subject to Detention without Physical Examination (DWPE) at US ports. The Import Alert has been updated as of March 10, 2016, while a petition has been submitted to allow the candy in the US, currently to no avail (Mitchell 2013).

European Union

Europe regulates toys within food and only bans those that require consumption to get direct access to the toy. The European Commission Enterprise and Industry Directorate-General Toy Safety Directive 2009/48/EC set guidelines for toys in food, but allowed compliant products to circulate freely throughout EU member states (European Commission 2013). After the deaths of three children in the UK from choking on the contents of Kinder Surprise Eggs, around the year 2000, the UK government considered but did not adopt restrictions on such toys concealed in food (Horton 2016).

2.2 Automobile Safety Standards in the US and EU

The comparative safety of motor vehicles in Europe and the United States is a topic of growing importance, in part because global automakers are seeking to offer the same (or similar) products to consumers throughout the world (Freund and Oliver, 2015; Center for Automotive Research, 2016). The globalisation of automotive production can make vehicles more affordable to consumers while also providing consumers more choice of vehicle designs (e.g., some German designs have already become quite popular in the United States and automakers based in Europe are seeking to offer more products in the large American market). A study by the Center for Automotive Research (2016) finds that differing US and EU regulatory standards for automobile safety yield extra costs of about US $3 to $4 billion per year for the industry as a whole, and several hundred dollars higher incremental costs per vehicle for consumers. We explore here why vehicle safety regulations in Europe and the US are different, why it is difficult to make a technical case that European vehicles are safer than American vehicles (or vice versa), and why the emergence of automated and autonomous vehicles provides a new opportunity for US-EU regulatory cooperation.

2.2.1 Vehicle Safety Regulation in the US and Europe

The auto safety regulatory processes in North America and Europe began to diverge in the 1950s and 1960s. Spurred by the advocacy of Ralph Nader and the nascent consumer movement, the US Congress in 1966 established a new federal regulatory agency -- now called the National Highway Traffic Safety Administration (NHTSA) -- to set minimum safety standards for all new cars sold in the US (Graham, 1989). As a result, dozens of new Federal Motor Vehicle Safety Standards (FMVSSs) have been established governing vehicular features such as headlights, brake lights, safety belts, airbags, tires, bumpers, and fuel-tank safety. The Canadian government established a regulatory process that is largely harmonised with the US process. From the industry's perspective, the North American vehicle market is subject to roughly one set of safety standards (Canis and Lattanzio, 2014; Center for Automotive Research, 2016: 22).

Prior to the establishment of the European Union, most European countries signed on to an international standard-setting process organised under the auspices of the United Nations (UN). The UN Economic Commission for Europe (UNECE) is now the forum for establishing auto safety standards that are recognised throughout the European Union, yielding harmonized automobile safety standards across Europe (Center for Automotive Research, 2016: 22). With the exception of the US and Canada, most countries in the world are either signatories to UNECE standards or accept them as an alternative to their own standards (through some form of recognition process).

At various times over the last 50 years, efforts have been made to harmonise NHTSA and UNECE regulations but success has been slow and piecemeal. One study examined 43 auto-safety regulations in the US and Europe that have shared safety objectives. They found that only 11 were equivalent; 14 require major changes in the design of vehicles sold on the two sides of the Atlantic; the remaining 18 exhibit more minor differences. Asian regulations are typically closer to the EU regulations than to the US regulations (Associated Press, 2008).

2.2.2 Compliance Testing and Enforcement for Autos

Even when the goals of safety standards are identical, there may be differences in how compliance with performance standards is measured and enforced (Canis and Lattanzio, 2014). For example, to demonstrate compliance with frontal-crash protection standards, NHTSA requires automakers to use a fixed barrier that absorbs no energy, as might occur when a passenger car collides with a heavy truck or an impenetrable bridge abutment while Europe requires automakers to use a deformable barrier that simulates the energy absorption of another car's bumper and frontal structure. When automakers design vehicles to survive crashes with a fixed versus deformable barrier, there are potential ramifications for the frontal structure of the vehicle, optimal materials use, steering wheel design, and occupant-protection systems such as safety belts and airbags.

Other facets of compliance tests and consumer information tests have also been a source of cross-Atlantic disagreements. Despite many years of discussions, US and European regulatory officials have not been able to agree on how a crash dummy is designed (from a biomechanics perspective), how the crash dummy should be seated in a test vehicle, or whether a compliance test should be conducted with an unbelted or belted crash dummy (Muscat, 2013). As a result, basic safety features such as safety belts and airbags are designed somewhat differently for vehicles sold in the US and Europe (Associated Press, 2008).

The enforcement processes in the US and Europe also differ (Canis and Lattanzio, 2014). Automakers and suppliers in the US typically self-certify their vehicles and components, affirming that they comply with FMVSSs. NHTSA has the power to recall vehicles that are defective, and the US product liability system is designed to punish car makers that do not design and certify their vehicles with the safety of consumers in mind. In Europe, safety regulators typically employ a type-approval approach that requires manufacturers to demonstrate to regulators that each vehicle model complies with standards, before the model is allowed to be sold (Boston Consulting Group, 2015). Risks from product liability lawsuits are lower in Europe than the US, since Europe relies more on its regulatory system.

Nor should it be assumed that regulatory standards are the only or critical drivers of motor vehicle safety in the US and Europe. Over the last 30 years, more sophisticated consumer information systems have been developed that provide vehicle purchasers useful information about the safety characteristics and performance of alternative models. In the United States, the Insurance Institute for Highway Safety (financed by private insurers) and the non-profit organisation Consumer's Union (again privately funded) provide at least as much safety information to consumers as does the US government. In Europe, the development of privately-sponsored consumer safety systems is less advanced than it is in the United States but public authorities in the EU do provide consumers with substantial information about the safety of alternative models.

2.2.3 Future Regulation of Automated and Autonomous Vehicles

Looking to the future, the regulation of automated and fully autonomous vehicles is a new area where regulators could strive for enhanced coordination, since most regulations in the EU and the US are still in development. The field is evolving quickly because the technology is improving rapidly, with companies taking different approaches to innovation.

For example, Google is collaborating with Fiat Chrysler Automobiles to create a fleet of 100 2017 Chrysler Pacifica minivans. The vehicles will couple a hybrid powertrain with autonomous vehicle technology. FCA engineers will refine the Pacifica designs to accommodate the array of onboard radar, laser-radar, and cameras that allow vehicles to drive themselves. Google test cars have already logged 1.5 million miles with only one at-fault accident (della Cava, 2016).

European regulation of autonomous vehicles is affected by the Vienna Convention on Road Traffic of 1968, a treaty ratified by 73 countries worldwide. Most European countries have ratified the convention (the

United Kingdom is an exception) but the United States is not a party to the Convention, as the 50 states are responsible for developing their own traffic laws (e.g., speed limits, alcohol-related laws, and limitations on use of cell phones while driving) under discretionary federal guidance. The Vienna Convention was amended with effect from March 2016, to allow automated driving technologies transferring driving tasks to the vehicle, provided that these technologies are in conformity with the United Nations vehicle regulations or can be overridden or switched off by the driver.

The State of California has also proposed some standards that might require a specially licensed driver to be present in the vehicle at all times (Nelson, 2016). Google has objected to the California proposal because their self-driving car has no steering wheel and pedals and some ride-sharing schemes that are being developed by innovators do not envision a driver being present in the vehicle. To hedge its bets, Google is looking to do testing of its self-driving car in Texas and Massachusetts, where the standards may be more permissive (Nelson, 2016).

NHTSA developed some guidelines in 2013 that envision five different levels of automation, including the possibility of a driverless vehicle. NHTSA has publicly signalled to Google and other innovators that it seems possible to devise safety standards that would permit a fully driverless vehicle (NHTSA, 2013; Nelson, 2016). NHTSA held a public hearing on these issues in April 2016 and plans to issue more detailed guidelines by the end of 2016.

2.2.4 Comparing Traffic Safety in Europe and the United States

The World Health Organization reports traffic fatality rates per 100,000 population for countries throughout the world. In 2014 the overall rate for the European Union was 5.1 per 100,000 (a figure that includes pedestrians and cyclists as well as occupants of vehicles). The comparable figure in the United States is 10.6 per 100,000 population (WHO, 2014; European Commission, 2015e).

Does this comparison mean that European cars are safer than US cars? No. For starters, the average American drives almost twice as many miles per year as the average resident of Germany, France, the UK, and Italy (EU-wide mileage data are not reported) (LSECities, 2015). Moreover, there is at least as much variability in traffic fatality rates among the 28 EU member states and among the 50 US states as there is between the EU and the US. The traffic fatality rate in the Czech Republic is far larger than it is in the Netherlands; the rate in Mississippi is far larger than in Massachusetts. Traffic safety experts believe that some of the key sources of variability relate to driver and roadway characteristics: the number of male drivers on the road who are under the age of 25, the average speed of vehicles on the road, the blood alcohol concentrations of drivers, and the rates of use of safety belts, helmets and child restraint systems.

It is not obvious whether US or European vehicles deliver superior overall levels of safety. Consumers in Europe and the US have somewhat different tastes in vehicle size and type: European consumers tend to prefer smaller vehicles, though often with high levels of performance (i.e., horsepower and torque). American consumers tend to prefer vehicles with more interior volume and seating positions, in part because the average American household is larger than the average European household. Moreover, Americans also purchase a larger share of pickup trucks and sport-utility vehicles than Europeans do, though the market for SUVs in Europe is growing rapidly. The long-term trend is toward more similarity between European and American vehicles, as global automakers seek to improve efficiency and vehicle affordability by making use of one global platform for vehicles sold in numerous countries.

The US government has made larger investments in traffic safety data systems than have the European Union and many EU member states. The US has national data systems on the number of vehicle collisions, the number of collisions resulting in driver or passenger injury, and the number of fatalities. The US systems also supply data of uniform quality in the 50 states on numerous features of the vehicle, the occupants, and the roadway. Based on these data, it has been demonstrated that the safety of vehicles in the US --

considering both probability of collision and survivability of collisions -- has steadily improved over the last 10-20 years (NHTSA, 2012; NHTSA, 2013, IIHS, 2015).

Less is known about trends in vehicle safety throughout the EU because the data systems are not of comparable uniformity and quality. However, a recent study (Flannagan et al, 2015) did seek to make use of the best available European and US data for comparative purposes. The authors came to a complex set of conclusions, with no clear answer as to the overall level of safety of European and US vehicles.

Specifically, cars designed to meet European safety standards appeared to have a lower risk of serious injury in frontal and side crashes and reduced frequencies of lane-changing crashes (presumably due to the special EU requirements for driver-side mirrors). But, cars designed to meet US standards appeared to have lower frequencies of injuries in rollover crashes and fewer injurious collisions with pedestrians (perhaps due to headlamps that make pedestrians more conspicuous). The study concluded that more study of different vehicle features and crash modes are required to reach confident conclusions about the real-world safety impacts of the differences between European and American standards (Flannagan et al, 2015).

2.2.5 Automobile Emissions

In addition to differing standards for automobile safety, the US and EU also have differing standards for automobile emissions. US regulations limiting automobile emissions of major air pollutants such as lead (Pb), particulate matter (PM), sulfur oxides (SOx) and nitrogen oxides (NOx) have been more stringent than EU regulations (Walsh 2011). The US phased out lead in automobile fuel about a decade before Western Europe (and even longer before Eastern Europe). US restrictions on NOx and on PM (especially PM2.5), both by the federal EPA and by the state of California, have steadily reduced ambient NOx and PM2.5 levels in the US and have stringently limited the market share of diesel engines in passenger vehicles in the US (Walsh 2011; Klier and Linn 2016) (diesel engines emit higher quantities of NOx and PM than do gasoline/petrol engines). While the market share of diesel passenger vehicles in the US is less than 3 percent, in the EU it has risen from 14 percent in 1990 to 52 percent in 2015 (Klier and Linn 2016: 4).

Further, monitoring and enforcement to ensure compliance with these standards have been more stringent in the US than in the EU, as evidenced in the recent controversies over Volkswagen and perhaps other vehicle manufacturers attempting to evade US emissions tests, and in a growing gap between lab test vs. real-world emissions especially in Europe (Klier and Linn 2016: 6-7).

More generally, the current regulatory standard for the annual average concentration of PM2.5 in ambient air quality is 12 µg/m3 in the US, and 25 µg/m3 in the EU (i.e. about twice as high in the EU). Beyond this difference in regulatory standards for ambient air is the question of actual concentrations: a new World Health Organization (WHO) study finds that more than 80 percent of the US is below the WHO's even more stringent air quality goal of 10 µg/m3 for PM2.5, whereas more than 60 percent of the EU exceeds that WHO standard (WHO 2016: Figure 5). "About 60 percent of European cities exceeded WHO limits, compared with 20 percent in North America. That difference is probably the result of many more diesel-powered vehicles in Europe" (Bajaj 2016).

'The United States primarily has done an excellent job, moving from being a very dirty place in the 1950s to quite a clean place today,' said Dr. Carlos Dora, the [WHO's] coordinator for its department of public health, environmental and social determinants of health. Europe, he added, 'has also moved from being extremely polluted,' but it has lagged — a delay that experts have speculated may result from factors that include wider use of fertiliser in urban areas, weaker environmental regulations and the popularity of diesel-powered engines' (Goode 2016).

The mortality risk associated with PM2.5 levels is accordingly significantly higher in Europe than in the US, although it is even higher in more polluted areas such as China and India (WHO 2016; Lelieveld et al. 2015).

On the other hand, EU regulations and fuel taxes have been more protective than US policies in reducing carbon dioxide (CO2) emissions from automobiles (Klier and Linn 2016: 4-5). The difference in US and EU regulatory standards for diesel vehicles and emissions may reflect simultaneous precaution against two conflicting sets of risks: greater US precaution against the public health risks of Pb, PM, SOx and NOx, vs. greater EU precaution against the risk of climate change from CO2 (Walsh 2011).

2.3 Chemical Regulation in the EU and United States

Chemical substances are produced and used every day by billions of people all over the world. Chemicals are substances, which have the potential to damage humans, and the environment. Most substances have undergone only a partial or no health risk assessment at all (Abelkop et al. 2016: 13-16, 261-62, Spieker 2003:3, NAP 1984:12 f., Applegate 1991: 262). To protect people and the environment against such unknown impacts, the United States and the European Union have each established a framework for chemical risk regulation. In both parts of the world, these regulations follow the approach to identify toxic substances, and based on risk assessment (based mainly on dose-response relationships and exposure assessments) chemicals are regulated ranging from labelling, risk reduction measures to banning them from the market.

Therefore it is important to know which substances have the potential to cause negative health impacts or environmental damages. Furthermore, it is important to know the dose-response functions between agents and outcomes and to understand the exposure of target populations to the substance in question. The government requires data on hazards (potential for harm), exposure (who is and could be affected in what concentrations?) and dose-response relationships (what impact can we expect from what concentration of substance?) All this information is crucial to assess risks to human health and the environment (Spieker 2003: 3). Often, sufficient data for conducting a risk assessment is missing or associated with uncertainties. In this case, information about hazards (such as toxic potential, flammability, etc.) may act as substitutes for missing risk data.

In addition to dose-response and exposure, the targets of risk assessments are also a point of debate: Do regulators test the final product in which such substances are embedded or do they test the chemical in isolation? This is particularly a problem for products containing nanomaterials or for food products containing potentially carcinogenic substances along with antioxidants that may mitigate this effect (for example, acrylamide in potatoes).

Another point of debate is the combination effect of several chemicals or chemicals from several sources. Their health effects may be additive, synergistic or antagonistic (Streffer et al. 2003). If chemicals compete for the same receptors in the target organ, their health effects tend to be antagonistic (offsetting). If they align to different receptors they may be additive or even superadditive (synergistic). If low exposure to one chemical interacts with a high exposure to another chemical (for example, smoking in combination with air pollution) synergistic effects are more likely to occur. Therefore, risk assessments need to consider cumulative and combined effects of chemicals on human health and the environment (Asmuth et. al. 2010, Asmuth and Hilden 2007:71). This is not easy to accomplish as human beings are exposed to thousands of chemicals at the same time. Assuming additive relationships in cases of uncertainty about combined effects is usually done in regulatory decision-making in order to be on the safe side in the majority of cases (Streffer et al. 2003). There are hardly any differences between the US and EU in this principal approach in spite of differences in applying the precautionary principle (which might be interpreted as demanding for synergistic effects as a means of ultimate precaution).

Additionally, residues of chemicals like, for example, Glyphosate, can accumulate in food, water and the environment and can pose long-term risks. An integrated risk assessment includes such bioaccumulation and persistence (Abelkop et al. 2016). However, the data are often ambiguous and long-term studies over long time periods are missing. At present, there is heated debate in Europe about the regulatory

requirements with respect to Glyphosate. Although yearly exposure is below the threshold of what is considered tolerable, concentrations may accumulate over many years as the toxic effects decrease only marginally over time. Similar debates are also present in the US but with less potential for conflict and political outrage.

2.3.1 Chemical Regulation in the United States

Chemical regulation in the United States has a long-standing history going back to 1976, the year the American Congress passed the Toxic Substances Control Act (TSCA), 15 USC. §§2601-2692. The Congress authorised the Environmental Protection Agency (EPA) to implement the Act (15 US Code § 2601). In June 2016 the new Lautenberg Act was adopted that gives the EPA more power to ask for data and additional testing (Sneed 2016). In addition, it adds more power to the regulator to intervene even if the evidence is not conclusive, thus adding more precautionary elements into the US regulatory system.

In addition to protecting human health and the environment, the act emphasises that regulation of 'chemical substances and mixtures should be exercised in such a manner as not to impede unduly or create unnecessary economic barriers to technological innovation... (15 US Code § 2601)'. Therefore, the EPA must consider three important policy goals, which are difficult to reconcile (GAO 2007: 10, Spieker 2003: 11):

- The chemical effects on human health and the environment
- The benefits of use and the availability of substitutes
- The effects on the economy and innovation

The EPA regulates the entire life cycle of substances (GAO 2007:11); under TSCA it has the authority to ban or restrict the production, distribution or the disposal of chemicals if it sees an 'unreasonable risk' for environment and humans (15 US Code § 2605). The objective is not to eliminate risk, but to weigh the risk against social, economic and environmental benefits (Kuhn 2010: 11) and make reasonable trade-offs between risk, cost and benefit.

All chemical substances imported or produced in the US must be listed in the Chemical Substance Inventory. This inventory includes about 62 000 'existing substances' produced and traded before 1979 (GAO 2007: 11). Those have been long on the market. They were considered as safe or with tolerable effect on environment and humans, if used as regulated. The control of newly developed substances was until June 2016, however, limited and many risk assessments were either incomplete or missing (Spieker 2003: 68). The new Lautenberg Act gives EPA now the power to evaluate the safety and it plans to review thousands of new, but also existing chemicals in the following years (Sneed 2016). EPA started with a list of ten chemicals, which were on the market since decades and will review them in the next years.

During the last decades, the EPA has reviewed about 45 000 'new substances', among which 20 000 were added to the inventory (GAO 2007: 11). When a company intends to produce a chemical substance it has to give a pre-manufacture notice (PMN) 90 days before production starts (Kuhn 2010:13). During the 90 days the EPA is authorised to collect and review the information, calculate the dose-effect functions and exposure levels, and assess the potential risk. Any company intending to produce a chemical is obliged to provide only the data that are available. It is not obliged to conduct any new test series (Kuhn 2010: 14). The EPA is hence faced with the challenge to decide on the basis of limited information on the tolerability of the risk posed by the chemical. EPA could only ask the companies for existing data to evaluate, but could not require additional tests to produce new data unless they had clear evidence that a high risk could be expected (Sneed 2016). The EPA is legally not obliged to quantify the risks, but needs to take regulatory decisions on the basis of scientific evidence. This makes regulatory actions difficult to defend if quantitative assessments are missing. Therefore, the EPA is active to develop their own database about toxicity and carcinogenicity as well as exposure to humans and environment (Applegate 1991: 290; Abelkop et al.

2016). The main problem for the EPA is defending their risk assessment in this process with high uncertainty, limited access to data and ambiguity in defining a plausible trade-off between risk and benefit.

The EPA is driven by the following principles when conducting its assessments: (Applegate 1991: 271):

- 'Regulation of risk instead of actual harm'
- 'A regulatory goal of acceptable risk rather than complete safety'
- 'Facilitation of cost-risk-benefit balancing'
- 'Implementation through case-by-case determinations'.

If the EPA sees an 'unreasonable risk', it can demand additional testing of the substance (test rule) and can ban or restrict the production or distribution (15 US Code § 2605). The EPA has banned or restricted the use of special chemicals in the last decades in less than 5% of cases (Spieker 2003: 12). Since the enactment of TSCA a total of nine substances ´have been banned between until 2016. The chemical regulation process does not pose a serious burden on the industry and allows effective and quick innovation cycles with low costs for the registration and risk assessment process (Spieker 2003: 12, Sneed 2016).

In addition, within the TSCA, a more detailed dossier evaluation for substances which involve exposure in high doses to humans and the environment can be demanded (High Production Volume testing program). Substances of high concern, for example carcinogenic, mutagenic and toxic substances, are part of the Toxic Release Inventory and are required to be registered and authorised. For a more comprehensive evaluation of the TSCA and for suggestions for how it might be improved, see United States Government Accountability Office (2005); Abelkop et al. 2016. Not all chemical substances are included in the TSCA, particularly (15 US Code § 2602): mixture, pesticides, tobacco products, nuclear material, food, food additives, drugs, and cosmetics are excluded and regulated under other laws such as the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), and the Federal Food, Drug and Cosmetics Act (FFDCA), a.o. (GAO 2007: 10).

The regulation by the EPA under the TSCA, 15 USC. §§2601-2692 is only one part of the chemical regulation in the US. In addition, there are federal regulatory requirements for transportation, handling, environmental release and clean-up (RCRA and CERCLA/Superfund), information disclosure (Toxics Release Inventory, TRI), as well as separate regulatory requirements for special products, such as pesticides (FIFRA), drugs (FFDCA) and consumer products (CPSA). There are also additional regulatory provisions in each of the US States. Moreover, chemical companies face the threat of product liability lawsuits under civil tort law doctrines. This complexity reflects the American philosophy of multiple, overlapping sources of authority, which tends to characterise US regulatory law (checks and balances). Several US statutes constitute a type of 'toolbox' that gives a regulatory agency a variety of different tools to manage a particular problem with a substance.

In addition, Congress passed the Frank Lautenberg Chemical Safety for the 21st Century Act of 2016 (often called the TSCA Modernization Act), which was signed into law by President Obama on 22 June 2016 (US Congress 2016). This new law, enacted by large bipartisan majorities in Congress and supported by the Obama administration, environmental groups, and the chemicals industry, amends the TSCA in several ways to promote the testing, risk evaluation and regulation of existing chemicals (for details on the new law's key provisions and legislative history, see US EPA 2006; EDF 2016).

2.3.2 Chemical Regulation in Europe

In June 2007, the new chemical REACH regulation - Registration, Evaluation, Authorisation and Restriction of Chemicals – became the official regulatory framework for all Member States of the European Union. It was the result of a long discussion and negotiation process with all member states that started almost a decade before the regulatory framework was enacted. In 1998, the Commission of the European Union identified significant deficits in chemical regulation in Europe. As a result, stakeholders from industry, research, NGOs, and regulators consulted with the Commission in order to establish strategies for chemical policy (Kuhn 2010: 67, Penman 2015: 59). Finally, this process led to the publication of the White Paper on a 'Strategy for the future EU Chemicals Policy' in 2001 (Assmuth et al. 2010: 3954, Kuhn 2010: 67, CEC 2001).

For the first time, a harmonised and uniform system of chemical regulation was implemented for all Member States (Kuhn 2010: 97). 'Applying the precautionary principle is a key tenet of its policy, and the choices it makes to this end will continue to affect the views it defends internationally, on how this principle should be applied' (European Commission, 2000: 3). REACH provides four procedural steps (ECHA 2016, European Commission, 2000):

1. Registration
2. Evaluation
3. Authorisation
4. Restriction.

How intensive these procedural steps are conducted depends mainly on the amount of the substance, the magnitude of exposure to humans and the environment and on the presumed or proven level of harm (Kuhn 2010: 97). In contrast to the EPA and US regulation, REACH demands collection of data or risk assessment from the manufacturer and supplier *before* a substance is permitted to be produced and transported. The burden of proof resides with the industry (Kuhn 2010: 97, Penman 2015: 62). Similar to the EPA, REACH distinguishes between 'existing' and 'new substances'. Existing' substances are those that had been introduced before 1981; 'new' chemicals are those that have been introduced since 1981.

Any substance produced or imported into the EU that exceeds one ton per year must be registered with ECHA, the European Chemical Agency based in Helsinki (ECHA 2016a, Penman 2015: 61). If a company manufactures or imports a substance in amounts less than one ton a year, it does not need to register the substance. If it reaches or exceeds this threshold, the characteristics of the specific substance determines which information is needed for registration.This requirement is based on the assumption that exposure and potential risk increase with the volume and amount of the substance produced.

If a company intends to produce or import a substance, it has to register it with ECHA and submit a technical dossier, which contains information about the physical, toxic character of the substance and, in quantities of more than 10 t/year, a Chemical Safety Report (CSR) (ECHA 2016a). The technical dossier and the CSR are assessed by ECHA, as well as by national regulation authorities such as the German UBA and BfR (European Parliament, Council of the European Union (2006), Art 20. Abs.1). The scope of the dossier depends on the amount of the chemical substance produced (European Parliament, Council of the European Union (2006), Art. 12). After the data and dossier are submitted, ECHA is given three weeks - for phase-in-substances up to three months - to decide if the information provided by the company is complete or if further testing is required (European Parliament, Council of the European Union (2006), Art. 20, 41, 42).

2.3.3 Comparison of the Regulation Approaches in US and EU

Looking at chemical regulation, both the US and EU still face problems of lack of data, high uncertainties of risk assessment, burden of proof, high cost of testing and low incentives for substitution of hazardous chemicals (Karlsson 2011: 258).

At first glance, the US approach to chemical regulation is following a 'risk-based' and the European a 'precautionary approach '. The TSCA does not follow the precautionary principle, is less preventive and the proof of harm must be demonstrated, before chemicals can be regulated. It pursues a low level of intervention and does not require companies to provide necessary quantitative data for assessing risks to human health and the environment. This regulatory style facilitates innovation as it places less of a burden on companies compared to REACH. But according to analysts of regulatory practice, the distinction between risk-based and precautionary regulation is not as clear-cut as it may seem (Karlsson 2011: 258). First, the actual standards are not much different in the US and Europe and the missing company data is compensated for by the EPA's own assessment activities (Wiener and Rogers 2002; Elliott and Renn 2011). Second, in the US, the threat of tort cases has a strong effect on companies to monitor its impacts as they may be brought to court even if they produce within the permissible standards of the EPA (Abelkop et al. 2016: 16). In essence, the TSCA provides little incentive to collect more chemical data but it is in the interest of chemical producers to reduce uncertainties as a means to avoid costly tort cases. Nevertheless, there are also voices that characterise the knowledge about chemicals in the US as static and not responsive enough to new scientific insights (Spieker 2003: 17). Critics claim that learning in risk assessment is very low in the US in comparison to the European chemical risk assessment. The new Lautenberg Chemical Safety Act adopted in 2016 to amend the TSCA strengthen US law regarding existing chemicals with clear and enforceable deadlines, new testing and risk-based safety standards, and increased public transparency for chemical information (see US EPA 2016; EDF 2016).

It must also be noted that REACH is not as precautionary as it sounds (European Parliament, Council of the European Union (2006), Art. I (3)). Hansen et al. 2007 seriously doubt that REACH meets the precautionary promise because it includes a rather restrictive understanding of scientific uncertainty, follows a distinct separation between risk assessment and risk management (thus underestimating risks in the process of production and use), and does not provide enough incentives for creating substitutes as a safer alternative to the existing chemicals (Godard 2012: 25).

Since the burden of proof and the requirement for collecting data resides with the companies, the company has no other choice but to provide the data before it can sell the product (European Parliament, Council of the European Union (2006), Art. 5., Penman et al. 2015: 62). This approach motivates companies to collect and produce relevant data for gaining deeper knowledge about chemical substances and their risks –otherwise they can place it on the market - and to continuously invest in learning more about the effects of chemicals they use or market. REACH forces the companies to conduct between 22 and 54 tests, depending on the quantity, whereas the TSCA does not require tests for existing substances and 14 voluntary tests for new substances with volume above 100 t (GAO 2007: 25, Karlsson 2011: 258) (but the new Lautenberg Chemical Safety Act of 2016 will require testing of existing chemicals, see US EPA 2016). However, the tests demanded by REACH are only partially challenged by the EPA so that many risk assessments do not have the quality that is legally required. For example REACH has restricted over 64 substances most of which are still allowed in the US law (from 1976), 1378 chemicals are banned in the EU for cosmetics as compared to 11 in the US, 82 pesticides banned which are still allowed for use in the US (Reineke 2016).

Several analysts claim that REACH is lacking effectiveness and is impeding innovation (Fleurke and Somsen 2011: 357, Karlsson 2011: 250). The key element of REACH is not to ban a substance but to substitute it with safer alternatives or devise other options to contain its negative potential. This can also be seen as an incentive for substitution compared to an 'industry-friendly' approach that places the burden of proof on

the potential victims (Fleurke and Somsen: 388). Finding alternatives for substances forces the companies to develop substitutes that meet the REACH standards. If companies outside the EU want to export products to the EU, they have to produce these substitutes as well and are not allowed to export substances that are allowed only in their own country. At the same time, a consumer outside of the EU may rather want to purchase the safer substitutes than the original substance, which is not registered in the EU. Since the implementation of REACH the sales of chemicals have increased and the EU is today the leading importer and exporter of chemicals (Silbergeld et al. 2015: 186). The European Commission has come to the conclusion that the monetised health benefit of REACH exceeds by far the costs of implementing REACH (Silbergeld et al. 2015: 186).

2.3.4 Transatlantic Trade and Investment Partnership (TTIP) and its impacts

The envisioned Transatlantic Trade and Investment Partnership (TTIP), which is expected to expand trade and increase economic growth, has been criticised as a step backward in consumer and environmental protection by many environmental groups. Concerns include that all substances that are permitted in one country could automatically be permitted in any other contract state (Raza 2016: 171). This would undermine the burden of proof policy mandated by REACH if such a clause is not adopted in the US. The German chemical industry claims that they will not accept any lower safety standards than what REACH would prescribe (VCI 2016). A mutual approval of substances by either European or US chemical regulation is not included in the draft TTIP proposal, because the regulatory mandates will not be changed. TTIP requires, however, a closer collaboration between the regulation agencies in the US and Europe.

The aim to harmonise and align the different EU and US standards in regulations is misleading. While it is true that most standards do not differ much in substance, the processes to arrive at these standards are not identical. In addition, there are fewer standards in the US than in the EU as the US system relies more on civil liability law and less on administrative law (Abelkop et al. 2016: 16). The US framework lacks standardisation in many areas in which the EU law prescribes standards or technical procedures. "A mutual recognition of standards" (Pelkmans 2015: 46) as proposed by the US might soften the high-safety standards of the EU framework if the US standards are taken as the starting point. At the same time, if all the European standards were adopted in the US, many chemical operations would need to engage in multiple changes. One solution is to accept the different density of standards in both countries and demand mutual recognition of each system's regulatory provisions. Only where standards are identical or closely similar, harmonisation (also of procedures and processes to reach these standards) would be useful and acceptable to both parties. The mutual recognition of rules, which exists in the European market, especially in the case of chemicals, will pose a high challenge. Neither reducing the safety standard on the lowest common denominator nor always taking the strictest available standard is an acceptable solution.

So what could cooperation in chemical regulation look like? One option, often claimed by critics of TTIP, is to exclude the chemical regulation of REACH from TTIP so that both parties need to respect the rules of the other party. The European Chemical Industry Council (CEFIC) as a supporter of TTIP, however, demands to develop a better EU-US-framework with "aligning the classification and labelling" (Cefic 2016). This would "provide users a clearer product information", "making the risk assessment more efficient and effective", and "reduce compliance costs for industry" (Cefic 2016). Another option that we deem appropriate is to seek harmonisation where both systems reach almost the same conclusion (regardless of the pathway by which this conclusion has been reached) and to leave the remaining standards untouched in both systems. Similarly, Abelkop et al. (2016: 256-57) propose, in the near term, informal dialogues on a case by case basis among US, European, Canadian and Japanese regulators and stakeholders, rather a formal treaty to harmonize chemicals standards across the board. Exporting from one system to the other would then entail a check whether the product falls into the harmonised or non-harmonised section of the chemical products.

Regardless which solution is chosen, TTIP could at least improve the transparency and encourage product information sharing. This could include:

- Data sharing, common testing protocols
- Aligned classification and labelling
- Early and transparent cooperation and exchange of scientific information
- Common guidelines for risk evaluation, which should lead to lower bureaucratic hurdles and costs in practice, but not to identical outcomes in regulatory decisions (Pérez and Dudley 2016).

Already today, before any agreement on TTIP, data-sharing agreements between companies make testing less expensive and time-consuming so that innovative forces can be released (Penman 2015: 62). REACH also allows for more transparency on the potential impacts of substances. This includes more opportunities for informed public involvement in chemical risk regulation (Fleurke and Somsen 2001: 386) that they can decide which products the use. At the same time, however, Europe lacks the scope and breadth of the US Freedom of Information Act. Whatever is publicly known about a chemical is much more accessible to a US citizen than to a citizen of Europe.

Both approaches in US and EU distinguish between 'existing substances' which exist already on the market and the supply chain, and 'new substances' which the companies intend to produce or import. Existing substances did not need to undergo the same amount of testing as new chemicals under the TSCA regulations but, as mentioned above, the new Lautenberg Chemical Safety Act of 2016 will require testing of existing chemicals (US EPA 2016; EDF 2016). The same is true for REACH until 2018. After this date registration and quantitative risk assessments are legally prescribed for existing (now called) 'phase-in substances' (ECHA 2016b).

Table 1: REACH vs. TSCA

REACH	TSCA (before 2016)
Precautionary approach (on paper)	Risk-based approach (on paper)
Distinguish between new and existing substances, only new substances are regulated until 2018.	Distinguish between new and existing substances, only new substances are regulated.
The 'burden of proof' resides with the industry. It has to be able to demonstrate that the chemical can be used safely. All actors in the supply chain will be obliged to ensure the safety of the chemical substances they handle. This will place a high burden on the company and lead to higher costs for conducting the assessment.	The 'burden of collecting data' is on industry. Each company has to deliver existing data only. There is no requirement of testing, tests are voluntary. The burden of proof that chemicals pose unreasonable risks resides with the EPA. Time, effort and cost of the company are moderate.
Registration and risk assessment will be required when production/import reaches 10 ton. As far as possible, animal testing will be minimised. Information on chemical use, exposure and toxicity is required.	The TSCA does not require companies to perform risk assessments on new chemicals, risk assessment is voluntary.
High quality of risk assessment and overall high-performance standard in protecting humans and the environment.	Overall high-performance standard in protecting humans and the environment for those chemicals that are regulated under the TSCA. For others, additional regulation is either in place or is indirectly covered by other legal institutions such as tort law
Innovation of safer substances will be encouraged under REACH through more incentives for research and development, lower registration costs for new substances, obligation to consider substitute substances for decisions on authorisation and restrictions, and overall high incentives for learning.	Innovation for safer substances is not required or encouraged. If no substitute is available, the substance can still be marketed if risk is reasonable. Emphasis is on facilitating innovation; overall, there are fewer incentives for learning.
The disclosure of information under REACH aims to guide downstream users for safe use and handling, provide information to the public (safety sheets), educate a risk-informed society, and facilitate data-sharing for complex chemical agreement between industries.	The disclosure of information under TSCA is voluntary only, but EPA can force the disclosure if they see an unreasonable risk. Once disclosed information is available to everyone (Freedom of Information Act).

'REACH is an ongoing regulation and there has been a significant development in the way it is administered and implemented, as all stakeholders gain a greater understanding of the requirements and all of the science / processes involved', (Penman et al. 2015:64).

2.3.5 Conclusions

From taking a close look at the risk regulation of chemicals in the United States and Europe it can be concluded that the differences between REACH and the old TSCA act form 1978 are not so pronounced as it may appear at first glance. The underlying assumption that Europe is governed by the notion of precaution and the United States solely by evidence based on risk assessments is less pronounced in practice than on paper. The new Lautenberg act gives the EPA the power to act more preventive as the REACH regulation already is doing and the two systems will probably align in the next years.

Charnley and Elliott (2002) have also argued convincingly that a simplistic opposition between the precautionary principle in Europe and quantitative risk-assessment in the US is actually a 'false dichotomy.' Even the new REACH target of 2018 by the European Union does not substitute risk assessments with a pure 'better safe than sorry' attitude. On the contrary, the REACH proposal places a strong emphasis on a scientific assessment of hazards and risks for both existing and new chemicals and places the burden of providing these assessments on industry. The new Lautenberg Chemical Safety Act of 2016, amending TSCA, requires testing of existing as well as new chemicals (similar to REACH), and calls on US EPA to conduct risk evaluations, set priorities, and regulate (US EPA 2016).

REACH is more concerned with traceability than looking for precautionary methods for dealing with uncertainty. Still, it is probably one of the strictest preventive chemical regulations worldwide. It had significant effects on other countries (Silbergeld et al. 2015: 185). For example Japan, Turkey, Taiwan and South Korea all developed a regulatory framework similar to REACH, China adopted a REACH-like regulatory framework in 2010 which forces companies to submit a notification of new substances and develop and conduct toxicological and ecotoxicological tests (Silbergeld 2015: 185), and the Lautenberg Chemical Safety Act updates US regulation in several ways similar to REACH. This shows the high impact of REACH on the worldwide practice in chemical risk regulation.

With regard to chemical regulation, there are definitely some elements of 'precaution' in the US system under the TSCA. For example, the EPA has successfully prevented some new chemicals from entering the market, not because they were proven to be hazardous, but because there was inadequate evidence proving their safety and because they were similar to other chemicals that were known to be hazardous. On the other hand, there have also been some notable failures in the US to review previous authorisations, principally when a substance was already on the market and the burden was on a government agency such as the EPA to build a factual case that would stand up in court to ban or regulate the substance (the new Lautenberg Chemical Safety Act of 2016 will strengthen EPA's oversight of existing chemicals). But other structural features of the US law-making system tend to encourage precautionary action, such as the threat of tort liability and the expansive authority of US agencies to interpret existing statutes to deal with new problems. Some observers have suggested this broad authority to reinterpret statutes enables US regulators to be more 'agile' than their colleagues in Europe in responding to emerging technologies. This would enable US regulators to be more 'precautionary' in the sense of regulating earlier in some circumstances that would require new legislation in Europe (Elliott 2005).

REACH greatly expands the obligations of manufacturers to provide test data for certain chemicals, especially existing chemicals that are already on the market. This will be even more pronounced after 2018 when all chemicals are registered which are on the market. As pointed out above, however, it remains to be seen whether requiring more test data will necessarily translate into regulatory decisions that are more precautionary. At the same time, the practical implication of the TSCA has shown that the standards derived from its analyses are not more lenient than those of Europe and that, in some instances where tort cases are threatening companies, chemical concentrations in products have been even more limited than in Europe. Yet there is clearly a tendency in the US to foster innovation while Europe prioritises risk aversion and safety over economic potential, but the new Lautenberg acts have aligned both system for more precautionary regulation.

2.4 Pharmaceuticals Licensing and Reimbursement in the EU and US[2]

2.4.1 Introduction

The pharmaceuticals sector provides an archetypical example of proactive public sector risk governance under conditions of uncertainty. Unlike ordinary consumer products, drugs may not be marketed without advance regulatory approval. Effective access to pharmaceuticals is also affected by the decisions of payers on whether a drug is eligible for reimbursement, for what conditions, and at what prices.

Licensing decisions are based on projections of safety, efficacy, and manufacturing quality, with revisions to the conditions of licenses as safety, efficacy or quality issues arise in use. The European Medicines Agency (EMA) and US Food and Drug Administration's (FDA) approaches to drug licensing are marked by commonalities and differences. Both the EMA and FDA are committed to rigorous evaluation of pharmaceuticals in advance of market access with feedback from post-market experience. The FDA is augmenting traditional licensing procedures with Breakthrough Product Designation. The EMA is developing integrated adaptive pathways for licensing, with formal pilot tests to provide a practical proof of concept.

Reimbursement decisions are based on evaluations of effectiveness and in some countries on cost-effectiveness. EU reimbursement standards vary across member nations, with less intra-European harmonisation on payment than on licensing. US reimbursement standards vary across public payers including Medicare/Medicaid Services and the Veterans Administration and across hundreds of private payers including insurers and Health Maintenance Organizations. The US reimbursement landscape is in flux, with recent provisions for FDA-CMS parallel review, the consolidation of private payers through mergers and acquisitions, and US payers questioning the pricing of monoclonal antibodies such as PCSK9, curatives including nucleotide analogs such as sofosbuvir used in combination with other drugs to treat hepatitis C virus (HCV) infections, and other new drugs. While the absence of centralised reimbursement decisions complicates simple EU-US comparisons, several generalisations emerge. Relative to their US counterparts, EU payers typically set higher standards for evidence of effectiveness as a condition of reimbursement, impose tougher limits on reimbursement by indication, and drive harder deals in negotiations over prices.

This paper provides the historical context for evolving licensing and reimbursement policies, describes recent developments in the EU and US, and concludes with comparisons of existing differences and a projection of trends.

2.4.2 Context

Existing licensing policies have been shaped, piecemeal, by a series of crisis-prompted reforms in drug licensing within the OECD. In the late 1950s and early 1960s, birth defects produced by Thalidomide prompted adoption of more stringent standards for demonstration of efficacy and safety in advance of approval and to the strengthening of adverse effects reporting systems. In the 1970s and 1980s, the demands of HIV and cancer patients for earlier access to live saving medicines prompted the development of accelerated approval and conditional marketing authorisation pathways, with deferred validation of biomarkers. In the 2000s, adverse effects caused by Vioxx® (rofecoxib), Accutane® (isotretinoin) and other drugs prompted improvements in aftermarket surveillance programs and to the development of FDA Risk Evaluation and Mitigation Strategies (REMS) and the European Risk Management Strategy (ERMS) to

[2] Note: The views presented in the pharmaceuticals section of this report are those of the authors and do not represent the views of the Massachusetts Institute of Technology, the European Medicines Agency, Amgen, the Food and Drug Administration or the Organization for Economic Cooperation and Development. The authors of the pharmaceuticals case have not reviewed the report as a whole and neither endorse nor dissent from the views expressed in other sections of this report.

manage known risks. Finally, U.S. backlogs in licensing were produced, in part, by the challenge of simultaneously demonstrating safety and efficacy, providing early access to drugs, managing known risks and strengthening after market surveillance. These crisis-driven reforms have improved detection of severe adverse effects, improved management of identified risks and accelerated patient access to drugs for unmet life-threatening medical needs. Current calls for reform in licensing follow less from crises than from sustained evolutionary pressures on regulators, drug developers, patients, providers and payers. Some elements are direct extensions of the trends above, while other elements have emerged in the past ten years.

First, patients with unmet medical needs continue to press for earlier access to drugs. The highly visible mass protests and sit-ins of HIV activists have given way to communications and outreach strategies of the National Organization for Rare Disorders and other patient groups. Social media and web-based communications have increased the impact of such bottom-up organizing.

Second, subjects with comorbidities and subjects taking other drugs are often excluded from clinical trials to enable detection of treatment effects. But patients often suffer from more than one ailment, take other drugs, and fail to adhere to labels. As a consequence, subjects in conventional trials are imperfect surrogates for patients taking drugs in the real world. Confounder cleansing of populations of subjects taking drugs in trials increases the ability to detect a drug effect if it is there, but decreases external validity. Progressive reduction of resulting uncertainties will need to be achieved by way of subsequent studies that could range from clinical trials to the use of data from observational studies and real world health records. Observational studies and real world data should complement, not replace, RCTs.

Third, within both the United States and Europe, increasing evidentiary demands and rising late stage failures during clinical trials have increased the cost of drug development. Drug companies have added effectiveness studies to traditional safety and efficacy studies to meet demands from payers for evidence-based reimbursement. Marketing requirements, specifically the need to support the addition of new drugs to managed care drug formularies, have contributed to a rise in drug development costs. Globalisation of markets has also led to multi-regional clinical trials and additional data collection needs. In the United States, R&D efficiency has been declining steadily, with the 2010 cost of bringing a drug to market running at about $US 1.5 billion. Within Europe, national payers have varying evidentiary requirements that are not coordinated with regulators. The cost of bringing a complex new drug to market in the EU now approaches € 1.7 billion, heavily loaded toward the cost of trials conducted at the back end of the process.

Fourth, as the scientific revolution in genetics reshapes medicine, an increasing number of treatments in development now target smaller genetically defined subpopulations instead of larger heterogeneous populations. This splintering of disease populations and narrowing of labelled indications is improving the effectiveness of medicine. It is also increasing the difficulty of recruiting adequate numbers of subjects for the clinical trials that provide an evidentiary basis for projecting the safety and efficacy of drugs. Drugs serving small numbers of patients are priced high. The splintering of indications has also created smaller market niches that are often filled by only one drug rather than two or more competing drugs, weakening or eliminating market pressures to ease pricing. Smaller market niches affect the size of the base from which sponsors may recover costs, as development and testing expenses are spread across fewer patients. Taken together, these evolutionary changes have simultaneously increased drug development costs and raised drug prices.

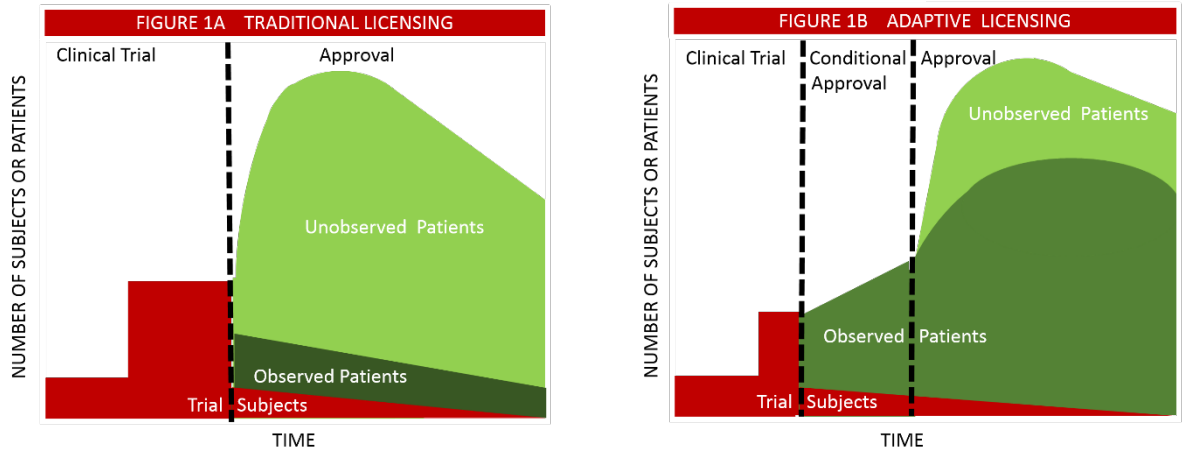
These developments define a complex setting for benefit-risk management in pharmaceuticals. Risk management in medicine now entails engaging with risks associated with medical and other health products, risks to public budgets from the adoption and coverage of new therapeutics, and risks to patient privacy from novel uses of medical data. The traditional focus on benefit-risk in the context of evidence generation on safety and efficacy for licensing must now be broadened to include a second focus on benefit in the context of evidence generation on the effectiveness for treatment and reimbursement.

Faced with rising costs for pharmaceuticals and increasing political pressure to contain costs, patients, physicians and payers are demanding better information on the effectiveness of drugs. Although beyond the purview of traditional pharmaceuticals regulatory agencies such as the EMA and FDA, the acquisition, analysis and interpretation of evidence on the effectiveness of drugs in use will be an increasingly significant element of health care policy.

2.4.3 Current Developments in Europe

Under traditional approaches to drug licensing, drug companies rely on models, in vitro studies and animal studies and randomised clinical trials using populations of subjects free of confounding factors to demonstrate the safety and superior efficacy of a drug. Under traditional licensing systems, there is a 'magic moment' when a drug is either approved or rejected. Carefully monitored subjects become lightly observed patients, experimental therapeutics become accepted treatments, and drugs are transformed from unproven to safe and effective.

Figure 1: Traditional and Adaptive Licensing



In the European Union, this traditional binary model of drug approval, described by the left diagram in Figure 1, is now changing rapidly toward explicitly adaptive approaches to licensing with patient experience contributing to evidence development. The diagram on the right describes an adaptive approach to licensing. At the front end, approval would come earlier, would be limited to patients with the most favourable priors benefit/risk and would be conditional. At the back end, observations of patient experience would be strengthened through greater reliance on registry and electronic health records, with a systematic analysis of that experience to evaluate safety and effectiveness, and with modification of labels and the terms and conditions of licensing based on patient experience. Conditions now favour implementation of adaptive approaches to risk governance, with both demands for more adaptive approaches to licensing and factors enabling implementation of adaptive approaches strengthening. These points are developed more fully in Eichler et al (2015).

The EU turn toward adaptive pathways has been enabled by dramatic improvements in post-licensing identification of adverse drug effects. In the 1950s and 1960s, thalidomide use in pregnancy caused phocomelia, a highly visible adverse effect with a low background incidence. It took around 10.000 cases before healthcare professionals made the connection between thalidomide use and phocomelia. Contrast this tragically slow learning with recent rapid detection of adverse effects. Adverse effects of Tysabri® (natalizumab for multiple sclerosis) were detected after only three cases of Progressive multifocal leukoencephalopathy (PML) were reported. Adverse effects of H1N1 pandemic flu vaccine Pandemrix® were investigated after the Swedish Medicines Agency received only six reports of narcolepsy following vaccination. Yet our ability to detect adverse drug reactions with small risk ratios on high-background events is limited within both conventional and adaptive licensing frameworks. In both contexts, it is

essential that all parties improve adherence to after-market commitments to monitor for safety, efficacy and effectiveness.

EU reliance on adaptive pathways is also enabled by targeted prescribing. When a drug is initially intended for use by a well-defined subset of patients, wide-spread use by patients outside of the target group might open the door to negative patient outcomes. Regulators have some limited tools to steer drug utilisation by way of controlled access programs, prescriber restrictions, educational requirements, and clinical reminder systems. In practice, payers, healthcare systems providers and professional societies, rather than regulators, are the stewards of appropriate prescribing. As new premium priced drugs enter the market, payer interests in effectiveness and cost-containment are leading to increasingly regimented use through pre-reimbursement requirements, prescribing audits, prescriber restrictions, tiered co-payments and mandatory treatment protocols. Regulator and payer actions in cooperation with the bodies that produce clinical practice guidelines are likely to improve prescription controls, particularly for diseases that are treated in specialist centres.

Finally, EU reimbursement policies are of increasing importance in risk management. Only a small and shrinking fraction of expensive new drug treatments are paid out-of-pocket by patients. Decisions by third party payers on whether and how to reimburse are gaining increasing importance to both patients and marketing authorisation holders. Regulatory approval is a necessary but not sufficient pre-condition for effective patient access. There is growing awareness among many payers that they, like the regulators, cannot escape the acrimonious debate over access versus evidence. Payers recognise that the distinction between experimental versus medically necessary is based on a simplified view of evidence and uncertainty, with explicit recognition of the evolving strength of evidence. Many payers are shifting from seeing decisions on reimbursement as a one-time binary decision, to seeing reimbursement decisions as an on-going process aiming at providing greater certainty about value for money as evidence accumulates. Once a coverage decision has been made, payers have an interest in limiting initial use to subpopulations with the best benefit-risk ratios, in improving patient adherence, in monitoring treatment outcomes and in modifying conditions of reimbursement in light of evidence on effectiveness.

Some of these issues may be partially addressed through harmonised adoption of adaptive approaches to drug development, licensing and reimbursement. Industry is moving from blockbuster to niche buster business models, even as payers increase evidence requirements for reimbursement and regulators seek to revise licensing terms in light of evolving evidence from use. While regulators have achieved some degree of interregional harmonisation of evidence standards, payers are at an earlier point in that dialog. The lack of alignment results in differences in standards for drug development and reimbursement. How will adaptive pathways help? Because adaptive licensing requires early engagement with all stakeholders, an adaptive approach to licensing should catalyse consensus building among payer both within and across regions. In fact, the Innovative Medicines Initiative (IMI) in the EU is now working to create a framework for implementation of 'Medicines Adaptive Pathways for Patients' (MAPPs).'

2.4.4 Current Development in the US

The US FDA frames risk management decisions across the life cycle of a drug in terms of a benefit-risk framework with emphasis on transparency and continuous learning. Recent FDA initiatives include Patient-Focused Drug Development and FDA Breakthrough Product Designation early in the drug life cycle, the use of pharmaceutical quality metrics in manufacturing of generics late in the drug life cycle to cover off patent drugs 80 percent of which are generic, and the use of benefit-risk analysis throughout the life cycle.

The FDA uses a formalised benefit-risk assessment approach to structure and manage new drug assessment. While the idea of using benefit-risk assessment is not unique to FDA, the way that benefit-risk assessment is conducted by the FDA takes account of emerging information on medicine, science and policy with sensitivity to emerging knowledge in a manner analogous to U.S. case law. The law and

regulations concerning the drug review process generally provide broad principles and are not case-specific, so FDA works to develop consistent policy in taking action within its legal and regulatory authority, to make decisions in a way that is fair, not arbitrary or capricious. FDA communicates this policy through guidance. However, in a given case it may determine that generally applicable guidance is inappropriate, and in such cases retains the flexibility to take a different approach. Since each decision is made either in the context of established policy or establishes new policy, this serves FDA as a sort of 'case law'. Although the quantity of information to be evaluated and considered by FDA is substantial, there are residual uncertainties resulting, for example, from the gaps in the data or current scientific understanding, and human judgment and values must come into play. The framework for benefit-risk decision-making summarises the relevant facts, uncertainties, and key areas of judgment, and clearly explains how these factors influence a regulatory decision. This helps inform and clarify the regulatory discussion. It also serves to communicate the basis for FDA's regulatory decision to the public, while documenting the decision for reference as FDA considers similar benefit-risk assessments in the future.

The FDA framework for benefit-risk assessment is structured in terms of five major considerations: the analysis of severity of the disease condition being targeted by the drug; a review of current treatment options to determine the degree of unmet medical need; benefits observed in clinical trials; risks reflected by the safety findings from clinical trials; and consideration of whether the identified risks can be managed to ensure benefits would exceed risks. Each of these considerations is further structured into two areas to identify (a) the facts that are known versus residual uncertainties for each consideration, and (b) the conclusions and reasons of the reviewer based on their assessment of the evidence and uncertainties. The FDA uses a qualitative approach that is grounded in the quantification of data elements at the time of marketing approval. Benefits are grounded on data on efficacy endpoints from controlled clinical trials. Risks are grounded on data on harms reported in clinical trials and from spontaneous adverse effect reports. The evaluation of benefits and risks is dynamic, with understandings of both benefits and risks evolving over the product life cycle.

FDA developed the Patient-Focused Drug Development program (PFDD) in recognition that patients are uniquely qualified to inform clinical context for FDA's benefit-risk assessment: in particular the impact of disease on patients, i.e., the analysis of condition, and the effectiveness of currently available therapies in treating the disease impacts that matter most to patients. The traditional patient representative program only enabled participation of individual patients who receive conflict of interest screening and some regulatory process training, and those patient representatives have had the burden of speaking for all those with a disease. Yet one size does not fit all who are afflicted with a given disease. The FDA needed more diversity. In a pilot exercise, FDA set up 20 public meetings each focused on a different disease area. Only patients are allowed to speak. The meetings held since the start of this initiative in 2013 have been well-attended by patients and have provided powerful insights for FDA reviewers and also for industry sponsors who have attended the meetings. Public stakeholders and industry have identified this initiative as a priority for further expansion in the coming years.

The FDA established 'Breakthrough Therapy Designation' to foster the more rapid development of drugs that offer the potential of substantial improvement in patient outcome. The FDA Safety and Innovation Act (FDASIA) of 2012 Section 902 provided for a new 'Breakthrough Therapy Designation.' A breakthrough therapy is a drug which: (a) is intended alone or in combination with one or more other drugs to treat a serious or life-threatening disease or condition; and; (b) preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Breakthrough designation is based on preliminary clinical evidence of potential improvement on a clinically significant endpoint relative to available therapies. By contrast, fast track designation is based on nonclinical or clinical evidence of the potential to address unmet medical needs. Both Breakthrough and

Fast Track programs are intended to expedite the development and review of drugs for serious or life-threatening conditions.

If a drug is designated as a breakthrough therapy, FDA will expedite development and review of the drug. The program established a rolling review process with additional engagement between FDA staff and applicants. Prequalification based on the criteria outlined in Section 902 is required. Requests for breakthrough designation may be submitted with the Investigation of New Drug (IND) application with at least one phase one trial complete. Breakthrough designation has substantial benefits to the sponsor, with almost unlimited meetings to discuss study designs and development processes to avoid delays and mistakes. These measures have reduced clinical development time by half, down from an average of 7 to 10 years, with clear benefits for sponsors seeking to reduce development costs and patients seeking earlier access. As of June 2016, 440 applications for breakthrough designation had been submitted and 144 applications had been accepted.

2.4.5 Conclusions: Existing Differences, Current Trends and Emerging Challenges for TTIP

The European Union and the United States have been converging in their approaches to drug licensing, but some differences remain. There are substantial similarities in the US and European approaches to risk management. There are substantial flexibility and differentiation within both EU and US processes, with degrees of acceleration, strength of controls on initial use, and reliance on adaptive elements tuned to patient interests in safety, efficacy and early access to address unmet needs. Contrary to conventional wisdom, there do not appear to be differences in attitude to risk on population level, but some differences in regulation on a case by case basis. With reference to speed, the US FDA approves cancer drugs more quickly than the EU EMA. With reference to process, the US FDA is more demanding than the EMA for biosimilars[3]. The EU offers generalised handling of Patient-Reported Outcome Measures (PROMS) while the US retains a symptom-specific approach. With reference to outcomes in licensing of oncology drugs, 50 percent of drugs are treated identically, 30 percent of drugs have some differences in labelling and in 20 percent of cases a drug is accepted by one and rejected by the other. The US and EU share common goals, with similar upstream pre-licensing processes, similar policies addressing quality problems in licit, counterfeit and illegal drugs, albeit with some differences in implementation.

There are differences between the European Union and the United States in post-licensing downstream risk management. Most downstream differences are a product not of philosophical differences but of sharp differences in the structure of reimbursement. The EU has public payers while the US has a plethora of public and private payers. Within Europe, payer policies on reimbursement may control off-label use and limit inappropriate utilisation and prescription. Within the US, the FDA may indirectly affect utilisation and prescription by altering labels and issuing warnings, thereby reshaping liability exposure and altering payer and provider behaviour. European public payers had a theoretical option to 'dereimburse' drugs if warranted by emerging evidence on safety or effectiveness. Although not widely used, a payer-based approach to adherence could be used to encourage physicians and patients to practice evidence-based medicine, with practices updated on the basis of emerging information. Alignment of payer requirements may simultaneously strengthen incentives to improve practices while reducing delays in access and costs caused by variations in payer standards for effectiveness.

Looking ahead, present trends suggest continuing convergence, further reducing the potential for international conflict over licensing and reimbursement issues. In both the US and EU, we can expect to see greater patient involvement in defining meaningful benefit and willingness to accept risks, with lifecycle approaches to the management of risks of product and with integrated assessments of benefits

[3] A biosimilar is a biologic medical product which is almost an identical copy of an original product that is manufactured by a different company

as well as risks. Environmental changes have increased demand for adaptive approaches to benefit risk management and that enable the transition from traditional to adaptive approaches. However, significant challenges remain if the potential benefits of de facto and de jure adaptive approaches to licensing are to be realized.

Some potential problems are technocratic and legal. Adaptive approaches to risk governance require the integration of lessons from post-marketing observational data and data from controlled clinical trials in a manner that compensates for the weaknesses of each. Observational data including payer records and electronic health records are subject to selection biases, misrepresentations of indications, simple errors and noise, presenting problems in terms of internal validity of inferences. The development of methods of data standardisation and curation and methods of causal inference suited to data with biases and selection effects present technical challenges. Clinical trials of limited duration, with high patient adherence in populations cleansed of comorbidities and use of other drugs present problems in terms of external validity – generalisation from trials to ordinary treatment populations. The integration of observational and trial based information, including working back from hypotheses generated from post-market observational data to limited trials to confirmatory targeted trials, presents legal as well as technical challenges. To make adaptive approaches function effectively will require work on terms of access to data, including intellectual property rights, human subject protocols and privacy rules.

Some potential problems are political and economic. First, experience has shown that it is politically challenging to remove a drug from the market or to restrict payment should the initial benefit-risk balance not be confirmed post approval. Once patients have access to a drug, resistance to withdrawal can be intense. These issues will require substantial discussion before rather than after conditional approval of drugs, with the inclusion of patient groups as critical stakeholders. Second, once early access is obtained, not all developers will be interested in making good on controls, observation and potential narrowing of terms of access that constitute the 'back end' of adaptive licensing. Care must be taken to ensure that this post-marketing 'back-end' of adaptive licensing is fully implemented. Controls on initial prescriptions, systematic post-marketing observation of safety and effectiveness of drugs-as-used, and modification of the terms of licensing and reimbursement based on real-world experience are critical to effective management of uncertainty over the life cycle of drugs. In practice, this will depend on engagement with payers – with a clear interest in evaluating effectiveness - as well as sponsors.

Finally, implementation of adaptive approaches to licensing will be more difficult in the US than the EU. For example, limiting access to an approved drug to a subset of the population will be more difficult in the US, where the practice of medicine allows for off-label use, than in the EU. While sponsors, regulators, HTA bodies and payers are now collaborating in the EU, other jurisdictions, notably the US, do not have national healthcare systems with centralised management on access and payment. Conditions within the EU have allowed the EMA to conduct pilot projects to assess the feasibility of adaptive approaches to regulation. At the end of the day, the characteristics of adaptive approaches to licensing will be shaped by differences in national and regional conditions and by observation, analysis and feedback from regulatory experience.

3 Application in Practice

The variation in regulatory standards examined in Chapters 1 and 2 is important, but it is not fully determinative of the products, benefits and risks that societies face. There can be a difference between the law on the books and the law in action. For example, some regulatory standards might be effectively monitored and enforced, but others only weakly, so knowing the official standard may not fully predict compliance or behaviour. And the process of regulatory decision making may be similar in some respects but different in others, so that opportunities for public input, executive oversight and judicial review occur at different timing and with different influence in each system (Parker and Alemanno 2015).

In addition, even in full compliance, industry might respond to differences in regulatory standards across jurisdictions (such as the EU and the US) in several ways, producing:

(i) a different product to meet the different regulatory standard in each jurisdiction and thus selling a variety of products matched to the variety of regulations.

Or (ii) a single product that meets the most stringent regulatory standard in any jurisdiction and thus selling one product everywhere.

Or perhaps (iii) an intermediate version, such as an industry producing two products to meet five different regulatory standards.

Or (iv) a more fine-grained version, in which each firm (enterprise) in the industry chooses a different strategy (e.g. multiple products or one product) to sell its product(s) in multiple jurisdictions with multiple varying regulatory standards.

Or (v) only making the product for its own jurisdiction, and not exporting it to the other jurisdiction at all (because the other jurisdiction is more restrictive, or bans the product).

Do industries produce one product to meet the most stringent standard everywhere, or differentiated products to meet different standards in each jurisdiction? The answer may vary by sector/industry (or by firm within an industry), and by specific regulatory standard – because different industries (or firms) may face different costs of compliance, and different costs of producing differentiated products, under these different standards. Meanwhile, the jurisdictions that initially had different regulatory standards may evolve toward a single standard, through a 'race to the bottom' (relaxing standards to reduce costs and thereby attract industry away from competing jurisdictions) or a 'race to the top' (tightening standards to raise societal protection levels and thereby attract voters away from competing jurisdictions) (Bradford 2012). Which patterns occur is an empirical question and difficult to predict.

It is difficult to find strong evidence on this question. Our case studies in 4 key sectors, presented in Chapter 2, addressed the regulatory standards in effect, and did not explore the ensuing industry responses at the sector or firm level, nor did they identify strategic 'race' behaviour by the involved jurisdictions. A few examples are evident: Food producers make some foods for one jurisdiction and not the other (e.g. GMO foods, chlorine-washed chicken, foods containing trans fats, unpasteurized cheeses, and foods containing hidden toys). Automobile manufacturers make some variations in models so that the vehicles can meet different standards in different jurisdictions, such as a different vehicle model for the US and for Europe, and a different emissions system for California than for the rest of the US (as allowed under the US Clean Air Act), even though the manufacturers would prefer to make a single global vehicle model (Center for Automotive Research 2016). Some chemicals are marketed in one jurisdiction but not the other (e.g. pesticides). And some pharmaceuticals are marketed in one jurisdiction (e.g. Tylenol/acetaminophen) while an apparently similar pharmaceutical is marketed in the other jurisdiction (Panadol/paracetamol). These are illustrative examples. A much broader empirical research project would be needed to characterize the actual variation in industry practices in each product sector.

4 Conclusions and Recommendations

4.1 Findings

This report has sought to examine the similarities and differences in EU and US regulation, overall and especially in 4 key sectors: Food, Automobiles, Pharmaceuticals and Chemicals.

A major finding is that the reality of transatlantic regulation is not a simple dichotomy of a European approach versus an American approach. It is not EU precaution versus US reaction, or ex-ante versus ex-post legal systems, or civil law versus common law, or uncertainty-based versus evidence-based regulatory systems. Rather, the reality is parity and particularity: both overall EU-US similarity, and also selective application of precaution on both sides of the Atlantic, including both cases of greater European precaution and cases of greater US precaution.

Evidence for this complex reality has been presented in earlier research, summarised in Chapter 1 above (e.g. Sand 2000; Zander 2010; Wiener et al. 2011; Wiener et al. 2013). Our case studies in 4 sectors, although they are not a random or representative sample of all regulation, help illustrate this more complex reality. They are summarised below:

Table 2: Findings in 4 Sectors (based on Chapter 2)

	Sector	Case	Comparison
1	Food Safety	GM Foods / Crops / Fish	EU more precautionary
2	Food Safety	Hormones in Beef	EU more precautionary
3	Food Safety	Mad Cow (BSE/vCJD)	US more precautionary, especially regarding blood
4	Food Safety	Antibiotics	EU more protective
5	Food Safety	Pesticides	US ADIs more protective than EU MRLs
6	Food Safety	Organic	Convergence on agreed standards
7	Food Safety	Chlorine-washed poultry	EU more precautionary regarding chlorine (US more precautionary regarding salmonella?)
8	Food Safety	Trans fats	US more precautionary in labelling and broad phase-out of trans fats
9	Food Safety	Unpasteurised dairy	US more precautionary
10	Food Safety	Choking hazards	US more precautionary (e.g. ban on Kinder Surprise eggs)
11	Automobiles	Safety	Approximately equivalent results, yet differences in numerous regulatory specifications. Opportunity for regulatory cooperation on autonomous vehicles.
12	Automobiles	Emissions	US more precautionary as to NOx, PM, etc.
13	Chemicals		EU REACH may be more precautionary than US TSCA, but both are complex systems, both are precautionary in key aspects (but not fully). Note: TSCA reform legislation is pending in US Congress.
14	Pharmaceuticals		US FDA and EMA differences, with convergence on several key aspects. Distinctive pathways toward improved benefit-risk management.

To be sure, the number of cases studied here that reflect greater EU or greater US precaution are not necessarily representative of the full array of policies, products and services. This is not a contest to count the number of cases on each side. Nor can generalized patterns be inferred from these cases. Still, they do illustrate the complex pattern, and undermine claims of greater EU (or US) precaution across the board.

4.2 Implications for Trade Agreements and International Regulatory Cooperation

The transatlantic regulatory differences that exist, even if they are unusual deviations from typical parity, and even if they go in both directions, can still pose barriers to trade. Regulatory differences can complicate trade both for large enterprises and perhaps especially for small and medium-sized enterprises (SMEs). Converging regulatory standards could potentially reduce such barriers and enhance trade for mutual benefit. At the same time, converging regulatory standards to reduce barriers to trade may raise a concern that doing so might entail relaxing regulatory protections on one side. For those who hold the comparative viewpoint discussed above – the view that European regulatory standards are always or generally more protective than US regulatory standards – the concern may be that reducing regulatory barriers to trade would entail weakening European regulatory protections. This concern has been expressed as a criticism of TTIP, and could also arise regarding international regulatory cooperation outside trade agreements.

But even if this comparative viewpoint were accurate, it would not necessarily follow that harmonizing standards requires weakening European regulatory protections, because the trade agreement could 'harmonise up' to the more stringent standards, rather than 'harmonise down' to the less stringent standards. Or it could provide for "mutual recognition," in which the jurisdictions retain their own standards domestically, and agree to allow imports that have satisfied the other jurisdiction's standards.

Further, if this comparative viewpoint (that European standards are generally more stringent) is indeed inaccurate – because the reality, as described above, is a more complex array of EU-US parity and particularity, going in both directions (sometimes more stringent European protections, sometimes more stringent US protections) – then converging transatlantic regulations could entail a mix of changes that makes (some) protections more stringent on each side.

International regulatory cooperation does not necessarily entail choosing one side's current standard over the other. The question is not which side can impose its regulation on the other, but whether together they can learn from experience with regulations on both sides of the Atlantic, and adopt the best approach – which may be the current approach on one side or other, or a third new approach. Current variation in policies can inform better future choices (Wiener and Alemanno 2015). There is scientific uncertainty and regulatory ambiguity on each side of the Atlantic, and it may be worthwhile to review the regulatory differences that do occur (often without great controversy) and find solutions that are scientifically sound and improve societal well-being. There may be a few cases that trigger strong feelings, and several that offer opportunities for learning from variation.

Further, international regulatory cooperation can proceed even if large trade negotiations such as TTIP do not. Specific agencies and ministries can cooperate on particular policies, and regulatory oversight bodies such as US OIRA and the EU RSB can cooperate on approaches to ex ante impact assessment, retrospective review and evaluation, and improved regulatory design.

In some instances, differences in regulatory practices do not have clear implications for trade. For example, variations in US and EU practices in pharmaceuticals licensing and reimbursement are not easily characterized as differences in regulatory stringency and do not translate into a simple list of priorities for trade negotiations under a WTO or TTIP framework. In pharmaceuticals, variations in regulatory policies and reimbursement policies do not confer systematic advantages for firms in the US or EU that then become the focus for trade negotiations. While licensing and reimbursement policies may have some

effect on the location and magnitude of investments, the implications for US and EU trade negotiations are limited. Simply put, the modern pharmaceuticals sector is transnational, with headquarters and subsidiaries of indistinct nationality. And the complex patterns of variation in policies described in this essay do not have clear effects on trans-Atlantic flows of goods, capital or technology.

4.3 Learning from Regulatory Variation

The variation that we observe across risk regulations in the US and Europe can also be a source of learning. Different regulatory standards and instruments can yield different results: different effectiveness in achieving intended outcomes, and also different social costs and ancillary impacts (unintended consequences, such as countervailing harms or co-benefits).

Rather than only seeking to achieve harmonisation or convergence on regulations, TTIP (and other efforts at international regulatory cooperation) could also create a platform for continuing study and learning from regulatory variation (Listokin 2008; Wiener and Alemanno 2015). Just as variation across member states within a federal system offers a crucial 'laboratory' to test alternative policy approaches, variation across the regulations in the US and Europe can serve as a 'transatlantic policy laboratory' – a step toward a 'global policy laboratory' that can improve our understanding of regulatory performance, consequences, and innovation (Wiener and Alemanno 2015). Purposeful experiments could be conducted to test and compare regulatory approaches (Greenstone 2009; Ludwig et al. 2011; van Gestel and van Dijck 2011).

Both the US and Europe could benefit from such learning – to improve effectiveness, lower costs and ancillary harms, and reduce unnecessary trade barriers. Successful learning from regulatory variation will require careful work to collect data, structure comparisons, and evaluate results through retrospective impact assessments. We suggest that this process can be launched or augmented through TTIP and other efforts at international regulatory cooperation. For example, EU and US ministries/agencies could conduct joint or parallel evaluations of existing regulations to assess their empirical impacts and which policy design elements are most effective or yield optimal outcomes. And the EU Regulatory Scrutiny Board (RSB) and US OIRA could conduct joint or parallel evaluations of multiple regulations to assess policy designs. Independent bodies, such as national academies of science, and academic research groups at think tanks and universities (perhaps supported by private foundations), could also provide such data collection and evaluative research to learn from regulatory variation.

4.4 Toward Planned Adaptive Regulation

Further, trade agreements such as TTIP, and other efforts at international regulatory cooperation, could promote planned adaptive regulation (PAR) – an approach in which each regulation is designed from its initiation to learn from experience and update over time (Greenstone 2009; McCray, Oye and Petersen 2010).[4] Global and US–EU policy laboratories for regulation can facilitate experimentation with different ways PAR can be implemented.

PAR is a policy tool to which risk regulators have given too little thought. PAR sounds logical: in the face of uncertain evidence that was used to underpin a rule, regulators plan both for scheduled adaptation of the rule and for the production of decision-relevant knowledge that further characterises or reduces the uncertainties pertaining to the risk regulated. It is actually rare to see this purposeful combination of planning for future review and revision, for instance periodic review, and funding targeted research, in a

[4] PAR has been the topic of a conference organised by IRGC and University College London in January 2016. The conference report is available here: https://www.irgc.org/wp-content/uploads/2016/07/IRGC-Conference-Planned-Adaptive-Regulation-Summary-Report-final-WEB.pdf. A background information note is available here: https://www.irgc.org/wp-content/uploads/2015/12/A_short_introdution_to_Planned_Adaptive_Risk_Regulation-19Nov15.pdf.

way that is credibly overseen for quality and relevance, and that explicitly feeds into the reassessment of the knowledge base. One example, where regulators have learned from each other on both sides of the ocean, is the regulation of criteria pollutants in the atmosphere, the US National Ambient Air Quality Standards (NAAQS) and the European Air Quality Standards (Petersen et al. 2006). Under the US Clean Air Act, the NAAQS require reviews every 5 years. In the new Lautenberg Chemical Safety Act (LCSA) (June 22, 2016), section 26(L) embodies a similar version of planned adaptive regulation. Key text in section 26(L) reads:

'(1) DEVELOPMENT - Not later than 2 years after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, the Administrator shall develop any policies, procedures, and guidance the Administrator determines are necessary to carry out the amendments to this Act made by the Frank R. Lautenberg Chemical Safety for the 21st Century Act.

(2) REVIEW - Not later than 5 years after the date of enactment of the Frank R. Lautenberg Chemical Safety for the 21st Century Act, and not less frequently than once every 5 years thereafter, the Administrator shall—

(A) review the adequacy of the policies, procedures, and guidance developed under paragraph (1), including with respect to animal, non-animal, and epidemiological test methods and procedures for assessing and determining risk under this title; and

(B) revise such policies, procedures, and guidance as the Administrator determines necessary to reflect new scientific developments or understandings.'

PAR requires an initial intention to incorporate learning into the life of a regulatory standard. It requires some form of data collection and periodic analysis of these data. Whereas efforts at "retrospective review" of regulation to date have often been ad hoc and without initial plans for data collection and analysis (Wiener and Ribeiro 2017), PAR depends on such advance planning for monitoring, data collection, and evaluation over time. It involves a series of repeated occasions for policy makers to review these analyses and consider making revisions to the regulation. The duration of the interval period for each analysis and review (i.e. the frequency of such reviews) is a key choice, and may need to match the expected pace of change that the PAR approach is trying to manage in each area, while avoiding so much instability that the costs of compliance rise too high and/or the incentives for investment in the regulated industry fall too low. Another key choice is whether the review period is an opportunity for review (at least a nudge to policy makers to consider revisions at regular intervals), or an obligation (in the sense that the regulation would terminate (sunset) unless the review is carried out and recommends continuation or revision of the regulation). A further question is who should conduct the analysis and review – e.g. the staff of the ministry that developed the initial regulation, or an oversight body, or an independent outside body. The regulating ministry may have greater knowledge about the regulation, but also disincentives to reviewing it and reporting publicly on that review, whereas outside bodies may be more objective reviewers but lack key knowledge (Wiener and Ribeiro 2017). Despite these important challenges, PAR offers the potential of incorporating continual iterative improvement into otherwise static regulatory systems.

The general idea that governments (e.g. the EU or the US governments) should not ignore evolving evidence on the actual effects of their existing rules is one that has actually had a lively history in administrative law on both sides of the ocean. In the EU, many Directives have had review clauses inserted in them, with evidence gathering and involvement of stakeholders appearing as common elements in such scheduled reviews. In the US, as early as 1946, the Administrative Procedure Act laid out an explicit provision allowing interested and affected groups to ask for the amendment of an existing rule, and prohibiting the authorizing Federal agency from declining to consider such requests without explaining why. Subsequent Presidents from both political parties have issued Executive Orders calling on agencies to review existing rules and to revise or rescind them as needed (e.g. President Carter's Executive Order

12044 (1978), President Clinton's Executive Order 12866, section 5 (1993); and President Obama's Executive Order 13563 (2011). But it has been difficult to mobilize agencies to collect data on regulatory performance, to conduct and report their retrospective views, and to use these reviews not just to revise individual rules but more broadly to learn how to improve the accuracy of ex ante impact assessments (McCray, Oye and Petersen 2010; Bull 2015; Wiener and Ribeiro 2017). Thus there may be a role for outside groups to propose and conduct ongoing data collection and evaluation.

However, while the demand for self-corrective mechanisms in regulation is persistent as a general nonpartisan "good government" principle, it seems to have been unpopular in application. Recently, though, we have seen an increasing number of examples of the implementation of Planned Adaptive Regulation, for example in Dutch Delta Management, in US and EU air quality regulation, in the adaptive licensing of new drugs by the European Medicines Agency, and in US synthetic biology regulation.

There are several reasons behind the unpopularity of PAR in the past, the precise causes of which deserve fuller study. While government leaders might lean toward it, public bureaucracies often prefer the status quo to new ways. Conducting reviews of ongoing policies can be costly and time-consuming (and an unfavourable review may be awkward for the agency). Regulatory agencies are busy, and reviewing past policies can be a low priority for agency officials compared to implementing new laws and addressing new problems. Budgets for analysing and writing expensive new rules are already stretched, and re-examining past rules can look like an unaffordable luxury at lower levels in bureaucracies.

A deeper reason to be wary of repeated revisions is the need for regulations to be enforceable and credible to those who must comply with them. The anticipation of revision may undermine the credibility and perceived fairness of the initial rule, and thus weaken industry compliance. Also an agency's public reputation may be threatened. In policy, as in politics, "flip-flopping" is an unappealing trait. It may imply weakness or, worse, unprincipled malleability in the face of political pressure. On the other hand, the prospect of revisions may enable some stakeholders to agree to the adoption of an initial regulation that they would otherwise have opposed.

Concerns about accountability and predictability of PAR are often raised through public criticisms of regulations from external groups, both groups that want tougher regulation and those that want milder regulation. In some cases, regulated interests and their usual opponents (consumer, environmental, and other advocates) might form a constituency favouring the re-visiting of existing rules. It is common, for example, for some subset of contending parties to feel that a regulatory agency has reached the wrong conclusion in writing a new rule. One might expect that such aggrieved interests groups would favour both the systematic gathering of new evidence on the actual costs and benefits of the rule and the subsequent reopening of what seems to them to be a flawed decision. On the other hand, some regulated actors may favour maintaining the current regulation, if it gives these actors competitive advantages over their rivals or new entrants (Smith and Yandle 2014; Wiener and Richman 2010); periodic updating of the regulation might reduce such barriers to entry and competition (though, depending on its content, each periodic update could also raise a new barrier).

PAR does not have to involve radical policy change. Regulation can often be updated within pre-defined limits or objectives, if administrative law does not pose too tight a constraint. This thus allows the introduction of performance-based management, with a view to reaching more effectively and flexibly an initially determined performance objective (an approach already in place in Europe in many sectors, such as automobile safety). For example, the jurisdictions could coordinate experimentation, as one conducts a pilot policy treatment while the other acts as a control group, or the two jurisdictions agree to experiment two different policy solutions, and they then compare results. Thus, PAR can be a mechanism for policy learning – from regulatory variation across countries, and from ongoing accumulation of knowledge over time – to improve regulatory designs and outcomes.

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