Non-Measurable Negotiations: The EU between Transnational Regulation of Pharmaceuticals and Private Law

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1. Introduction – Transnational Regulation and Private Law: Two Stems Apart

The aims of this chapter are to look at the role of the EU in regulating pharmaceutical safety in the internal market, and to contrast that role with the EU’s peculiar capacity of co-regulator in the transnational space of pharmaceutical safety and efficacy governance. The intent of the analysis proposed in this piece is to highlight a dichotomy between the internal and external roles of the EU in the pharmaceutical rule-making arena. Whereas throughout the second half of the 20th century the EU has gained internally an ever more prominent and centralized role in the regulation of medicines, culminating with the adoption of Directive 2001/83/EC1 on the Community Code relating to medicinal products for human use (and subsequent amendments and addenda), externally the situation is one of significant complexity. The intricacies of the transnational institutional framework of pharmaceutical regulation need to be addressed and described in order to propose an understanding of the regulatory role for the traditional private law dimension. What is contended here is that while a form of ‘regulatory private law’ has been developing at a transnational level with intrinsic limits (what will be referred to as ‘non-measurable negotiations’), traditional forms of private law have the potential to vindicate a significant role in guiding the EU as a negotiator in the transnational ‘regulatory private law-making’.

2. The Frame and the Argument

Ever since the International Conference of Drug Regulatory Authorities (ICDRA) held by the World Health Organization (WHO) in 1989, regulators from the US, EU and Japan have underlined the necessity for transnational common ground in the making and implementation of regulatory standards leading to marketing approval of new pharmaceutical

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products. The reasons for this push are associated with the global nature of the pharmaceutical market and the multinational dimension of the major industries involved, strongly advocating for simplified procedures allowing speedier global marketing of new products. With the institution of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) in 1990, the regulators of the US, EU and Japan created an informal forum where regulators and regional representatives of the pharmaceutical industry could negotiate guidelines touching upon all major aspects of pharmaceutical regulation, ranging from safety to efficacy, with the declared purpose of facilitating new products’ access to global marketing, avoiding duplication of procedures caused by regulatory diversity.

Within this informal transnational regulatory network, the EU, represented by both the European Medicines Agency (EMA) and the Commission, participates as a co-regulator (or perhaps, more appropriately, as a negotiator), exercising one vote within the Steering Committee (the executive body of the ICH), alongside the US and Japan governments and representatives of industry from those three regions (a total of six voting members). This chapter analyses the mechanisms of adoption of ICH guidelines as contrasted with the internal mechanisms of the EU – inspired by the concept of ‘deliberative democracy’.

Secondly, the piece focuses on the procedural mechanisms of the ICH to suggest a second dichotomy, between the formal and substantial role of the EU representatives within the Steering Committee. Formally, the EU is one of the ICH founders, and acts as a voting member among peers in the adoption of negotiated guidelines. However, a closer look at ICH output suggests a strong and hardly regulatable power play among the prime actors of the network. The actual contribution they make to each matter is highly dependent on the political and/or economic influence they are able to exercise in a given field. The completely informal nature of the forum’s practice makes it difficult to introduce rigorous procedural checks and balances to counter this phenomenon. Therefore the actual weight of each actor within the ICH is a rather complicated element to measure. The extraordinary impact of ICH guidelines in the international regulation of medicines makes it crucial to open the issue to debate.

To support these claims the chapter will refer to the adoption of key harmonizing guidelines. The two cases that will be touched upon as ‘pilots’ are the following:

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- The case of ICH guideline E6 on good clinical practice (GCP) – the key document on which acceptance of global clinical trials results is built.
- The case of ICH guideline E9 on statistical principles for clinical trials (SPCT) – providing a set of general principles on the applicable standards for global trials (with a result highly deferent to the interest of maintaining a plurality of approaches to the use of placebos in the conduct of trials on humans).

Finally, in light of the analysis provided on this double dichotomy, the discussion will switch to the consequences (actual or potential) of the described mutations in the regulatory arena on a traditional pillar of private law – the law of torts, and specifically products liability law (PL). Starting from the solidly argued idea that complementarity between PL and regulation is an essential factor to the successful achievement of both sets of rules’ endgame (product safety and consumer protection), the piece argues that a changing landscape in regulation calls for a reconsideration of PL’s role – as suggested below, a new role for old rules. The focus is on the concepts of ‘complementarity’ and ‘regulatory compliance’. A seemingly consolidated judicial ‘formalistic and deferent’ approach (to regulatory decisions) could (and possibly should) evolve into a more ‘substance-oriented’ test.

The chapter will therefore be structured as follows. Part 2 will give a brief account of the development of the functioning of the EMA (describing how the EU has internally overcome the issue of transnational regulatory practices), while Part 3 will move to a similar description of the ICH, focusing on its controversial nature. This will bring out the first suggested dichotomy between the strong internal EU regulatory design and its ‘lighter’ external position. Part 4 will critically analyse the mechanisms of adoption of essential ICH guidelines, highlighting the second suggested dichotomy between the formal and substantial role of the EU as a transnational ‘regulatory negotiator’. Part 5 describes the structural difficulties that ensue from the attempt to systematize a regulatory framework that has the ICH at its top through theoretical constructions very much dependent on the EU internal architecture (and therefore ill-suited to address the external role of the EU). The tentative conclusion here is that the ability of the EU to expand the scope of its policies and vision in the field of pharmaceutical safety and efficacy regulation is highly dependent on its strength as a negotiator – hardly measurable in the absence of clear transparency guarantees. Part 6 will finally explore the other side of the pharmaceutical safety and efficacy coin. In the unsettled regulatory space described throughout the piece, old rules of torts can claim a renewed role in adequately complementing pharmaceutical regulation.
3. EU Internal Regulatory Framework

The EU regulatory system for medicinal products is the oldest, most extensive and most complex of any vertical product regulatory system, comprising a ‘very substantial body of Community legislation and case law’. It has been amended regularly since the first Directive was introduced in 1965 as a response to the Thalidomide tragedy (at which time only a few countries already had regulatory systems in place). In parallel to EU regulations, Thalidomide was also the trigger for the adoption of the stringent mechanisms devised by the German law of pharmaceutical products (the 1976 Arzneimittelgesetz). This legislation will be further discussed below in the analysis of the EU Product Liability (PL) Directive and its relationship to special national regimes of liability for specific product categories (including pharmaceuticals). As suggested above, exploring the potential for an approach based on complementarity between regulation and liability requires first an analysis of the regulatory environment. It is however significant to notice at this preliminary stage that both the birth of regulatory requirements for marketing authorization and the embryo of the debate that will lead to the adoption of the PL Directive share a common historical root.

The full historical account of the evolution that occurred between the 1960s and today is beyond the scope of this piece, but it is worth keeping in mind some key developments in regulatory evolution. To promote collaboration between the Member States (MS) and the EU Commission, in 1977 the Committee for Proprietary Medicinal Products (CPMP) began its mandate. As an independent networking scientific committee, its function was to foster harmonization of assessment standards and facilitate cooperation between

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6 See for example the US Food Drugs and Cosmetics Act (FDCA), 1938.
10 This short reconstruction owes very much to the works of Cuvillon, ‘The Role of the European Medicines Evaluation Agency in the Harmonisation of Pharmaceutical Regulation’, in R. Goldberg and J. Lonbay (eds), supra note 4, 137; and Sauer, ‘New Drugs in the Global Economy: Risk Assessment and Risk Management in the EU and Co-Operation with the US’ (Lecture held at the University of Pittsburgh, 13 November 2000).
national agencies and the EU Commission. The result of this initiative was to provide ‘the first EU-level forum for MSs representatives, from which grew networks of contacts’ among scientific experts coming from their authorities of origin in the MSs.\(^{13}\)

Alongside the legislation provided by the Directives, through the CPMP work, detailed scientific guidelines on drug testing emerged, contributing to the creation of a body of supplementary technical ‘soft law’.\(^{14}\)

During the 1980s a significant trend started at a European level, combining and complementing harmonization with mechanisms of mutual recognition of national rules and standards on the premise that they complied with EU legislation minimum requirements.\(^{15}\) The reasoning being that even in the presence of full harmonization of the rules, final decisions on marketing authorizations would always have to be made on a case-by-case risk/benefit assessment by MSs authorities.\(^{16}\) As a consequence, in the absence of unified decision-making procedures,\(^{17}\) there would always be the potential for divergent assessments. In response to the intricacies of conflicting regulatory outputs, the decision taken was to temporarily rely on mutual recognition of MSs authorities’ decisions.

A common ground was being established through the harmonization and mutual recognition of basic rules. On this basis MSs and the Commission proceeded with the natural step forward, entailing a shift ‘from harmonisation of rules to harmonisation of decision-taking’.\(^ {18}\) The key move in this direction was the creation of a properly European marketing authorization system with Council Regulation 2309/93/EEC, reinforced by the establishment of the EMEA (now EMA)\(^ {19}\) as an advisory body for the Commission. In agreeing to create the EMA, MSs began to partially renounce their sovereignty over the authorization of

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\(^{12}\) Sauer, supra note 10.


\(^{14}\) As explained by Cuviller, supra note 10; and Hodges, supra note 4.

\(^{15}\) Sauer, supra note 10, and Cuviller, supra note 10; for a recount of the ‘trend’ see R. Rhodes, Understanding Governance: Policy Networks, Governance, Reflexivity and Accountability (1997).

\(^{16}\) Sauer, supra note 10, and Cuviller, supra note 10

\(^{17}\) See Cuviller, supra note 10, at 140, but this topic is addressed by several authors, see among others Feldschreiber, ‘Marketing Authorisation’, in P. Feldschreiber (ed.), The Law and Regulation of Medicine (2008) 103, at 103-111.


Alongside the inauguration of the EMA, the regulation introduced the marketing authorization architecture that is still in place with two alternative procedural mechanisms, centralized and decentralized.  

The centralized procedure was, at its origin, compulsory exclusively for pharmaceutical products derived from biotechnology, and left as an option for other innovative products. Since 2004, the scope of the compulsory application of the centralized procedure has been expanded and specified. In the centralized procedure a marketing authorization application (MAA) must be made directly to the EMA for evaluation by the CPMP (renamed CHMP – Committee for Medicinal Products for Human Use, since 2001). The actual marketing authorization is then issued by the Commission on the basis of the EMA’s advice. Once granted, a centralized marketing authorization is valid in the whole EU. The post-marketing surveillance is now disciplined by the recently adopted Directive 2012/26/EU, whereby the EMA avails itself of the network of national MSs authorities to effectively perform pharmacovigilance.

The decentralized procedure was (and still is) based on the principle of mutual recognition of national authorizations between MSs as elaborated in the 1980s. While it was originally widely adopted for the majority of non-biotech new medicines, its use for innovative products is progressively diminishing. The procedure allows for a national marketing authorization holder to extend the validity of his authorization to one or more selected MSs markets. Under this procedure the EMA functions as an arbitrator in case a MS refuses to recognize the validity of an applicant’s authorization. The main committee involved is the Coordination Group for Mutual Recognition and Decentralised Procedure – Human (CMDh) created in 2005 to mediate disagreements between MSs. If conciliatory attempts

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20 A phenomenon that is increasing through time given the greater reliance on the centralized procedure that the EU pharmaceutical approval system is progressively showing, as suggested below.

21 A third route exists for purely national marketing authorization, where the product will be marketed in one MS only.


24 Note that the Commission never departs from EMA’s opinions.


26 Sauer, supra note 10.

fail, the matter is referred to the CHMP for arbitration (the decision is then enforced by the Commission).\textsuperscript{28}

The history of the creation of the EMA is therefore eminently supranational. At the time the first EU legislation was adopted in the field, almost no MSs had in place an autonomous legal framework for the regulation of medicines. The parallel development of national authorities and EU legislation in the field was a key factor in facilitating harmonization of both rules and decision-making.\textsuperscript{29} As we shall stress in the following parts of the chapter, an ever stronger move towards centralization of procedures suggests that the EU can be considered a highly integrated market in the pharmaceutical field, and that its legislation is \textit{de facto} domestic in nature.

The regulatory system of pharmaceutical products safety was extensively revisited in 2001 (and regularly amended ever since), being subject to a significant codification process.\textsuperscript{30} That reform did not substantially modify the peculiar feature of the EU pharmaceutical regulation model, the coexistence of two procedures.\textsuperscript{31} As already suggested though, there has been a trend towards greater reliance on the centralized procedure, reshaping the EU regulatory model in a centralized fashion,\textsuperscript{32} thus reinforcing the decision-making power of the CHMP. Although the committee's function is formally purely advisory, its decisions are in practice always conclusive, as there has not been a case where the Commission has departed from the committee's advice in the formal decision-making process.

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\textsuperscript{29} Feldschreiber, ‘The Structure and Function of Medicines Regulation in Europe’, in Feldschreiber (ed.), \textit{supra} note 18, at 3.


\textsuperscript{31} The regime was introduced by Council Directive 65/65/EEC, OJ 1965 L 22/369, and subsequent amendments. See Rizzi, ‘Regulating Risks in Pharmaceutical Law: the Need of an Optimal Interplay between Product Safety and Product Liability’, 1 \textit{Opinio Juris in Comparatione} (2011) 25, at 6 note 17, when introduced, Directive 65/65/EEC called for the introduction of national authorization systems, and reforms to the mutual recognition procedures have slowly but gradually been introduced since then, for example under Directive 87/22/EEC, which required that applications for high technology products had to be referred to the CPMP for an opinion before a (national) marketing authorization could be granted. The centralized procedure introduced by Regulation 2309/93/EEC was effectively established on a trial basis, restricted to certain categories of products, which have been significantly expanded over time. Whereas some authors suggest that the system is outdated and about to be abandoned altogether, see Hodges, \textit{supra} note 4, at 40, others suggest that it is still of great importance and should be taken as a model for an international marketing approval procedure: see Purnhagen, ‘The Challenge of Globalisation in Pharmaceutical Law: Is an International Drug Approval System Modeled after the European System Worth Considering?’, 63 \textit{Food and Drug Law Journal} (2008) 623, at 644-645.

\textsuperscript{32} Since the creation of the EMA in the 1990s, the mandatory scope of application of the centralized procedure has been regularly expanded. It is now regulated by the Annex to Council Regulation 726/2004/EC, \textit{supra} note 23. The procedure is optional for other products, but progressively preferred for the reasons explained below in the text.
Among the factors that demonstrate this trend towards centralization, we shall mention on the one hand the greater coherence of such a model in the context of a European single market, and on the other hand the fact that the operational history of the mutual recognition system has proven itself to be less than satisfactory. It has shown to produce inefficiencies and anomalies in the delivery of safety. The reasons that progressively led (and are still leading) towards a preference of the centralized procedure over the decentralized one are manyfold. First, the two procedures differ in their wordings insofar as they regulate the risk-benefit assessment that leads to marketing approval. The major factor introducing an element of uncertainty is the definition of risk as provided by Article 28 of Directive 2001/83/EC. According to this provision, risks related to the use of medicinal products are: ‘any risk relating to the quality, safety or efficacy of the medicinal product as regards the patients' health or public health; any risk or undesirable effects on the environment’. According to the subsequent Article 28/a, the risk-benefit balance consists of: ‘an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks as defined in point 28’. A risk is, therefore, ‘any risk’. A study conducted in 2010 among EMA regulators has shown that there is no clear understanding of what a ‘risk’ is under the current regulatory framework for the EU pharmaceutical market. And here is the major argument contra to the decentralized procedure. Since conceptions of risk vary considerably within a single regulatory authority, the degree of variation is consistently increased by involving multiple regulatory authorities.

The EMA was therefore born as a networking agency, with explicit centralized powers only for a limited number of cases, but because of the operational failure of the decentralized model, it has acquired a significantly more centralizing position. We argue that this creates a strong domestic framework (the EU) which is however vulnerable when permeated from the outside, for the very reasons that suggested a shift from decentralized to centralized procedures within the EU.

33 The need for a more consistent use of the centralized procedure is stressed by Peter Feldschreiber, arguing that the decentralized procedure does not seem to have been achieving its functional scope of facilitating pharmaceutical distribution in the EU market, and has rather created confusion, see Feldschreiber, supra note 17, at 103-111.
34 The lack of clarity regarding a key notion such as ‘risk’ in the regulatory process that leads to market approval suggests that the CHMP's de facto decision-making power is in fact a policy-making power, as the regulation's vagueness leaves room for substantial discretion on the part of the decision-makers.
35 Phillips, ‘EMA Risk-Benefit Project’ (presentation at the British Institute of International and Comparative Law, 29 September 2010), pointing out how among EMA regulators 51 different definitions of ‘risk’ were collected.
4. An International Conference or a Pure Negotiating Platform?

Whereas the European regulation for pharmaceutical approval is situated within a precise legal framework, at an international level the situation is substantially different, and very much dependent on negotiating processes rather than clear legal regulations, notwithstanding the ever wider transnationalization of production and testing. To briefly account for the dimension of the phenomenon let us consider what is suggested by the EU aggregate figures. Reports published by the EMA in December 2013 provide interesting overviews of the distribution and number of patients, investigator sites and pivotal clinical trials included in Marketing Authorization Applications (MAA) submitted to the EMA during a period spanning January 2005 to December 2011. The data presented shows that 62% of the overall patient population in pivotal clinical trials submitted to the EMA during the relevant period were from non-EU countries, comprising 37.3% from the ROW region (Rest of the World, comprising Africa, Middle East/Asia/Pacific, Australia/New Zealand, Central/South America, CIS, Eastern Europe non-EU), and 31.5% from North America (US and Canada). The number of patients recruited in the EEA is substantially decreasing, and the major contributors are Finland, Germany and Poland. In contrast, the number of patients recruited in the ROW area, primarily middle and low income countries, is proportionally growing. In this case the major contributors are China, Costa Rica, Philippines, Japan, Brazil, Russia Thailand and South Africa (with a range of 120 to over 200 patients recruited per pivotal clinical trial per country in MAAs submitted to the EMA in the relevant period). The overall trend as regards clinical trial site increases in ROW countries (and especially developing countries) is substantially proportionate to that of patients. A further element of interest is the number of patients per site as registered in submitted clinical trials reports to the EMA for MAA. The average for the ROW area is significantly higher than in the other regions. The EU/EEA/EFTA registers 13 patients per site, North America 10, while the

36 The data is extremely partial as, first, not all products for the considered period are included, and secondly, most trials are excluded as not published and/or not registered. See the full report, EMA, Clinical Trials Submitted in Marketing Authorization to Applications to EMA: Overview of Patients recruitment and the Geographical Location of Investigator Site, Doc. Ref. EMA/INS/GCP/676319/2012, 11 December 2013, available at http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/12/WC500016819.pdf (last accessed 1 October 2014).
37 Ibid., at 9, Table 2.
38 Ibid., at 22, Figure 12.
39 Ibid., at 23, Figure 13.
41 The number is inflated by the higher average number of patients per site in the new European countries (16 per site) compared to older western European countries.
ROW averages 17 (the peak being Africa with 23, followed by Central/South America with 19).42 These rates are particularly significant because of structural difficulties in quality control by investigators in developing country sites.43

We suggested above the existence of a dichotomy between the domestically designed EU regulatory framework and the role of the EU in addressing the transnational dimension of regulatory processes. Since 1989, regulators and the pharmaceutical industry began to find a common interest in attempting to eliminate unnecessary delays in the global development and distribution of new treatments, and more generally in harmonizing the requirements for drug approval at a transnational level, an initiative consistent with the global nature of the pharmaceutical market. The mission of the ICH is accordingly to make recommendations towards achieving greater harmonization in the interpretation and application of technical guidelines and requirements for pharmaceutical product registration.44

The ICH is organized as a hybrid public/private transnational regulatory network; its Steering Committee (SC) is the main body, which can issue legally nonbinding guidelines for its members.45 Decision-making is structured as a negotiation process among the members of the committee, the composition of which is worth recalling: EMA (together with a representative from the Commission), the United States Federal Drug Administration (FDA), the Japanese Ministry of Health, the European Federation of Pharmaceutical Industries and Associations (EFPIA), the Japan Pharmaceutical Manufacturers Association (JPMA), and the PhRMA (Pharmaceutical Research and Manufacturers of America).46

The harmonization activity of the ICH can take four different procedural shapes: the development of a new guideline (Formal ICH Procedure), the creation of questions and answers to assist the implementation of a new guideline (the Q&A Procedure), the revision or modification of existing guidelines (the Revision Procedure), and the addition of standards to existing guidelines and recommendations (the Maintenance Procedure).47 The output of ICH

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42 EMA, supra note 36, at 21, Figure 11.
43 Major concerns comprise (1) structural deficiencies in data control quality, (2) divergences in therapeutic culture, (3) ethical misconduct with scientific implications, and (4) issues related to patient recruitment, treatment-naïvety, and genetic aspects of treatments' success or failure.
45 The nature of those guidelines is rather controversial. It has been argued that they possess a de facto binding effect, the major example being that the E6 ICH guidelines on GCP have been largely copied in the draft of Directive 2001/20/EC on GCP, as noted by S. Krophil, Risk Regulation in the Single Market (2008), at 84 and Purnhagen, supra note 31, at 638. However, how these guidelines are implemented, not only in the EU but in all ICH constituents is quite problematic, as will be discussed below.
46 These are associations representing R&D pharmaceutical industry, therefore representing companies engaged in the development of new drugs; the industry in general is not included.
work is translated into domestic regulatory frameworks through policy documents that escape the normal processes of adoption.\footnote{See Part 4 below.}

Analysing a decade of work in the year 2000, the ICH announced that it has been ‘successful in achieving harmonisation, initially of technical guidelines and more recently on format and content of registration applications’.\footnote{ICH SC, \textit{The Future of ICH – Revised 2000} (Statement on the occasion of the Fifth International Conference on Harmonisation, 9 November 2000), available at http://www.ifpma.org.ichI.html (last accessed 1 March 2015).} Topics discussed by the forum have ranged over the entire terrain of drug testing, from \textit{pharmacokinetics} to packaging requirements. After 20 years, ICH celebrated the achievement of significant steps forward in the achievement of common procedures and harmonized marketing application forms.\footnote{ICH, \textit{The Value and Benefits of ICH to Drug Regulatory Authorities – Advancing Harmonization for Better Health}, available at http://www.ich.org/fileadmin/Public_Web_Site/News_room/C_Publications/ICH_20_anniversary_Value_Benefits_of_ICH_for_Regulators.pdf (last accessed 1 March 2015).} Overall, activity in the second decade has been less frenetic and slowing down, and only a few guidelines and standards are in various stages of the ICH process at this time.\footnote{At this very moment, only one is undergoing a process of open consultation, and four are under Q&A procedure: see http://www.ich.org/products/open-consultation.html (last accessed 1 March 2015).} Whereas consensus was reached quickly in a series of non-controversial areas,\footnote{Such as basic guidelines on drug quality standards, necessary toxicity tests, and expectations for good clinical practice. A full account is available at http://www.ich.org/products/guidelines.html (last accessed 1 October 2014).} others are proving much more difficult to harmonize. And on this observation it is necessary to raise some critiques.

First, the composition of the decision-making body raises an immediate problem in terms of legitimacy: the negotiation process excludes representatives of patients, while providing for strong inclusion of representatives of the industry (international and regional representations). As it has been appropriately argued, ‘the pharmaceutical industry is involved in the harmonization process right from the beginning and is able to influence the ICH directly from its heart as a member of its main working unit’.\footnote{See supra note 31, at 638-639.}

When ICH negotiations are successful in finding consensus for the adoption of guidelines, local implementation shows significant variations, thus bringing into question the effectiveness of their harmonization potential. For example, the GCP guidelines as outlined by ICH\footnote{ICH, \textit{Tripartite Harmonized Guidelines – Guideline for Good Clinical Practice E6} (1996), available at http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html (last accessed 1 October 2014).} have been fully implemented in the EU,\footnote{Overall, pharmaceutical industry representatives have been able to influence the ICH directly from its heart as a member of its main working unit.} including the parallel Good Manufacturing

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\textsuperscript{48} See Part 4 below.  
\textsuperscript{51} At this very moment, only one is undergoing a process of open consultation, and four are under Q&A procedure: see http://www.ich.org/products/open-consultation.html (last accessed 1 March 2015).  
\textsuperscript{52} Such as basic guidelines on drug quality standards, necessary toxicity tests, and expectations for good clinical practice. A full account is available at http://www.ich.org/products/guidelines.html (last accessed 1 October 2014).  
\textsuperscript{53} Purnhagen, supra note 31, at 638-639.  
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Practice (GMP) guidelines, whereas the two issues are considered separate and are independently regulated in the US.\textsuperscript{56} The GCP guidelines, however, were intended to integrate the two aspects, as ‘the authors of this clinical guideline had an excellent appreciation for the ramifications of inadequate manufacturing or packaging on the clinical program’.\textsuperscript{57}

In a global environment in which harmonization of regulatory procedure is struggling to overcome resistance from competing regulatory styles, a transnational regulatory practice is well underway. The ability of the EU to have an impact on the negotiations leading to the adoption of harmonized guidelines has implications for the quality of its internal regulatory framework, going beyond the major focus of this part of the book – whether informal negotiating processes would give the EU more leeway to transnationally expand the scope of its own policies.

5. The Transnational Way: Negotiation over Deliberation

How are ICH guidelines adopted and what roles are played by the actors involved? Let us first have a look at two excerpts from essential guidelines as adopted by ICH and subsequently implemented in the regulatory frameworks of state participants.

ICH guidelines E6 on GCP:

Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s)… A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB).\textsuperscript{58}

ICH guideline E9 on Statistical Principles for Clinical Trials SPCT:\textsuperscript{59}

\textsuperscript{55} Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ 2001 L 121/34.

\textsuperscript{56} See the FDA’s guide to regulations on GCPs, available at http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090259.htm; and separately its guide to regulations on GMPs, available at http://www.fda.gov/Food/GuidanceComplianceRegulatoryInformation/CurrentGoodManufacturingPractices CGMPs/ucm110877.htm (both last accessed 1 October 2014).

\textsuperscript{57} Simmons and Bernstein, ‘Navigating Differences between FDA and EMA for Regulatory Compliance During Drug Development’, \textit{BioPharm International} (2006), at 2; see also ICH, \textit{supra} at note 44, section 5.14.

\textsuperscript{58} ICH, \textit{supra} note 54, at 9.

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The focus of this guidance is on statistical principles. It does not address the use of specific statistical procedures or methods. Specific procedural steps to ensure that principles are implemented properly are the responsibility of the sponsor. Integration of data across clinical trials is discussed, but is not a primary focus of this guidance.60

These guidelines are both very complex documents, technically and procedurally specific, that however provide no firm guidance on the interpretation of data and risk-benefit parameters.61 On the substance of data interpretation, the terrain where experience, funding and therapeutic cultures play crucial roles, investigators enjoy a very wide margin of appreciation. It is interesting for the purposes of our study to focus on the mechanisms of production of guidelines such as the ICH E6 and E9. We contend that far from being a simple set of minimum technical standards, these rules are rather the clear expression of a trade-oriented attitude, where rapid access to market and free flow of products are the fundamental value choices, overriding health protection – notwithstanding strong commitments in the founding ICH documents62 – to the extent that the key question for observers is ‘who makes the fundamental value choices?’

We have already outlined the structure of the ICH, which consists of representatives of the EU, Japan and US regulatory authorities and regional representatives of the pharmaceutical industry, focusing on the harmonization of technical requirements for drug approval.63 The decision-making process for the adoption of technical guidelines is based on negotiation among all these members. In addition to the six original members, three ‘observers’ participate in the ICH.64 The role of this group of non-voting members is to foster communication between countries that are not organized through the ICH and those that are. The current observers are the WHO (which plays a strong role in connecting ICH and non-ICH countries for the purpose of ensuring comparable minimum standards, circulating ICH

56 Selected principles on data gathering and monitoring are spelled out in other guidelines, but they tend to be extremely sector specific, and not quite oriented at providing general principles of good conduct.
57 The guidelines are deferential to the autonomy of investigators in this matter. It is interesting to note how in other fields, the idea of risk assessment is narrowly defined instead of broadly suggested, such as in the case of nuclear and radioactive materials, where the risk/benefit assessment is stroked down through a precise equation, Council Directive 2013/59/EURATOM laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, OJ 2014 L13/1, at 137 ff.
guideline drafts around non-ICH – especially developing – countries for comment and criticism), the European Free Trade Association (EFTA), and Canada, represented by Health Canada.

The main ICH decision-making body, the SC, is supported by ICH Coordinators and the ICH Secretariat. As the main working unit of the ICH, the SC not only determines procedures and policies for the ICH and selects topics for harmonization, but also monitors the progress of all harmonization activities. The SC consists of 15 members (the six voting members – each having double representatives – plus the observers described above), with an additional seat provided for a non-voting member of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). The SC operates directly from the IFPMA office in Geneva.

In developing harmonized guidelines (the Formal ICH Procedure), the ICH follows a five-step consultative mechanism. The process is triggered by one of the members or non-voting observers, which presents a ‘Concept Paper’ on the issue at stake to the SC. Once the SC has endorsed the Concept Paper, an Expert Working Group (EWG) drafts a preliminary guideline based on the Concept Paper’s desired goals. After the preliminary guideline has been approved by the SC, it undergoes regulatory consultation processes in the three regions (US, EU, Japan). The key actors at this stage become the regional agencies responsible for the consultation process. As for the EU, the EMA follows its Procedure for Guidelines and provides for a public consultation mechanism. Comments can however also be submitted directly to the ICH, and the WHO circulates the draft guidelines among its members for comments and observations. Commenting is therefore open to anyone from any country interested in taking part in the discussion. The results of the consultations are sent back to the ICH EWG, which elaborates, on the basis of the received comments and observations, an amended draft guideline to be adopted by the SC as a harmonized ICH guideline. While the commenting procedure is conceived as open and inclusive, the internal deliberative mechanisms are exclusive and scarcely transparent, as the proceedings of the SC and the negotiation processes are not published: actual decision-making is left to the internal

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65 All decisions, both in the Steering Committee and in the subordinate working groups, are taken by way of consensus. The five steps of the Formal ICH Procedure are: 1) Consensus building – Technical document; 2) a. Six-party consensus on technical document – b. Draft guideline adopted by ICH regulators; 3) Regional regulatory consultation and discussion; 4) Adoption of ICH harmonized tripartite guideline; 5) Implementation.


mechanisms within the SC, and the lack of access to the SC’s internal proceedings does not allow for a full appreciation or evaluation of the fate of regional consulting results.

The final stage of the five-step Formal ICH Procedure, implementation, is in the hands of the regional agencies, which adopt ICH guidelines for the conduct of internal marketing approval procedures (within the legal framework governing the margins of autonomy of agencies for their rule-making activity, but outside the rule-making mechanisms domestically in place68). While ICH guidelines are accepted as generally legally non-binding, it is arguable that they can be considered de facto binding69 – despite their origin in open negotiations with industry – due to the nature and extent of their use at a domestic level.70 The de facto binding role of ICH guidelines is strikingly suggested by the heavy reliance on these guidelines by national lawmakers designing domestic and regional legislation.

The majority of ICH guidelines do not actually end up being adopted as formal acts of law: they instead remain in the domestic legal framework as policy documents (for example, administrative updates of the existing regulatory system) or instruments of ‘governance’ (which are not strictly speaking legal).71 But when agencies, for example, interpret national pharmaceutical law, they consult ICH guidelines and interpret the respective national rules and procedures in their light. The domestic impact of such guidelines can therefore be dramatic in light of the dimensions of the global clinical trials phenomenon briefly suggested in the previous section.

To summarize at this point, industry and regulators have found their interests converging over the last two decades, with a mutual desire to reduce the use of ‘human, animal and material resources’ as they work to ‘eliminate unnecessary delay in the global development and registration of new drugs’.72 The opportunity to cut costs and draw from large pools of potential patients is a potent driver for globalizing pre-marketing procedures.

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68 In the example of the GCP, the guideline was adopted by the FDA and published in the Federal Register, 9 May 1997, Vol. 62, No. 90, p. 25691-25709; and by the EMA in July 1996, issued as CPMP/ICH/135/95/Step 5 – subsequently translated (as a consolidated administrative practice) into Directive 2005/28/EC laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products, OJ 2005 L 91/13. Whereas in both cases the preliminary guideline underwent the comment consultation procedures, the final outcome is the result of a further negotiation which is not accounted for as the proceedings are exclusive and not accessible.


70 See Purnhagen, supra note 31; S. Kraphol, supra note 45, at 86 et seq.


Criticisms have long being levied against the EMA for taking too long to review and approve drugs. The opportunity to concretize market pressures into a set of regulatory guidelines represents a way for Western agencies to lessen their regulatory burden, and for the industry to substantially cut costs and delays in new products approvals. The protection of health and safety appears to be a subsidiary focus, both in the structure and in the stated goals of the venture. The answer to the question ‘who makes the fundamental value choices?’ finds its answer in a negotiation process between industry and regulators, who act within broad legislative frameworks leaving them ample margins of manoeuvre – originally conceived for internal mechanisms and therefore scarcely equipped for transnational permeations.

5. What kind of Governance and What Role for the EU?

Describing which type of governance model (among those suggested and analysed in a quite florid literature) is in place in the pharmaceutical system is a rather difficult endeavour. This section proposes an interpretation that underlines the dangers of the dichotomies referred to in the introduction.

Part 2 of this chapter briefly showed how advisory committees have over time gained power going far beyond simple consultancy and becoming real policy-makers. One of the most comprehensive accounts of the evolution of administrative law in this sense has been

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74 A goal clearly stated by the ICH itself: ‘Regulatory harmonisation offers many direct benefits to both regulatory authorities and the pharmaceutical industry with beneficial impact for the protection of public health. Key benefits include: preventing duplication of clinical trials in humans and minimising the use of animal testing without compromising safety and effectiveness; streamlining the regulatory assessment process for new drug applications; and reducing the development times and resources for drug development’: ICH, Vision, available at http://www.ich.org/about/vision.html (last accessed 1 October 2014).
75 A statement reinforced by the marginal role played by stakeholders outside the restricted ‘regulator-industry’ sphere.
76 Reaching clear conclusions on the actual role and power exercised by each agent in informal international bodies such as the ICH is a rather laborious and potentially frustrating task. Depending on one’s standpoint, the outcome of the analysis can take very different directions. See, for example, in this book the chapter of Antonio Marcacci compared to the one by Wouters and Odermatt. Whereas the first concludes that there is indeed a greater role for Europe to be played in the financial regulatory arena (see ‘Conclusions’), the latters point out that so far Europe has not lived up to its international ambitions in the same area (see ‘2. Why Financial Regulation is Unique’). While it can be argued that Marcacci’s conclusion is prospective whereas Wouters and Odermatt are being descriptive, nevertheless it appears that a measure of uncertainty casts its shadows over the exact modus operandi of transnational informal regulatory bodies.
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provided by Karl-Heinz Ladeur, who depicts thoroughly how this process of power attraction by administrators is an inherent trait of administrative law since its very origins. In this interpretation, such a process is natural and somehow finds its balance in terms of legitimacy through experience, insofar as administrative law is much more the result of administrative experimentation (and subsequent judicialization) than the output of a legislative mechanism. To consider administrative law as a self-generating endeavour, only at a subsequent stage stabilized by courts or the legislators, allows for an interpretation that focuses on the societal dynamics that lead the evolutionary process of norm self-generation.\(^\text{79}\)

In this regard, societal dynamics are described as moving from the ‘society of individuals’ intimately linked with a form of administrative law based upon individual decisions, a stage that coincides in the language of statecraft with the age of the ‘state-nation’.\(^\text{80}\) The following stage runs in parallel with the move to the ‘nation-state’, and as such is defined as the ‘society of organizations’, where individual decisions give way to more collective concerns such as planning laws and forms of welfare state. Subsequently, as the state has moved to its most recent evolution, referred to as the ‘market state’, societal dynamics have evolved to the current ‘network society’, which requires new administrative forms and procedures for decision-making.\(^\text{81}\) The core idea of Ladeur’s theory is that ‘the globalization process does not invade a stable domestic administrative… legal system from outside, but [is] also a consequence of an evolutionary process that disrupts the legal system from within.’\(^\text{82}\)

According to this idea, the move from domestic to transnational is a natural process which is consistent with national experiences, as it is considered to be a consequence of the societal dynamics that led to the kind of global networking of which the ICH is a perfect example. We contend that a general objection can be raised to this idea of the evolution of administrative law, specifically focusing on our field of interest. If it is true that regulators and regulated have always discussed the terms of the rules, the international dimension here introduces a rather new and different phenomenon. The regulators and the industry are participating as peers in the elaboration of ICH guidelines – guidelines that contribute themselves to the shaping and implementation of national or regional norms (for instance, the


\(^{79}\) Ibid., at 5 et seq.

\(^{80}\) We use here the evolution of statecraft as described extensively by Bobbitt as moving from the ‘state-nation’ that provided for the recognition and protection of individual rights and liberties, to the ‘nation-state’ that focused on collective goals through the provision of welfare to the nation, to the current ‘market-state’ where the state is now inhabiting a less pervasive and more permissive role in maximising economic opportunities. See P. Bobbitt, The Shield of Achilles (2003), Book I Parts II and III.

\(^{81}\) Ladeur, supra note 78, at 24 et seq.

\(^{82}\) Ibid., at 6.
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GCP or SPCT guidelines). Such a situation is hardly comparable to general administrative law as traditionally conceived in Western democratic nation-states. To exclusively describe the contemporary state of administrative law as reflecting the natural course of societal dynamics runs the risk, from a legal standpoint, of underestimating the profoundly different context in which the ‘networks’ are operating (uncharted transnational territories as opposed to the ‘organizations’ (previously operating in national or regional constitutionally and legally defined domains). Bringing the focus back to the question ‘what role for the EU?’; the risk here is to misperceive the nature of the shift – if transnational negotiation is the natural evolution of administrative law, the critical analysis of the role of the agents gets diluted in the descriptive concept of ‘administrative experimentalism’.

A different line of thinking has elaborated the idea of ‘experimentalist new governance’. The basic premise of this theory grounds the legitimacy of regulatory models in an alternative way to traditional representative democratic circuits, through the concept of ‘deliberation’. A deliberative process is a ‘soft process’, including all the major stakeholders of a given field, in which governance is achieved in functional rather than traditional structural or institutional terms. This soft process of consultation is accredited as legitimate by standards of ‘alternative deliberative democracy’. Typically, the deliberative democratic process is described to be ‘informal’, as the socialization of stakeholders involved in the decision process (something referred to as ‘epistemic communities’ – for instance the comitology mechanisms of the EU) does not necessarily descend directly from legislative acts. It is also considered to be ‘multi-level’, as it involves actors ranging from national administrations to supranational bodies without establishing a hierarchy between them, blurring the distinction between centralized and decentralized decision-making and instead favouring networks of diverse decision-makers. Moreover, to overcome the most immediate criticism identifiable in the departure from representative democracy's classic forms of

83 For a complete account of traditional Western concepts of administrative regulation see above all A. Ogus, Regulation: Legal Form and Economic Theory (2004).
84 Consider the example of the ICH: no administrative agency in the US, nor in the EU, would ever be constructed in a way that a) involves only one-sided stakeholders together with the regulators; and b) lacks clear procedural rules on transparency, participation and access to documents. But its informal nature, and the context in which it operates (the uncharted transnational territories), allow for greater flexibility. Arguably, the ICH exists because at a transnational level negotiations can happen in a much less scrutinized fashion.
85 See the essential contribution of Sabel and Zeitlin, supra note 77, at 271-327.
86 Ibid., at 274.
87 Ibid., at 273.
accountability and legitimacy, the deliberative process is essentially inspired by principles of transparency, access, and participation.  

It has been argued that pharmaceutical regulation falls within the scope of ‘experimentalist new governance’ because the EMA is built in a way that includes all stakeholders involved in the pharmaceutical market, recognizing a central role for scientific committees assisted by various actors, such as representatives of patients, physicians, and the government.  

Decisions within the agency bodies are taken by way of consensus through deliberation as much as possible, voting being the last resort option. As intriguing as this suggestion may be, we posit that it falls short of addressing properly the issue of transparency, which per se undermines the conclusion. If the potential for EU domestic regulatory mechanisms to fall within the scope of an experimentalist mode of governance can be argued for, such hypothesis does not fully confront the transnational dimension and its implications. The descriptions above of the ICH mechanisms, and of the substantial impact of its guidelines, strongly point to the necessity of moving the reflection to a transnational level. The rule-making mechanism here is structurally non-inclusive, and modelled around goals set by a restricted number of stakeholders. We have argued that the basic value choice is trade-oriented, and that no real counterpart is involved in the negotiation process. The fundamental guidelines on GCP and SPCT are good examples of procedural regulations, leaving a wide margin of appreciation in the substance of the standards, which have been incorporated by agencies supposed to ensure deliberative processes.  

The mechanisms of production and adoption of ICH guidelines raise a question about the fate of the numerous procedural standards conceived at the domestic level to balance the disproportionate margin of discretion the new governance agents benefit from vis à vis traditional rule-makers in representative democratic circuits. The scenario as described throughout this chapter suggests that there is (in the field of pharmaceutical regulation) a tendency to ‘hollow out’ procedural standards when the scene has been set at the transnational ICH level.  

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90 A recent, interesting, and comprehensive discussion can be found in Ehnert, supra note 71.
91 We refer to the Management Board of the EMA, which comprises two representatives of the Commission, two from the Parliament and one per each MS. As of 2004 with Regulation 726/2004/EC, representatives from organisations of patients and doctors were also given seats on the Board alongside scientific experts.
92 There is no real access to information about what participation has been guaranteed in the adoption process of the GCP and SPCT guidelines – the internal ICH documents are not accessible, only the final guidelines. What is striking, on the other hand, is the ultimate literal transplant of said guidelines into domestic regulatory frameworks.
The above discussion on the model of governance in place for the regulation of pharmaceutical products suggests very uneasy answers. While designed and described as an example of ‘new governance’ domestically, as a transnational phenomenon it appears to resemble more a reversed version of the transnational private law (TPR) theory elaborated by Calliess and Zumbasen in *Rough Consensus and Running Code* 94 While the theory proposes an understanding of bottom-up societal regulation of TPR, the pharmaceutical system seems to be organized in a very top-down fashion, whereby the consensus and the running code are reached and infused in the regulatory mechanisms by selected stakeholders and interests. Confronting such a pyramidal system (closed at the top – with access granted exclusively to the final outputs) makes it difficult to give an account of the role that each agent involved is actually able to perform.

The tentative conclusion of this discussion 95 is therefore that the EU is an active participant in the transnational regulatory arena in the field of pharmaceutical products, primarily through its voting membership within the ICH. The impossibility of analysing ICH documents leading to the final adoption of guidelines however invites the following remark. The role of the EU (as of any other ICH agent) is highly dependent on its ‘bargaining power’. Such power being intrinsically variable and dependent on political and economic strength (variable both in time and across the spectrum of negotiated topics), two separate but equally relevant points ought to be raised. First, because of the informal nature of the network, which is subject only to its own internal rules, it is difficult to imagine an internal system of checks and balances presenting strong procedural guarantees. Secondly, and as a consequence, depending on the topic at stake, the EU is either a strong agent – in which case it has the potential to expand the scope of EU policies and vision to a transnational level – or a weak one – which can cause internal policies and legal standards to be lowered to a potentially weaker negotiated level. We suggest in conclusion that a strong potential contribution of the EU to the current ICH system lies in the form of procedural negotiation, pushing for publication of internal proceedings, at least as regards the fate of the regional consultation process – thereby progressing from ‘hollowing out’ to ‘exporting’ procedural standards of transparency.

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94 G. P. Calliess and P. Zumbansen, *Rough Consensus and Running Code – A Theory of Transnational Private Law* (2010). The theory is based on the idea that a Rough Consensus among stakeholders in a given field becomes a Running Code through a pilot phase in which the content of the consensus acts as a proposed standard, followed by a recognition phase in which the standard becomes recommended, and eventually a binding phase where the standard is adopted. The process, being inclusive and non-hierarchical, is eminently bottom-up.

95 Bearing in mind the caveats suggested *supra* at note 76.
6. Transnational Regulation and Product Liability – Prospective Thoughts

This chapter (as others in this book section96) is primarily focused on that special kind of private law identified by Hans-W. Micklitz as ‘regulatory private law’.97 It is however necessary to keep in mind that the output of said regulatory private law (in the form of standards, guidelines and other ‘soft law’ instruments) does not exist in a vacuum. One must resist the temptation to relegate phenomena such as the one we have described here in the somewhat mystical realm of ‘hic est governance’ (a wild card too often joyfully played by lawyers) and ask instead what the legal implications of a transnational ‘soft law’ turn in regulation are. For this reason, the piece now adjusts its focus to a field of traditional private law, and specifically a very ‘European’98 branch of private law: product liability (PL). These brief thoughts on PL rotate around two main concepts, the nature of which is arguably in the process of (or has the potential to) undergo significant adjustments: complementarity and regulatory compliance. We will consider these in turn and, by way of conclusion, suggest an interpretation of the relationship between the external dimension of regulatory private law and the internal potentials of traditional private law.99

The first concept to be addressed is the one of ‘complementarity’.100 At its core, this is a rather simple idea, based on the premise that regulation alone is unfit to achieve the ultimate goal of product safety and efficacy for a variety of factors ranging from risks of ‘capture’101

98 Or tentatively so as divergences persist on key issues such as the notion of defectiveness, see for a discussion Fairgrieve and Howells, ‘Rethinking Product Liability: A Missing Element in the European Commission’s Third Review of the European Product Liability Directive’, 70 Modern Law Review (2007) 962–978. Product specific regimes are also in place, including in the field of pharmaceuticals (for instance in Germany and Spain). Yet, product liability remains one of the first attempts to create a unified regime within a pillar of private law such as the law of torts.
99 A fully fleshed analysis of such an intricate issue is way beyond the scope of this piece. These are, as the section’s title suggests, ‘thoughts’, suggestions the reach of which constitutes the research question of a PhD dissertation currently under completion. They should be read accordingly. As for the current state of pharmaceutical product liability, a fantastic descriptive account can found in R. Goldberg, Medicinal Product Liability and Regulation (2013).
100 F. Cafaggi, Institutional Framework of European Private Law (2006), at 191. The theory of functional complementarity a) on a positive level shows the reciprocal influences of the two techniques, and b) on a normative level calls for a high degree of coordination.
101 For a general definition see A. Ogus, Regulation: Legal Form and Economic Theory (2004), at 57: ‘the ineffectiveness of regulatory agencies in meeting the public interest goals assigned to them could most plausibly be explained by assuming that they had been subverted by pressure, influence, and “bribery” to protect the interests of those who were the subjects of the regulation.’ In the context of transnational
to the limited resources made available to regulatory agencies\textsuperscript{102} for the enforcement or monitoring of the correct implementation of regulatory requirements. More generally, highly technical fields tend to develop at a rate that is unmanageable for regulators.\textsuperscript{103} There is indeed reason to argue for a space of manoeuvre to be left to external actors (external to the regulatory architecture) to complement the efforts of regulators in achieving legislative endgames (in our case, pharmaceutical safety and efficacy\textsuperscript{104}). These factors are of general relevance, in the sense that they apply to regulatory schemes regardless to whether these are domestic or transnational, and therefore the idea of complementarity is not an exclusive feature of transnational phenomena as it attempts to address structural deficiencies of regulation. This argument was restated by the US Supreme Court in 2009\textsuperscript{105} in the case \textit{Wyeth v Levine}.\textsuperscript{106} The Court stroke down the unorthodox application of the doctrine of pre-emption introduced in pharmaceutical litigation by the Food and Drug Administration only 3 years earlier.\textsuperscript{107} Specifically, the Court rejected Wyeth’s argument, according to which tort claims ‘interfere with Congress purpose to entrust an expert agency to make drug labelling decisions that strike a balance between competing objectives’,\textsuperscript{108} stating that such an argument relies on an ‘untenable interpretation’ of congressional intent and an ‘overboard view’ of an agency's power to pre-empt state law.\textsuperscript{109} The conclusive argument being that traditionally, in the American legal system, regulation and product liability form two sides of a mechanism of checks and balances where the latter is there to correct failures of the first.\textsuperscript{110} The presence of collective redress mechanisms, specifically in the form of class actions has been (and

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\textsuperscript{102} See EMA, supra note 36, at 24-27, the rate of inspections of clinical trials sites is extremely low as only 357 sites have been inspected out of 70,291, primarily due to lack of resources.

\textsuperscript{103} The literature on this topic is extremely abundant, for our topic of interest, and related fields of risk regulation, see as a reference S. Jasanoff, \textit{Designs on Nature: Science and Democracy in Europe and the United States} (2007).

\textsuperscript{104} As laid down in Council Directive 2001/83/EC on the Community Code relating to medicinal products for human use, OJ 2001 L 311/67. Note that paragraphs (2) and (3) of the preamble discuss the complex relationship between the safeguard of public health and development of the pharmaceutical industry.

\textsuperscript{105} In this section the US scenario is mentioned several times. The reasons are manifold, ranging from a genuine comparative interest to the observation that EMA and FDA cooperate closely in regulatory processes leading to marketing approval of new pharmaceutical products (both bilaterally and, as discussed above, at the ICH level). There is a further motive shortly suggested infra note 105 – the possible adoption of the TTIP agreement.


\textsuperscript{107} FDA, Requirements on Content and Format of Labelling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (2006).

\textsuperscript{108} \textit{Wyeth vs Levine}, supra note 106, at 1199.

\textsuperscript{109} Ibid.

\textsuperscript{110} Ibid.
remains) the essential tool for the practical achievement of these traditional checks and balances.\textsuperscript{111}

The EU however has traditionally maintained a different approach to redress in case of damages (and generally to correctives of regulatory failures), relying heavily on compensations and indemnification schemes based on insurance and social security systems rather than on tort litigation.\textsuperscript{112} Arguably, this has created a sort of \textit{de facto} pre-emption of product liability litigation. The aggregate statistics on PL litigation in the EEA in a time span of twenty years, collected by the Commission in a series of quinquennial reports from 1995 up to 2011,\textsuperscript{113} confirm that European PL has faced structural obstacles in claiming a primary role in victims’ compensation. It is beyond the scope of this chapter to analyse in depth the vast range of reasons leading to this observation, but it is possible to identify some essential factors. In 2003 Mathias Reimann identified five explanations\textsuperscript{114} uncovering why PL litigation is a major feature of the American legal system while it lags behind in Europe (and in the rest of the world in his analysis). These explanation have to do with institutions (US courts being traditionally more activist than the European ones – and relying on specific features ranging from the role of juries to the exponentially higher damage awards),\textsuperscript{115} procedures (the much higher availability of aggregate litigation in the US makes it extremely easier for plaintiffs to prove the existence of both defect and causation, not to mention the availability of stronger discovery rules),\textsuperscript{116} the legal profession (European lawyers have a much lesser tendency to specialize than their US colleagues),\textsuperscript{117} the role of insurance (first party insurance is still the European prime method of victims’ compensation, through public or semi-public or private

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\item The most striking example of a dichotomy between the two sides of the Atlantic from the past decade is the case of \textit{Vioxx}. While in the US the prospect of aggregated litigation led to an out of court settlement little short of 5 billion dollars, there is little evidence of litigation in the EU despite a wide diffusion of the product in the internal market – approved through a mutual recognition procedure (see \textit{supra} Part 2). For an interesting perspective suggesting that out of court settlements of that magnitude favour closure of the settlement over consent of the plaintiffs (resulting in reduced compensation) see Erichson and Zipursky, ‘Consent versus Closure’, \textit{96 Cornell Law Review} (2011) 256.
\item As thoroughly explained in an analysis that remains substantially valid over ten years later in Reimann, ‘Liability for defective products at the beginning of the twenty-first century: emergence of a worldwide standard?’, \textit{51 American Journal of Comparative Law} (2003) 751. See brief discussion in the text.
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insurance, and/or no-fault compensation schemes),\textsuperscript{118} and the broader social environment (the levels of publicity that PL law receives in the EU, from media attention to the political debate, are simply incomparable to the US scenario).\textsuperscript{119} A common assumption underlying this divergence between the two sides of the Atlantic is that the EU is politically committed to achieving product safety through public (or publicly administered) regulatory requirements whereas the US rely more substantially on private litigation.\textsuperscript{120}

However, a closer look at the recalled Commission Reports on the application of the PL Directive in the EEA shows a progressive increase in the volume of litigation and out of court settlements.\textsuperscript{121} The reasons identified are an increase in ‘consumer awareness, better organization of consumer groups or improved means of accessing information’.\textsuperscript{122} While these explanations certainly play a significant role, we submit that there is more. Recent cases have put into question the reliability of the well-established European regulatory architecture for pharmaceuticals.\textsuperscript{123} Aggressive litigation in France on the widely diffused medicine Mediator\textsuperscript{124} has led to a withdrawal of the product from the market, signifying the existence of renewed scope for a complementary approach. A strong signal in this direction comes from the very recent CJEU decision in the Novo Nordisk Pharma case.\textsuperscript{125} The court has held that national product-specific legislations imposing stricter liability mechanisms than the one provided by the PL Directive are not affected by the Directive’s regime under Article 13.\textsuperscript{126} While this was always the goal of the provision, the novelty consists of the fact that amendments posterior to the adoption of the Directive’s regime are protected (and not only the legislation existing at the time the Directive was notified). This was of particular importance in the case at hand where the provision placed under the scrutiny of the court was a 2002 amendment to the Arzneimittelgesetz introducing paragraphs 84(2) and 84a.\textsuperscript{127} In

\textsuperscript{118} Ibid., at 822-832. See also Commission Reports, supra note 113.
\textsuperscript{119} Reimann, supra note 112, at 832-835.
\textsuperscript{120} Ibid. at 810; see also C. Hodges, supra note 4; Howells, ‘The Relationship Between Product Liability and Product Safety- Understanding a Necessary Element in European Product Liability Through a Comparison with the US Position’, 39 Washburn Law Journal (2000) 305.
\textsuperscript{123} See the brief description supra Part 2 of this chapter.
\textsuperscript{124} See the latest judgment of a prolonged saga – Tribunal Administratif de Paris, n. 1312345/6 (2014). Civil litigation involving the producer Laboratoire Servier is still pending.
\textsuperscript{125} Case 310/13, Novo Nordisk Pharma GMBH v. S., judgment of of 20 November 2014, not yet published.
\textsuperscript{126} Council Directive 85/374/EEC on the approximation of the laws and administrative provisions of the Member States concerning liability for defective products, OJ 1985 L 210, Art. 13: ‘This Directive shall not affect any rights which an injured person may have according to the rules of the law of contractual or non-contractual liability or a special liability system existing at the moment when this Directive is notified.’
\textsuperscript{127} Arzneimittelgesetz – AMG, supra note 7, the presumption of a causal link referred to in Paragraph 84(2) of the AMG and the right to information under Paragraph 84a of the AMG were inserted in the AMG by the
particular, the adoption of paragraph 84(2) created a presumption that, when the pharmaceutical product administered is generally capable of causing harm, the damage is caused by the product. Paragraph 84a introduced a consumer right to ‘require the manufacturer of a medicinal product to provide him with information on the adverse effects of that product’128 when the facts of the case suggest that the product has caused damage. The court recognizes that the German legislation does not ‘undermine the effectiveness of the system of liability provided for under Directive 85/374’,129 but rather intends to eliminate or reduce the asymmetry of information between the manufacturer and the consumer, helping the latter to prove defectiveness and causation.130 The combination of the two suggested factors represents a powerful means of both consumer protection and judicial monitoring. It appears then that while national courts are being increasingly solicited as recognized by the Commission’s reports, the CJEU, in sanctioning the strong German legislation, is endorsing a complementary approach, questioning the above mentioned traditional quasi-exclusive reliance on regulatory requirements.

What is argued here is that in the presence of the problematic transnational element described above, the scope for complementarity widens as the ‘non-measurable negotiations’ introduce exogenous elements into a regulatory scheme very much designed within and for the EU131 – if complementarity is first conceived domestically, it is called for a fortiori transnationally. On this premise it is possible to make a suggestion on ‘regulatory compliance’, and conclude with a remark on the interactions between ‘regulatory’ and ‘traditional’ private law.

In the realm of PL, regulatory compliance is a complex issue, the intricacies of which are not to be debated here. Suffices to say that it is not a defence for manufacturers as the only defence explicitly mentioning regulatory requirements is the one provided by Article 7(d) of the PL Directive132 – on the basis of which a producer will be shielded from liability where ‘the defect is due to compliance of the product with mandatory regulations issued by public authorities’. Short of that, compliance with regulatory requirements is not an automatic defence. It does provide ‘strong evidence’ that the product is not defective without freeing a

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128 Case 310/13, supra note 125, para. 29.
129 Ibid., para. 30.
130 Ibid., para. 32.
131 See again the discussion supra Part 2, describing the EU regulatory architecture as strongly EU-centered (with an ever growing move from decentralized to centralized procedures).
In other words the correct observance of a given standard, in PL litigation, is strong but not conclusive evidence of a product’s safety. This is confirmed by the wording of Article 25 of Directive 2001/83/EC whereby a marketing authorization ‘shall not affect the civil and criminal liability of the manufacturer and, where applicable, of the marketing authorization holder’.134

It is in this space that courts can exercise a meaningful form of complementarity, by questioning the actual value of compliance to standards the adoption of which is now beyond the safe heavens of EU’s procedural safeguards.135 While the general tendency in product litigation is to highly rely on regulatory decisions (the ‘deferent’ approach),136 the PL legislation allows for courts to take a ‘hard look’137 into the regulatory process that leads to a product approval. The goal being to question whether formal compliance can be considered substantially satisfactory in light of the legislative goals of safety and efficacy. If not, an adverse judgment would question the validity and legitimacy of requirements considered inadequate by European courts.

7. Conclusion

A concluding remark calls for the observation of two separate but (actually and potentially) mutually influential elements. Externally, the ‘regulatory private law’ through

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133 The issue of regulatory compliance in product liability litigation involving medicinal products has been recently discussed by Goldberg R., Medicinal Product Liability and Regulation (2013), at 136-161.
135 See Mendes, supra note 95. Furthermore, it must be noted that the chapter is willingly staying clear of the debate surrounding the possible future adoption of a Transatlantic Trade and Investment Partnership (TTIP) between the US and the EU. At the moment, with limited information available on the contents of the treaty to be, a sensible observation to make is that, in the event of an adoption, the EU should carefully get ready for a stronger role of litigation in complementing regulation. We have discussed how this is common practice in the US (in the field of pharmaceuticals), and Europe may need to adapt to that system of checks and balances. This is because the nature of TTIP as a ‘living agreement’, whereby regulators’ reciprocal commitments can become legally binding through sectoral annexes, has the potential to result in regulatory processes progressively detaching from the previously agreed policy choices as sharply suggested by A. Alemanno, A Reality Check of TTIP – Beyond Popular Account (2014), available at http://www.euractiv.com/sections/trade-industry/reality-check-ttip-beyond-popular-account-301443 (last accessed March 2015). See for an in-depth discussion Alemanno, ‘The Transatlantic Trade and Investment Partnership (TTIP) and Parliamentary Regulatory Cooperation’, European Parliament Policy Report (April 2014). Complementarity on the one hand, and a substance-based approach to regulatory compliance on the other may prove a fortiori necessary was the TTIP to be adopted.
136 The tendency that we call ‘deference’ is one that makes courts ‘reluctant to criticise’ regulatory decision, especially on technical matters such as marketing authorization of pharmaceutical products. A good overview of the phenomenon is provided by Goldberg, supra note 133, at 135-140.
137 The conceptual distinction between the ‘deferent’ approach and the ‘hard look’ doctrine is drawn by S. Jasanoff, Science at the Bar – Law Science and Technology in America (1997). The interesting suggestion she makes, for the purposes of this piece, is that a thorough judicial review of administrative decisions on risk regulation can have a pedagogical effect on regulators – a different way to suggest the similar conclusion drawn here.
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which the EU negotiates safety and efficacy standards seems to be hollowing out EU’s procedural mechanisms – the phenomenon we refer to as ‘non-measurable negotiations’. As suggested above, the EU could perform an important role in ‘exporting’ its internal procedural standards to the ICH scene for the sake of greater transparency and accountability. On the other hand, internal ‘traditional’ fields of private law can perform a review of transnational standards by allowing courts to foster complementarity and make substantial checks on satisfactory compliance to fundamental legislative goals. Concluding on the example used in this chapter, the internal dimension of traditional European PL law could gain an external regulatory function by putting the EU as a transnational negotiator in the position to pressure for the adoption or review of judicially scrutinized standards.