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REGULATING RISKS IN PHARMACEUTICAL LAW: THE NEED OF AN OPTIMAL INTERPLAY BETWEEN PRODUCTS SAFETY AND PRODUCTS LIABILITY

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REGULATING RISKS IN PHARMACEUTICAL LAW:
THE NEED OF AN OPTIMAL INTERPLAY BETWEEN PRODUCTS SAFETY AND PRODUCTS LIABILITY

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Marco Rizzi ♦

Abstract:

The aim of this paper is to call for the need of a theoretical model of pharmaceutical products safety in which the two systems of regulation and liability operate complementarily. The question is why two legal tools that are meant to achieve and protect the same goal (protection of consumers) are shaped in a way that hinders, instead of promoting, a positive interaction between the two. At present we have two separate sets of rules that operate independently: pre-marketing regulation with post-marketing surveillance duties, and ex-post facto liability, linked to the pre-marketing available knowledge. Since the key issue in both regulatory and liability assessments related to pharmaceuticals is the one of "relevant knowledge", we claim that the legal framework should be shaped in the way that better promotes the availability of such a knowledge. In the effort of identifying a global paradigm of pharmaceutical safety (coherent with the global nature of the relevant market), a comparison of the legal frameworks in force in the two major "regional" drug markets (US and EU) is not only necessary, but valuable in order to identify the shortcomings of "local" solutions, and their inconsistencies vis à vis the transnational nature of the issue. The fact that the two scenarios present substantial institutional differences does not hinder such a value. If we consider that the market is globalized at both the stage of production and at the one of distribution, the construction of a global governance of pharmaceutical safety has to confront with legal and institutional diversities.

Key words: pharmaceutical products; product liability; tort law; product safety; consumer safety; regulation; complementarity; regulatory compliance; preemption; harmonisation.

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Introduction

The pharmaceuticals safety regime is beset with fundamental problems which, when globally considered, present a clear and present issue of consumer protection. This is the basic claim that this paper attempts to raise, together with the question: why and how should we attempt to better enhance pharmaceutical's consumers safety in a globalised context?

It is impossible to address the "how" question here. What matters is to raise the issue and make some tentative proposals. As for the "why" is there a need to enhance consumer safety, this paper tries to demonstrate that the globalised nature of the pharmaceutical market imposes to reconsider the shape and functioning of the existing legal framework that is meant to ensure safety. It has been recognised that nowadays the pharmaceutical innovation is handled by a restricted oligopoly of multinational industries[1], but new products are marketed after they undergo clinical trials in different countries obeying different rules and standards[2] (e.g. US, EU, Russia, India, China, Brazil), and they often are the result of combining active ingredients produced, again, in different places. The safety of drugs' consumers shall therefore be understood as a globalised mass-phenomenon, and addressed accordingly. We believe that there is a need to rethink the global governance of pharmaceutical safety both on the regulatory side and on the one of remedies. A fragmentation of solutions is not desirable in a field where it is acknowledged that: 1) the innovators are few, and 2) the issues are globally similar[3].

This paper proposes a comparative study focused on the European Union and the United States. Two questions shall be preliminarily addressed. On the one hand one must ask if the two scenarios are comparable, and, on the other hand, what would be the use or value of such a comparison. We propose a joint answer. Since, as already suggested, we believe that there is a need to seek for the identification of a global paradigm of pharmaceutical safety (consistent with the global nature of the relevant market), a comparison of the legal frameworks in force in the two major "regional" drug markets (US and EU) is not only necessary, but valuable in order to identify the shortcomings of "local" solutions[4], and their inconsistencies vis à vis the transnational nature of the

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[1] O'Donnell J.T., *Drug injury – liability, analysis and prevention*, Lawyers & Judges Publishing Company, Inc., 2001, p. 121 and following; nowadays, the total amount of sales has increased also in export trade. In 2006 they were estimated 29.4 billion Euros, whereby 16.2 billion Euros of it resulted from export trade. Worldwide the total amount of sales was 643 billion U.S. dollars in 2006: see Purnhagen K., *The Challenge of Globalization in Pharmaceutical Law: Is an International Approval System Modelled after the European System Worth Considering?*, 63 Food and Drug Law Journal, 3, 2008, pp 623.

[2] See for example: Communication of the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, *Safe Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector*, Brussels, 10/12/2008.

[3] On the issue see http://www.ich.org/cache/compo/276-254-1.html on the reasons that led to the creation of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

[4] New products are marketed after they undergo clinical trials in different countries obeying different rules and standards (e.g. US, EU, Russia, India, China, Brazil), and they often are the result of combining active ingredients produced, again, in different places. Assuming that under normal circumstances (i.e. local, or, in other words, when confronted with drugs

issue. The fact that the two scenarios present substantial institutional differences does not hinder such a value. As a matter of fact, consumers are damaged in the same way regardless to such differences. If we consider that the market is globalised at both the stage of production and at the one of distribution, the construction of a global governance of pharmaceutical safety has to confront with legal and institutional diversities.

The two main bodies of law to be considered here are safety regulation and products liability. As for the former, substantial differences exist among the two main administrative bodies in charge of it (the Food and Drug Administration and the European Medicines Agency), both on the way they are organised and on the powers they can actually exercise, with inevitable differences among the outcomes of their decisions[5]. Pharmaceutical products lability, on the other hand is still a highly fragmented field. Few has been said on the link between these two bodies of law (in pharmaceutical law), and mostly to acknowledge the absence of such a link.

The aim of this paper is to succinctly depict the level of fragmentation of pharmaceutical law, and thus suggest the need of a theoretical model of pharmaceutical products safety in which the two systems operate complementarily. The question is why two legal tools that are meant to achieve and protect the same goal (protection of consumers) are shaped in a way that hinders, instead of promoting, a positive interaction between the two. There is in our opinion a need to move forward the traditional separation between private and public law tools, by considering the goal in its full empirical dimension, which cannot be confined within the boundaries of one solution or the other. Up to now, the issue of pharmaceutical safety has been approached in a classic manner: using "traditional" legal instruments and making the empirical matter fit into them in a "traditional" way. We therefore have two separate sets of rules that operate independently: pre-marketing regulation with post-marketing surveillance duties, and ex-post facto liability, linked to the pre-marketing available knowledge (development risks or state-of-the-art)[6]. We propose that it is the legal framework that must be shaped around the empirical issue, rather than the contrary. Therefore, since the key issue in both regulatory and liability assessments related to pharmaceuticals is the one of "relevant knowledge", we claim that the legal

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entirely produced and tested within the European or US territory) the systems of safety regulation work (i.e. by providing the best possible level of consumer safety), *quid* when such systems have to face the issue of a global process of production and testing? What happens in practice is that, in order to overcome the problem, the EMEA and the FDA have put in place a network of bilateral agreements with foreign agencies, meant to promote mutual recognition of the various steps that are held in different places obeying different rules. Such a system of bilateral agreements raises questions with respect to the black-letter regulation provided for the European or US market. The international harmonisation of general guide-lines justifies such a practice, however the differences in the substance between the specific regulations that govern the process of production imply different outcomes in terms of safety. The claim is therefore that local regulatory systems fail to address in a satisfying way the issue of the multi-local production of new pharmaceuticals.

[5] See *infra*, and for a general perspective on the matter a good overview can be found in http://biopharminternational.findpharma.com/biopharm/Article/Navigating-Differences-Between-FDA-and-EMEA-for-Re/ArticleStandard/Article/detail/371018

[6] The issue will be discussed in the following paragraphs.

framework should be shaped in the way that better promotes the availability of such a knowledge[7].

In this perspective, an issue that cannot be ignored is the federal preemption of state tort law, a doctrine first spoken in drug litigation in the US in 2006. More specifically, in the preamble to its January 2006 prescription drug labelling rule, the Food and Drug Administration (FDA) asserted that "FDA approval of labelling under the act . . . preempts conflicting or contrary State law"[8]. This approach raises several safety concerns in light of the unavoidable level of scientific uncertainty that inherently characterises a new pharmaceutical. We submit that preemption of tort law weakens the protection of consumers' safety, and we intend to oppose an approach grounded on the theory of "functional complementarity"[9]. This issue is critical, especially in a context, like the US, where tort law has historically played a major regulatory role, balancing trough litigation the numerous shortcomings of regulation[10]. It is worth to underline that there is nothing similar to the doctrine of preemption in the European Union (in the field of drugs' litigation). Regulation and liability are two systems that operate independently (as will be discussed in the proceeding) and regulatory compliance *per se* is not a defence in products liability claims. It must also be recalled that a "preemptive shift" in European drug litigation wouldn't have at all the same effect that it has in the US, as regards consumers' compensation. Contrary to the US, in the EU product liability is a rather minor field in litigation. Consumers are indeed often protected by different private or public legal tools, namely insurance or social security systems[11].

Finally, two issue shall be suggested. First, we believe that there is a need to simplify the legal framework in a field that is deeply globalised[12]. A more conscious use of tort law rules (by definition simpler than specific sectorial regulations) is in our opinion the key in order to achieve this goal. Secondly, a topic that has been barely developed, and that shall be investigated more thoroughly is the one that could be referred to as "pure knowledge loss". By that we mean the knowledge that is dispersed where there is no clear link between the regulatory and the litigation systems, not to mention the knowledge that doesn't even have a chance to rise where regulatory compliance preempts tort law.

This paper is structured as follows. In the first part we will suggest some differences existing between the regulatory and liability regimes of the United States and European Union, the two biggest pharmaceutical markets. Since the major differences are to be found in the liability regimes, the analysis

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7 For a discussion of the concept of "relevant knowledge" see Mildred M., "The development risk defence", in Fairgrieve D., *Products Liability in Comparative Perspective*, Cambridge University Press, 2005.

8 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (effective June 30, 2006) (21 C.F.R. Pts. 201, 314, 601), for a comment see Sharkey C.M., "Preemption by Preamble: Federal Agencies and the Federalization of Tort Law", *De Paul Law Review*, 56:227, 2007.

9 Cafaggi F., *Institutional Framework of European Private Law*, Oxford University Press, 2006, p. 191 and following. The theory of functional complementarity: a) on a positive level it shows the reciprocal influences of the two techniques, and b) on a normative level calls for a high degree of coordination.

10 See for a comprehensive discussion Viscusi W.K., *Regulation Through Litigation*, Brookings Institution Press, 2002.

11 As thoroughly explained by Reimann M., "Liability for detective products at the beginning of the twenty-first century: emergence of a worldwide standard?", *American Journal of Comparative Law*, 2003.

12 This interesting idea is generally discussed in the book of Richard Epstein, *Simple Rules for a Complex World*, Harvard University Press, 1995.

will focus mainly on the products liability rules. In the second part we will then confront with a specific issue: the federal preemption of state tort law in pharmaceutical products liability claims in the United States. In the third part, we will raise some critiques to the existing legal frameworks of pharmaceutical safety.

1. Divergences...

a)...in regulation

A first glance will now be given to the safety regulation regimes. Both scenarios, the US and the EU, seem to be deeply harmonised on the regulatory side. More precisely, in the United States safety regulation is handled by a centralised Agency (the FDA), the authority of which covers the whole national territory (and, therefore, it would be more accurate to speak in terms of centralisation rather than harmonisation), whereas in the European Union, the role of the EMA, a "networking agency" as it has been defined[13], has led to substantial steps forward in the harmonisation of the national pharmaceutical regulatory systems[14].

The Food and Drug Administration is an executive-branch agency that is led by a Commissioner who is appointed by the president, with Senate confirmation, and who reports to the Secretary of Health and Human Services. The agency's role is to establish the safety and efficacy of a new drug, supervising a long process that goes from the preclinical to the clinical trials, and finally to the pharmacovigilance of such a drug[15]. In addition to issuing approval of the drug, the FDA must also approve the label that accompanies it. This label typically provides information on the drug's pharmacological properties (such as the rate at which the drug enters and exits the body), contraindications (medical conditions that preclude use of the drug) and side effects, as well as brief summaries of the clinical trials reported to the FDA. The label also lists the indications (or diseases) that the drug is approved to treat. Thus, approval by the FDA is not merely approval of the drug, it is approval of the drug for specific uses.

A few words shall be spent for the European regulatory framework. In fact, two are the possible marketing authorisation procedures: the centralised and the mutual recognition procedures. The first one is compulsory for all medicinal products derived from biotechnology and for other

13 Permanand G., *EU Pharmaceutical Regulation*, Manchester University Press, 2006, p. 65.

14 For an overview of the step by step harmonisation process see Hodges C., *European Regulation of Consumer Product Safety*, Oxford University Press, 2005, pp. 39 and following.

15 For a comprehensive analysis of the FDA's task in regulating pharmaceutical drug safety see IOM (Institute of Medicine of the National Academies), *The Future of Drug Safety – Promoting and Protecting the health of the Public*, The National Academy Press, 2007.

innovative new medicines[16]. The marketing authorisation is granted by the Commission, once the EMA takes its decision, and is valid throughout the whole of the EU. On the other hand, the second procedure is based on the principle of mutual recognition of national authorisations between Member States. Under such procedure, a marketing authorisation granted by one Member State is extended to one or more other Member States selected by the applicant[17]. Because of the significant differences between national regulations related to marketing authorisation, with the EC Directive 2001/83 on the Community code relating to medicinal products for human use, the EU attempted to harmonise to a larger extent the national procedures[18]. Nowadays all highly innovative (and thus potentially more dangerous) products must undergo the centralised procedure[19], therefore undergoing the same test of safety and risk/benefit[20].

It shall be noticed that, given the recalled transnational nature of the approval process, involving regulatory bodies in different legal frameworks, the initiative of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) seems to be slowly softening the differences still existing on the two sides of the Ocean, even though the process is long, difficult and hindered by both national and private interests[21]. ICH is seeking to harmonise drug testing through protocols and voluntary agreements. As it has been well argued[22], drug testing is intimately linked to broader conceptions of how physicians, regulatory agencies, drug companies and consumers should interact. The interaction among those subjects composes the so called "therapeutic culture" of a country. In this regard, ICH has the potential to improve medical care by finding an appropriate balance among competing regulatory styles. But the task is hard and the challenges are tough. ICH participants are facing internal and external contrasts suggesting that enacting regulatory harmonisation to a higher level faces serious difficulties. On an

16 See first Regulation 2309/93/EEC, and then Regulation 726/2004/EC, art. 3 and Annex.

17 Hodges C., *European Regulation of Consumer Product Safety*, p. 40 "This state of affairs developed historically: when regulation was first introduced Directive 65/65/EEC crystallised the introduction of national authorisation systems, which was arguably all that could be contemplated either in practice or politically at the stage, 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 authorisation could be granted. The centralised procedure introduced by Regulation 2309/93/EEC was effectively established on a trial basis, in that it was restricted to certain categories of product, which are subject of extension, as noted above. The logical outcome would be that the mutual recognition system will be abandoned in the future."; for a different perspective, suggesting decentralized procedure should inspire an international system of durg marketing approval as suggested by Purnhagen K., *The Challenge of Globalization in Pharmaceutical Law: Is an International Approval System Modelled after the European System Worth Considering?*, 2008.

18 Hodges C., *European Regulation of Consumer Product Safety*, p. 40.

19 See Regulation 726/2004/EC, art. 3 and Annex.

20 See Feldshreiber, *The Law and Regulation of Medicines*, Oxford University Press, 2008, p. 103 ff; and Hodges C., *European Regulation of Consumer Product Safety*, p. 99 ff.

21 See on the issue Purnhagen K., *The Challenge of Globalization in Pharmaceutical Law: Is an International Approval System Modelled after the European System Worth Considering?*; Daemmrich A.A., *Pharmacopolitics – Drug Regulation in the United States and Germany*, The University of North Carolina Press, 2006, pp. 143-174.

22 Daemmrich A.A., *Pharmacopolitics – Drug Regulation in the United States and Germany*, The University of North Carolina Press, 2004, pp. 243.

"internal" front (within ICH member states), consumer representatives challenge the technocratic system that excludes their concerns and is built in such a way that it strengthens the industry's lobbying power[23]. On an "external" front, countries such as Brazil, India and China, originally excluded from the ICH forum, are now growing to become the new major innovators in the field of pharmaceuticals. Moreover, at present these countries already host significant portions of the research and testing process of new drugs[24]. How ICH participants respond and adapt to expectations for participatory democracy from constituents in very different political and cultural settings will determine the success of the venture.

For the purposes of our study, it is interesting to rapidly sketch the organisational differences that exist between the two main western agencies:

Comparison of the EMEA and the FDA[25]

	EMEA	**FDA**
Established in:	1991	1931
Dependent on:	European Commission, Directorate General for Enterprise	Department of Human Health and Human Services
Budget for 2006	€62 million (70% as fees from the companies)	over $2 billion (10% as fees from the companies)
Permanent Staff	250	9000
Evaluation of drug documentation by	External experts (two appointed by each Member State included in the scientific committee – CHMP – renewed every 3 years)	Internal (CDER review team) and external (Advisory Committee) expert
Compulsory procedures	Biotechnology products and products derived from human blood and tissues	All pharmaceutical products
Time of approval	7 months to 15 months	10 months (standard medicines), 6 months (priority medicines)

Thanks to the initiative of the ICH in softening the differences between the regulatory frameworks of pharmaceutical safety (especially in the US, the EU and Japan)[26], general guidelines are to a significant extent harmonised (at least in the major markets such as those mentioned above). However specific rules and standards differ, and such differences are intrinsically liable to result in

23 Daemmrich A.A., *Pharmacopolitics – Drug Regulation in the United States and Germany*, The University of North Carolina Press, 2004, p. 147.

24 Communication of the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions, *Safe Innovative and Accessible Medicines: a Renewed Vision for the Pharmaceutical Sector*, Brussels, 10/12/2008.

25 IOM (Institute of Medicine of the National Academies), "Regulatory Authorities for Drug Safety", in *The Future of Drug Safety – Promoting and Protecting the health of the Public.*

26 For a comprehensive description check ICH homepage, http://www.ich.org/cache/compo/276-254-1.html (follow "Structure of the ICH" hyperlink under "About ICH").

substantial variations in the level of safety of a new product[27]. An example may clarify the claim. Whereas both the FDA and the EMA enforce an procedure based on three phases and several subphases[28] for the approval of a new drug (harmonised general guide-line), the way the clinical trials are held presents a major divergence: whereas the EMA tests the experimental drug against the most advanced one of the same type that is already marketed, the FDA runs the same test against a placebo[29] (specific regulation, sub-step 3 of step 2 of the procedure).

b)...in tort law

There is an antique dispute over the liability regime that would better fit pharmaceutical products. The reason for this is easily understandable if we consider the inherent risk that characterises these products[30]. There is indeed no such thing as absolute safety and this poses serious problems over the extent to which a producer can be held liable for damages caused by his products. And such problems are even worsened by the extensive regulatory oversight established for pharmaceutical products all over the world, because of the time, costs and limitations that derive from such regulations[31].

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27 Again for a general perspective on the matter a good overview can be found in http://biopharminternational.findpharma.com/biopharm/Article/Navigating-Differences-Between-FDA-and-EMEA-for-Re/ArticleStandard/Article/detail/371018

28 Very broadly, the approval process is structured in the following way: 1. preclinical research (lab development and testing on animals); 2. clinical research (clinical trials then divided in several sub-steps, 3 in the EU, 4 in the US); 3. pharmacovigilance, the post-marketing surveillance system. See for example Arbour M.-E., "Sperimentazione dei Farmaci", Pisa, 2004, pag. 2 and following.

29 See 21 U.S.C. § 360c(a)(3)(D)(ii) (pre-market approval); and *ibidem* § 360c(i)(1)(D).

30 It is interesting for the purpose of defining the unavoidability of risks in pharmaceutical products to recall the definition of "unavoidably unsafe" as provided by *comment k* of Section 402/A of the *Restatement Second*. *Comment k* states: "*Unavoidably unsafe products*. There are some products which, in the present state of human knowledge, are quite incapable of being made safe for their intended and ordinary use. These are especially common in the field of drugs. An outstanding example is the vaccine for the Pasteur treatment of rabies, which not uncommonly leads to very serious and damaging consequences when it is injected. Since the disease itself invariably leads to a dreadful death, both the marketing and the use of the vaccine are fully justified, notwithstanding the unavoidable high degree of risk which they involve. Such a product, properly prepared and accompanied by proper directions and warnings, is not defective, nor it s *unreasonably* dangerous. The same is true of many other drugs, vaccines, and the like, many of which for this very reason cannot legally be sold except to physicians, or under the prescription of a physician. t is also true in particular of many new or experimental drugs as to which, because of lack of time and opportunity for sufficient medical experience, there can be no assurance of safety, or perhaps even of purity of ingredients, but such experience as there is justifies the marketing and use of the drug notwithstanding a medically recognisable risk. The seller of such products, again with the qualification that they are properly prepared and marketed, and proper warning is given, where the situation calls for it, is not to be held to strict liability for unfortunate consequences attending their use, merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk."

31 See Hodges C., *European Regulation of Consumer Product Safety*, p. 48: "The average cost of discovering and developing a new drug is now put at over $800 million and rising at an annual rate of 7.4% above general price inflation: Boston Consulting Group, *A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry*, Boston, 2003; DiMasi J., Hanson R.W., Grabowski G., "The Price of Innovation: New Estimates of Drug Development Costs", *Journal of Health Economy*, 22, 2003. It is well known that the potential profits can be enormous. It has been commented that the increasing cost of drug development is likely to promote the situation where companies invest only in the development of those new drugs that are expected to yield peak annual sales greater than $500 million: Rawlins M.D., "Cutting the Costs of Drug Development?", *Nature*, 3, April 2004."

Whether and how pharmaceuticals should be treated differently from other types of products has "consumed more time and effort than about any other particularised issue of products liability law"[32]. Such an issue can be summarised as follows. There is a paradox that is inherent to pharmaceuticals: "as one of the greatest triumphs of the twentieth century, their powerful chemicals and biologics save millions of human beings from suffering and death; yet, these same chemicals also cause great suffering and death"[33]. All prescription drugs possess substantial costs as well as benefits. This is because drug hazard are inherent and can be unavoidable. The question being: given the unavoidability of drug hazard, how to strike the optimal balance between risks and benefits?[34]

The urgency of the question lies in the fact that there is no such thing as a perfect regulator. It is widely recognized that legislative, budgetary and political constraints clash with "the ideal of a perfect regulatory body that optimally protects the public from exposure to potentially harmful products"[35]. Nor do product labelling always properly warn consumers from the inherent risks of taking the drug[36]. Because of these and other shortcomings in the regulatory structure for the production and distribution of drugs, products liability law needs to play a significant role in compensating and protecting consumers harmed by pharmaceuticals. Furthermore, we believe that products liability should be considered as an active component of the concept of "drug safety", which therefore must be intended as the sum of safety regulation and civil liability.

Therefore, the question of interest here is what role do the complex public regulatory schemes put in place to ensure safety, leave for the law of torts and products liability? The question is not easy to answer. Looking at some countries, we could say that because the regulation shows several shortcomings in practice, the answer appears to be that products liability law has a powerful role to play in compensating persons harmed unnecessarily by defective drugs, and some role (if a lesser one) in deterring production and sale of unsafe products, and promoting drug safety, on the basis of a system of rules which is, in the majority of cases, is substantially a negligence one[37]. But if we look at other countries, such as Spain or Germany, the law provides a regime of strict (or even absolute) liability for harms caused by pharmaceutical products. And finally, we must confront with a contentious doctrine,

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32 Henderson J. A., Twerski A. D., "Drug designs are different", *Yale Law Journal* 151, 2001.

33 Madden M. S., "The enduring paradox of products liability law relating to prescription pharmaceuticals", *Pace Law Review* vol. 21, 2000.

34 It is worth noting that there is a common understanding, especially in US literature, that drug hazard is inherent and simply cannot be removed. Now this is true to a certain extent, however, the hazard in some drugs may be reduced or eliminated by changing the prescribed dosage, the active ingredients in combination drugs, or the inert ingredients used in a drug. For further details see Green M., "Prescription Drugs, Alternative Designs, and the Restatement (Third): Preliminary Reflections", 30 *Seton Hall Law Review* 207, 1999.

35 Hodges C., *European Regulation of Consumer Product Safety*, p. 48. On weaknesses in the regulatory schemes see, for an analysis in the 'tort law perspective', Rabin R., "Reassessing Regulatory Compliance", 88 *Georgetown Law Journal* 2049, 2000.

36 See for example Smith R., "The Vagueness of Informed Consent", 1 *Individual Health Law Review* 109, 2004.

37 The topic is discussed by Reimann M., "Liability for detective products at the beginning of the twenty-first century: emergence of a worldwide standard?", *American Journal of Comparative Law*, 2003. The reference to negligence rules in drug litigation will be further explored in the proceeding.

started in 2006 in the U.S., which considers that the products approved by the regulatory agencies shouldn't undergo tort claims, or, put in different terms, that the marketing approval by the federal regulatory agency preempts state tort claims.

The following discussion will focus on the liability rules that are applied in the United States and in Europe, and how do these rules relate with the regulatory schemes discussed above. An issue of particular interest is the manner in which the U.S. system conceives the "state of the art" of scientific and technical knowledge that somehow differs from the hypothesis in which, in the European system, a "development risk" arises.

– United States

As already suggested, the key element of both regulatory and liability assessments is the one of "relevant knowledge". Therefore, the issue of interest here is to identify the attitude of product liability law towards such concept. In the US, the relevant idea is the one referred to as "state of the art", which is a weak concept that has never been accurately defined, neither by courts nor by statutes, as it has been demonstrated by David G. Owen[38], and several other North-American scholars[39]. More precisely, while state statutes or courts, singularly considered, actually have a definition of what is to be considered "state of the art", a uniform federal conception (or at least harmonized) is absent, and the *Restatements on Torts (Second* and *Third)* have not been able (up to now) to give an appropriate answer to the question. There are several causes to explain this phenomenon. The simplest one is to look at the problem from a semantic point of view: "state of the art" is an incomplete phrase: you need to know about which particular "state of the art" you are talking about in a particular situation. In other words the question is: state of the art *of what*? The answer depends and varies from state to state, being considered in some case the most up-to-date scientific knowledge, in others the industrial customary practice[40].

To summarize, in the American products liability law, "state of the art" is an unrefined concept whose meaning and proper role are in continuous evolution[41]. In the impressive variety of definitions and interpretations of such a phrase, it is possible to identify a thin common theme emerging from the cases and the statutes: "reluctance to impose liability on manufacturers for dangers that were unknowable, or unpreventable, at the time their products were sold: reluctance to hold producers responsible for risks they cannot control"[42]. This common theme has lead to a theoretical involution of the idea of "state of the art" from *Restatement 2nd* to *Restatement 3rd*, which is quite interesting and might

38 Owen D., *Products liability law*, Hornbook Series, Thomson West Group, 2005, pp. 675-681.

39 For example Henderson J. A., Twerski A. D., *Products liability – problems and process, 5th edition*, ASPEN Publishers, 2004.

40 Owen D., *Products liability law*, pp. 677-6781.

41 As suggested by Owen D., *Products liability law*, pp. 675-701; see also Fisher D. A., Green M., Powers W. Jr., Sanders J., *Products Liability – cases and materials, 3d edition*, American Casebook Series, West Group, 2002.

42 Owen D., *Products liability law*, p. 675.

be helpful to understand the further evolution of the legal regime of pharmaceutical products safety in the US. *Restatement 2nd* imposed a strict liability regime for damages caused by defective products, adopting the so called "consumer-expectation test" to evaluate the safety of the products[43]. Because of the harshness of such a rule, the American Law Institute introduced *comment j to Section 402A*, regarding the duty to warn for producers of unavoidably unsafe products[44]. Such a duty is imposed only for foreseeable risks (but foreseeability is linked with the most up-to-date scientific knowledge available[45]). Besides, *Restatement 3rd* is much more producer-friendly oriented, abandoning the straight interpretation of *comment j* and bringing back the idea of "reasonableness" which definitely doesn't fit in a strict liability regime, but is typically proper of negligence rules instead. Sections 6(c) of the *Products Liability Restatement (3rd)* provides: "A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients."[46] To fully understand the impact of such a provision, it is useful to recall that even Thalidomide would not have been captured by the Third Restatement test, because of its value in treating leprosy.

– European Union

On the other side of the Ocean the European "development risk", which is considered the European equivalent of the American "state of the art", is a more accurate (although not entirely clear) concept, as noticed by Jennifer Stapleton[47], among others. A "development risk", is an unknowable risk, that cannot be foreseeable because the state of scientific and technical knowledge, at the time the product is put into circulation, is not such as to enable the risk to be identified[48]. The European Court of Justice has given a quite controversial interpretation of art. 7 e) of the EU Directive 374/85, in the cases *C-300/95 Commission vs United Kingdom*, stating that Article 7(e) of Directive 374/85/EC is not specifically directed at the practices and safety standards in use in the industrial sector in question but concerns "unreservedly . . . the state of scientific and technical knowledge including the most advanced

43 See Twerski A.D.- Henderson C.J., *Products liability – problems and process, 5th edition*, ASPEN Publishers, 2004, pp. 321-327.

44 Unavoidably unsafe as defined by *comment k*, see *supra* note 31.

45 See the leading cases *Brown vs Superior Court*, 751 P.2d 470 (California 1988) and *Beshada v. John Mansville Products Corp*, 1001 N.J. 221 A.2d 1099 (New Jersey Supreme Court, 1982)

46 *Restatement (Third) of Torts: Products Liability*, § 6(c).

47 In Stapleton J., *Products Liability*, London Butterworths, 1994.

48 Directive 374/85/EC, art. 7 e): " It shall be a defence for the producer to prove: . . . . . (e) that the state of scientific and technical knowledge at the time when he put the product into circulation was not such as to enable the existence of the defect to be discovered."

level of such knowledge"[49]. The state of knowledge is, according to the Court, not that of which the actual producer "actually or subjectively was or could have been apprised, but the objective state of scientific and technical knowledge of which the producer is presumed to have been informed"[50]. The Court does not go further in its argument. For instance, an explanation of the key phrase "state of knowledge" and a tentative definition of "knowledge" as opposed to "hypothesis" is absent[51]. The very high standard that at first sight the Court sets for producers regarding discoverability, is, moreover, limited by the following part of the Court's analysis. The only basis it offers for the presumption of the producer's knowledge of the defect is that the relevant knowledge must have been "accessible" at the time at which the product was put into circulation but no explanation of what it means by the word "accessible" is offered[52], thus leaving considerable margins of manoeuvre to national courts, and reintroducing an element of "reasonableness" that is in principle excluded by definition in strict liability.

We have to say that despite the attempt of the EU to harmonise the products liability legislation in the Member States, the field of pharmaceutical products liability is still fragmented for two sets of reasons.

On the one hand there are several and significant exceptions to the general regime, such as the provisions of the German Law regulating pharmaceuticals (*Arzneimittelngesetz*), and the Spanish Law (*Ley 22/1994, Sobre Responsabilidad Civil Por Danos Causados por Productos Defectuosos*), both providing strict liability for pharmaceutical damages, even though those damages were caused by a development risk[53]. This is not the place to discuss in depth the historical reasons that led to this situation. It is however worth to recall that Germany was heavily hit by the *Thalidomide* disaster. The legislation that was in place at that time (Germany was the first European country to have a special legislation for pharmaceuticals, the statute was adopted in 1961[54]) appeared unable to sufficiently ensure drug security or provide a basis for recovery of damages by injured drug consumers. The new act of 1976 purported to eliminate these deficiencies, establishing, among other provisions, strict liability claims against damages caused by pharmaceutical products. As regards Spain, the reasons are substantially the same, as the country has been hit by four major drug disasters in the space of three decades[55].

On the other hand, in its interpretation of art. 13[56] of Directive 374/85/EC, the Court of Justice held that any scheme of products liability "founded on the same basis as that put in place by the

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49 Case C-300/95, *Commission of the European Communities v. United Kingdom*, §26.

50 Case C-300/95, *Commission of the European Communities v. United Kingdom*, §27.

51 Fairgrieve D., *Products Liability in Comparative Perspective*, Cambridge University Press, 2005, 167-170

52 Case C-300/95, *Commission of the European Communities v. United Kingdom*, §28.

53 Reimann M., "Liability for detective products at the beginning of the twenty-first century: emergence of a worldwide standard?"; and Wandt M., "German approaches to Product Liability", *Texas International Law Journal* 34, 1999.

54 *Gesetz uber den Verkehr mit Arzneimitteln*, 1961.

55 See for a discussion Vega M.I.A., "The defence of development risks in Spanish Law", *Consum. L.J.*, 1997.

56 Art. 13 provides: "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."

Directive and not limited to a given sector of production does not come within any of the systems of liability referred to in article 13 of the Directive"[57]. On the basis of this reasoning, and considering pharmaceuticals as a specific "sector of production", countries such as France and Italy, apply general tort law rules to pharmaceutical products liability claims[58]. We will come back to these scenarios in the proceeding.

2. Widening The Divergences *(Federal Preemption of State Tort Law)*

As suggested in the Introduction, a link should exist between regulation and products liability. A link whose role shall be to foster the availability of the knowledge meant to assess the safety of a new product. This part of the paper is dedicated to recent trends in American products liability litigation that raise various concerns in light of the aforementioned goal.

In the past recent years, specifically as from 2006[59], a new doctrine (the doctrine of preemption) gained momentum in the area of drug litigation in the US. Until then, the FDA used to consider its risk/benefit analysis as setting a floor but not a ceiling for product safety. FDA approval would authorize a product to be marketed, but manufacturers would still be held responsible if a court later decided that a product was defective or a warning was inadequate. Over the past decade, however, this view changed in light of the activism of policymakers, fiercely stressing the need to bring innovative medical treatments to market[60]. It has been argued, in this perspective, that the FDA review process should thus set both floor and ceiling: FDA approval of a new product shouldn't anymore simply indicate that the product can be marketed, but it should be the final word in the safety assessment of such new product. FDA officials who hold this view consider the tort system dangerous. According to their view, the threat of tort liability deters pharmaceutical companies and device makers from developing much-needed new technologies[61]. Whenever those innovations are delayed if not

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57 See Case C-183/00 *González Sànchez vs Medicina Asturiana SA* [2002] ECR I-3901.

58 See among others Fairgrieve D., *Products Liability in Comparative Perspective*, p. 221; and Ponzanelli G., "Armonizzazione del diritto v. protezione del consumatore", Danno e Responsabilità, 2002; Busnelli F. D., Ponzanelli G., *La responsabilità del produttore tra legge speciale e codice civile*, in *Il danno da prodotti in Italia, Austria, Repubblica Federale di Germania, Svizzera*, a cura di S. Patti, Padova 1990.

59 Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3922, 3934 (Jan. 24, 2006) (effective June 30, 2006) (21 C.F.R. Pts. 201, 314, 601).

60 Sharkey C.M., "Federalism in Action: FDA Regulatory Preemption in Pharmaceutical Cases in State versus Federal Courts", NYU School of Law, *Public Law &Legal Theory research Paper Series*, n. 08-04, 2008; Sharkey C.M., "Preemption by Preamble: Federal Agencies and the Federalization of Tort Law", *De Paul Law Review*, 56:227, 2007; Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", *Yale Journal of Health Policy, Law & Ethics*, 2005; IOM, "Regulatory Authorities for Drug Safety, in *The Future of Drug Safety – Promoting and Protecting the health of the Public.*

61 Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 590; and see also for a discussion Philipson T.J., Sun E.C., Goldman D., "The effects of Product Liability Exemption in

abandoned altogether, "the cost is felt not merely in financial terms but also in the suffering of people whose illnesses could have been treated with the new drug or device"[62]. These critics argue that the tort system should not be permitted to re-determine product safety, as courts may unduly nullify the assessments of the FDA's expertise[63]. The risk being that non-expert juries and judges would make weaker assessments in terms of scientific robustness and objectivity[64]. It has been demonstrated, however, that such a statement is inadequate because of the weakness of the FDA's post-marketing surveillance process, essentially based on the data furnished by the pharmaceutical industry itself, rather than autonomously reached by the agency[65]. The evolution of the relationships between products liability and products safety in the US shows a significant shift, in the past fifteen years, from a consumer-friendly to a much more producer-friendly tendency. It has been argued that the emergence of the doctrine of preemption promoted by the FDA might be explained in light of the agency's need to regain authority and reliability after the Vioxx scandal which lead to the withdrawal from the market of such a drug[66]. This shift is proven, for example, by the New Jersey case law, particularly by the case *Rowe v. Hoffmann-La Roche Inc*, of March 2007, applying the doctrine of preemption. This is a decision with dangerous potential because of the active and central role that the New Jersey Supreme Court always has had in the history of the American Products Liability law from the case *Beshada v. John Mansville Products Corp*, to the famous *Feldman v. Lederle Laboratories,* applying section 402A of *Restatement 2nd* in its strictest interpretation.

The future of drug litigation in the United States is nonetheless still very unclear. With its ruling of March 4, 2009, the US Supreme Court, in *Wyeth vs Levine*[67], seems, at first sight, to have "overruled" the doctrine of preemption in drug litigation. In this decision, the Supreme Court clearly suggests that state tort law can not be considered an obstacle to the achievement of safety assessments by the FDA,

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Presence of the FDA", *NBER Working Paper Series*, 15603, 2009. Philipson T.J.- Sun E. , "Is the Food and Drug Administration Safe and Effective?", *NBER Working Paper Series*, 13561, 2007.

62 Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 590.

63 See preamble to regulation on "Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products", 71 Fed. Reg. 3922, 3934.

64 Empirical data rather indicate that juries do better than their critics assert at handling technical issues, that juries are not as eager as some think to award damages against business defendants, and that punitive damages are awarded rarely in products liability suits (and mainly in cases involving egregious misbehavior). See on the point Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 592-593.

65 There is abundant literature on the point, an author who argued that the FDA's reliance on the regulated company to supply the necessary safety data can lead to problems is McGarity T.O., "Beyond *Buckman*: Wrongful Manipulation of the Regulatory Process in the Law of Torts", *Washburn Law Journal*, 41, 2002: 549-559 ("When the onus is on the regulatee to provide data establishing that its product is 'safe and effective' . . . , the temptation is strong for a company to discount data indicating that the product may not meet the statutory test."); see also Noah B.A., "Adverse Drug Reactions: Harnessing Experiential Data to Promote Patient Welfare", 49 *Catholic University Law Review*, 449, 470-71, 2000.

66 See Merck Press Release of September 30, 2004, available at www.merck.com/newsroom/vioxx/pdf/vioxx_press_release_final.pdf

67 *Wyeth vs Levine*, 129 S.Ct. 1187.

but it is rather a complement of it[68]. The fact that no Congress statutes clearly provide a preemption clause for FDA's decisions goes in this very direction[69]. Is this the end of the preemption debate for drug litigation[70]? We suggest that the answer is in the negative.

On the one hand, as it appears from the facts of the case, the defendant failed to disclose relevant information to the FDA, regarding alternative and possibly safer uses of the drug[71]. More precisely, what the defendant was seeking in *Wyeth* was not a simple "preemption defence", but a narrower "impossibility by preemption defence". In other words, the claimant was arguing that it couldn't introduce a new element (i.e. the alternative safer use of the drug) in the labelling on its own motion, since such a label had been approved by the FDA. And being the label approved by the FDA, the state court was preempted to find the claimant liable for failure-to-warn[72]. On the other hand, and on a more general note, the Court rejected Wyeth 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"[73], stating that such an argument relies on an "untenable interpretation" of congressional intent and an "overboard view" of an agency's power to preempt state law[74]. Thus narrowing down substantially the room for implied preemption.

Notwithstanding the clear cut wording of this particular judgement, it might be too early to argue that federal preemption cannot be invoked *tout cour* in drug cases (whereas it seems hardly disputable that it is precluded when the defendant fails to operate proactively on the basis of all information in his possession). As quite colourfully noted by Mary J. Davis, "trying to make sense of preemption opinions [of the Supreme Court] reminds one of being on a roller coaster […] The uncertainty of where the coaster will go, while exhilarating for the time, is also exhausting and frustrating"[75]. A quite accurate comment, if we compare *Wyeth* with the previous high profile implied preemption case decided by the Supreme Court, *Riegel*[76], where the Court showed a less narrow and

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68 *Wyeth vs Levine*, 129 S.Ct. 1187, §§ 10-11.

69 In pharmaceutical products cases, implied preemption was applied, by considering federal agency (FDA) determinations as substitutes for congressional intent. Deferring to agency position on preemption of state common law is however troublesome, see for a general discussion Davis M.J., "The New Presumption against Preemption", *Hastings Law Journal*, 61, 1217, 2010.

70 As somehow suggested by scholars such as Owen D.G., "Dangers in Prescription Drugs: Filling a Private Law Gap in the Health care debate", *Conn. Law Review*, 42, 2010, pp 733 ff, noting "the continued decline of the federal preemption doctrine as a bar to warning adequacy claims against drug manufacturers"; see also Ausness R.C., "The Impact of Wyeth v. Levine on FDA Regulation of Prescription Drugs", 65 *Food & Drug Law Journal* 247, 2010

71 *Wyeth vs Levine*, 129 S.Ct. 1187, § 6.

72 See *Wyeth vs Levine*, 129 S.Ct. 1187, § 1; see also § 6 where the Court helds: "Impossibility preemption is a demanding defence. […] Wyeth has failed to demonstrate that it was impossible for it to comply with both federal and state requirements. The CBE regulation permitted Wyeth to unilaterally strengthen its warning, and the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change."

73 *Wyeth vs Levine*, 129 S.Ct. 1187, at 1199

74 *Wyeth vs Levine*, 129 S.Ct. 1187, at 1199

75 Davis M.J., "On Restating Products Liability Preemption", *Brooklyn Law Review*, 74, 2009, p. 776, noting the high level of inconsistency in preemption Supreme Court Judgements over the last two decades.

76 *Riegel*, 128 S.Ct. at 1007-1008

much broader approach to the issue[77]. Whether or not preemption applies to drug litigation in state tort claims seems, at the moment, quite more complex than a simple yes/no question. The wisest option being to wait and see.

3. Critiques...

a)...in general

We claim that both scenarios, the European and the American, fail to fully understand the need of an interplay between regulation and liability rules, continuing to consider both regimes separate or conflicting rather than complementary.

From a strictly theoretical perspective, the regulatory and litigation systems could operate entirely independently: compliance with regulations would be irrelevant in litigation, and litigation outcomes would not directly affect agency regulation. It is however difficult to advocate total independence: "it seems clear that the agencies' expert assessments of product safety should not be irrelevant in litigation arising from asserted safety defects. Rather, the dispute is over what the *effect* of the agency's safety determinations should be"[78]. Moreover, as we will argue in the proceedings, even in the absence of formal connections, a strong and substantial interplay between the two regimes exists, the question being how to make it work to promote the best availability of knowledge that is relevant for safety assessments.

As noted above, in the past five years, in the US the FDA's expert balancing of product risks and benefits has been interpreted as leaving no room for disagreement within the tort system. There is no reason (according to this policy) for a tort claim to "second-guess" the FDA's judgements, and, indeed, second-guessing is likely to produce undesirable results as it consists in turning down experts' assessments in favour of judgements made by non-experts[79]. However, it has also been pointed out that the FDA cannot foresee and address all product safety issues ahead of time, and that the agency may not have the ability of responding quickly enough to those issues when they first arise after a product enters the market[80]. Courts, in the process of considering the effects of agencies determinations, have

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77 Davis M.J., "On Restating Products Liability Preemption", pp. 770 – 771.

78 Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 609.

79 See Davis M.J., "The Battle over Implied Preemption: Products Liability and the FDA", 48 *Boston College Law Review* 1089, 1089-94, 2007. Davis M. J., "Discovering the boundaries: Federal Preemption of Prescritpion Drug Labeling Products Liability Actions", *University of Kentuky Law Journal*, 2005. This was somehow already suggested by Posner R., *Economic Analysis of Law* (5th ed.), New York, Aspen Publishers, Inc., 1998.

80 There is abundant literature on the shortcomings of FDA regulation, see among others Philipson T.J., Sun E.C., Goldman D., "The effects of Product Liability Exemption in Presence of the FDA"; Philipson T.J.- Sun E. , "Is the Food

thus constantly balanced these competing considerations. This balancing has taken place until 2006 when the FDA autonomously established that certain types of its determinations should preclude litigation altogether[81].

We do not agree with a model such as the one promoted by the FDA. As it has been demonstrated in the field of general products safety, regulation and liability have to be considered as functional complements, because they are not necessarily functional equivalents[82]. Neither regulation nor liability considered on their own result in parties taking the desirable "first-best" level of care[83]. In addition to that, we have to notice that in other legal fields, for instance in labour law, the link between regulation and liability has become, through time, an essential starting point for any consideration upon labour safety[84].

The fragmentation of the field of pharmaceutical safety is puzzling. On the one hand, we have the US where the doctrine of preemption has played a significant role in the past years, and might keep doing so in the future, on the other hand we have, for example, Germany, where, notwithstanding an accurate regulation set by both the EMA and the German Agency on Pharmaceuticals, the *Arzneimittelngesetz*, imposes strict liability on drug manufacturers for any damage caused by their product even though it was unknowable[85]. Both these solutions are not satisfying in the light of an efficient balance of consumers protection and incentives to innovation.

As it appears clearly from these two examples, even in the absence of structural connections between the litigation and regulatory systems, strong substantial connections exist. In the US case, when FDA regulation preempts state tort claims, the regulatory system excludes the litigation system. Because no federal cause of action currently exists on product liability, preempting state tort claims

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and Drug Administration Safe and Effective?"; Davis M.J., "The Battle over Implied Preemption: Products Liability and the FDA"; Davis M. J., "Discovering the boundaries: Federal Preemption of Prescritpion Drug Labeling Products Liability Actions"; and Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation".

81 We are here working on the hypothesis that despite *Wyeth* preemption will continue to apply to drug cases. In the proceeding we will address the opposite hypothesis.

82 Cafaggi F., *Institutional Framework of European Private Law*, pp. 191 and following.

83 Shavell S., "A model of the socially optimal use of liability and regulation", *NBER Working Paper* Series n° 1220, 1983.

84 Shavell S., *Economic Analysis of Accident Law*, Cambridge (MA), Harvard University Press, 1987.

85 *Arzneimittelgesttz § 84*: "If, as a result of the administration of a drug intended for human use, which was distributed to the consumer within the purview of the present Law and which is subject to compulsory marketing authorization or is exempted by ordinance from the need for a marketing authorization, a person is killed or the body or the health of a person is substantially injured, the pharmaceutical entrepreneur who placed the drug on the market within the purview of the present law shall be obliged to compensate the injured party for the harm caused. The liability to compensate shall only exist if:

1.when used in accordance with its intended purpose, the drug has harmful effects which exceed the limits considered tolerable in the light of current medical knowledge and which have their origin in the development or manufacturing process, or,

2.the harm has occurred as a result of labelling, expert information or instructions for use which do not comply with current medical knowledge." See also Wandt M., "German approaches to Product Liability".

eliminates the very possibility of lawsuits concerning pharmaceutical product safety[86]. In a world where regulation struggles to confront with the issue of a production process that is more and more multi-localized, and where the number of regulatory bodies transnationally involved in the approval process increases, a pure "regulatory compliance" shield against tort claims appears to be a risky choice in light of the need to promote the best availability of "relevant knowledge" in assessing the safety of a product, before and after its marketing. The increasing number of said regulatory bodies involved across the world in the approval process of a new drug, combined with the incomplete international harmonisation of the relevant guidelines, generate in fact a non-negligible level of uncertainty.

Besides, in the German case, the harshness of the pharmaceutical products liability law potentially renders regulatory compliance totally valueless, so that non virtuous behaviours might be encouraged[87]. In addition to that, a structural separation between regulation and liability eliminates a potentially useful "cross-fertilization" between regulators and courts, causing what we might call a "pure knowledge loss". Since the concept of "relevant knowledge"[88] is of the greatest importance in assessing responsibility in the field of marketed drugs (where all decisions are made with reference to the state-of-the-art of scientific and technical knowledge), such a loss is not acceptable.

b)...deepening the critiques – United States

It has been accurately argued that permitting FDA approval to preclude the possibility of tort liability does more than ensure that product safety decision are reserved to the FDA, because preemption of tort litigation removes the opportunity for litigation to aid the FDA in its goal of monitoring product safety[89]. Moreover, taking into account the classic compensatory function of tort law, preemption *de facto* denies compensation to persons harmed by a product for the mere fact of being approved by the agency even if they were harmed after a safety problem first occurred but before the FDA took regulatory action to remove the product from the market or require additional warnings – and this is the case more often than one could think due to the weaknesses of the FDA's post-marketing surveillance system[90]. Moreover, there are serious concerns over the level of safety that

86 Davis M.J., "The Battle over Implied Preemption: Products Liability and the FDA"; Davis M. J., "Discovering the boundaries: Federal Preemption of Prescritpion Drug Labeling Products Liability Actions"; and Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation".

87 As pointed out by Wandt M., "German approaches to Product Liability".

88 Mildred M., "The development risk defence", in Fairgrieve D., *Products Liability in Comparative Perspective*, p. 179.

89 Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 615 ff.

90 The issue is raised by, among others, IOM, "Regulatory Authorities for Drug Safety, in *The Future of Drug Safety – Promoting and Protecting the health of the Public*; Philipson T.J., Sun E.C., Goldman D., "The effects of Product Liability Exemption in Presence of the FDA"; Philipson T.J.- Sun E. , "Is the Food and Drug Administration Safe and Effective?"; and Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", who accurately describes the differences in the budgets dedicated to the post- as opposed to the pre- marketing surveillance procedures, the post-marketing being underfunded and least than perfectly organized.

regulation alone can provide. In particular, the pharmaceutical regulatory system is not without its critics. The principal complaints that are relevant for the present purposes are those of potential systemic bias, secrecy, and the potential for fraudulent production of safety data, especially in toxicology or clinical research[91]. The recent Vioxx case, in which *Merck* has consciously not disclosed relevant safety data relating to well-known risks of adverse reactions is a demonstration that those concerns do have relevant grounds[92].

As suggested by Christopher Hodges, "it is undoubtedly true that the system is complex and provides a number of competing interests which a properly regulated society must seek to balance"[93]. To describe the scenario, the term "multi-regulation"[94] has been used by scholars. The very considerable sums of money that can be involved in the success or failure of pharmaceutical products[95] give raise to major concerns. It is particularly important in this sector that there should be "continuous confidence in the appropriateness and strength of the design and operation of the system, and rigourous compliance with its regulatory standards, through periodic review of its operation and transparency"[96].

There is a risk here to conclude with an assertion that the system is biased toward the interests of industry over the ones of patients and public health[97]. As it has been accurately argued, "modern drug regulation is not a proxy for medical accidents and the misfortunes of drug disasters but, above all,

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91 For discussion of whether unfavourable studies may not be published or reported quickly enough see: Hodges C., *European Regulation of Consumer Product Safety*, p. 48; Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation"; and from a more "journalistic perspective: "SSRIs: Suicide Risk and Withdrawal", *Lancet*, 361, June 2003; Laurance J., "*Sexorat* Ban Raises Doubts over Drug Licensing System", *The Independent*, 11 June 2003.

92 For a discussion of the issue see among others Daemmrich A.A., *Pharmacopolitics – Drug Regulation in the United States and Germany*, pp. 88 and following.

93 Hodges C., *European Regulation of Consumer Product Safety*, p. 47.

94 Hodges C., *European Regulation of Consumer Product Safety*, p. 47 quoting Hancer L., "Pharmaceutical Policy and Regulation: Setting the Pace in the European Community", in Davis P., *Contested Ground: Public Purpose and Private Interest in the Regulation of Prescription Drugs*, Oxford University Press, 1996

95 The average cost of discovering and developing a new drug is now put at over $800 million and rising at an annual rate of 7.4% above general price inflation: Boston Consulting Group, *A Revolution in R&D: How Genomics and Genetics are Transforming the Biopharmaceutical Industry*, Boston, 2003; DiMasi J., Hanson R.W., Grabowski G., "The Price of Innovation: New Estimates of Drug Development Costs", *Journal of Health Economy*, 22, 2003: 151-85. It is well known that the potential profits can be enormous. It has been commented that the increasing cost of drug development is likely to promote the situation where companies invest only in the development of those new drugs that are expected to yield peak annual sales greater than $500 million: Rawlins M.D., "Cutting the Costs of Drug Development?", *Nature*, 3, April 2004, 360.

96 Hodges C., *European Regulation of Consumer Product Safety*, p. 48, and see Medawar C., Hardon A., *Medicines Out of Control? Antidepressant and the Conspiracy of Goodwill*, Amsterdam 2004, and its review Collier J., "Regulating Regulators", *The Lancet*, 363, June 2004, claim that regulatory controls are creaking in their antiquity, the industry creates diseases and promotes ill-health, and the regulatory authority exercises the functions of the government because of the complexities involved, thereby favouring technocracy over democracy. In this light, for the American Scenario, see Avorn J., MD, *Powerful Medicines -The Benefits Risks and Costs of Prescription Drugs*, Vintage Books, 2005. For a converse view that medicine safety is well regulated, see Silcock J., Pritchard C., *To Heal and to Harm: An Economic View of Drug Safety*, London, Routledge, 2003. Many investigations are in course over the extent to which medicines regulatory agencies are independent of the pharmaceutical industries, and bans have been announced on regulators and their advisers holding shares in relevant companies, Kanavos P., Ross-Degnan D., "Measuring, Monitoring and Evaluating Policy Outcomes in the Pharmaceutical Sector, in Mossialos E. et al., *Regulating Pharmaceuticals in Europe: Striving for Efficiency, Equity and Quality*, Open University Press, 2004

97 Abraham J., Lewis G., *Regulating Medicines in Europe*, London 2000, p. 78.

a product of the state's negotiation with, and accommodation of, organised industrial interests"[98]. Therefore, the argument here is that as the outcome of safety regulation is substantially political[99], as a result of negotiation, there is an urgent need for an accessible, transparent and effective tool to bring back pharmaceutical product safety into the proper boundaries of a legal issue. What we do believe is that such a tool exists and has to be found in tort law.

Supporters for FDA regulation to preclude tort litigation can hardly meet the objection that the agency may not be in a position to discover all relevant safety information, nor act promptly enough upon the information that it does receive concerning safety issues. It thus seems only reasonable to claim that the tort system should maintain the ability of re-assessing product safety in light of the results of the discovery process. As the Supreme Court stated in *Wyeth* tort litigation functions as a complement to safety regulation and cannot be considered an obstacle to it[100]. It could theoretically be true that a carefully designed regulatory compliance defence might attempt to improve post-marketing surveillance, for instance by precluding liability exclusively in cases where the defendant had accurately complied with regulatory requirements, including full disclosure requirements[101]. In light of this reasoning, proponents have urged that the defence should be available only where there was full disclosure of all relevant safety information[102]. But due to the recently experienced shortcomings of FDA's performances, it seems quite unduly optimistic to expect the agency to act quickly and effectively in addressing all emerging safety problems, thus undermining a very prerequisite of the defence (the ability of regulation alone to provide a high level of safety). Moreover, we shall stress that a regulatory compliance defence could very well have the paradoxical effect of reducing a company's incentive to work proactively to address emerging safety issues[103], as the task would be entirely devolved to the FDA (which, again, seems less than advisable). A model based on the equation "disclosure = shield vs tort claims" would incentivize manufacturers to inundate the FDA with

98 Abraham J., Lewis G., *Regulating Medicines in Europe*, p. 79.

99 For a general discussion of the topic see Ogus A.I., *Regulation: Legal Form and Economic Theory*, Cambridge University Press, 2004.

100 *Wyeth vs Levine*, 129 S.Ct. 1187, §§ 10-11.

101 As suggested by Struve C.T., "The FDA and the Tort System: Postmarketing Surveillance, Compensation and the Role of Litigation", p. 615. On this issue, Michael Green has however pointed out that incorporating such nuances into the regulatory compliance defence will render that defence complex and costly to litigate. Green M.D., "Statutory Compliance and Tort Liability: Examining the Strongest Case", *University of Michigan Journal of Law Reform*, 30, 1997.

102 See ALI Reporters' Study, "Enterprise Responsibility for Personal Injury", 1991, arguing that a regulatory compliance defence should apply only if the defendant "publicly disclosed to the relevant regulatory agency any material information . . . of which it has reason to be aware . . . concerning the risks posed by the defendant's activities and/or the means of controlling them," and stating that the requirement should "extend to information indicating that agency standards or tests may be inadequate or inappropriate".

103 As Michael Green has noted, "with a regulatory compliance defence available, manufacturers would no longer have an incentive to seek labelling changes that would disclose additional risks discovered in the post-marketing period. The impetus for such changes would be left to the FDA . . . . *The specter of inadequate resources available to the FDA makes this role reversal of significant concern* [emphasis added]". Green M.D., "Statutory Compliance and Tort Liability: Examining the Strongest Case".

information, rendering its ability to provide thorough assessments nearly impossible[104].

On a different perspective, if we were to assume that the "roller coaster" is finally over and that the ruling of the Supreme Court in the *Wyeth* case goes in the direction of a full overruling of the federal preemption of state tort law in drug litigation cases[105], what claimants would be left with is section 6 (c) of the *Restatement Third*[106], which provides a negligence regime that can not be considered satisfactory for safety purposes. We believe that the situation would present substantial analogy[107] with the regime that is in place in the EU where the Products Liability Directive 374/85/EC is applied. We will therefore discuss the issue in the following paragraph.

c) ...deepening the critiques – European Union

The European scenario is different. There is no such thing as preemption in the EU, where the EMA has been playing a crucial role in the harmonisation of the pharmaceutical safety regulation, but by no means has it the authority (nor the intention) to displace tort litigation. The two questions here concern, on the one hand, (1) the harmonisation of liability rules, and on the other hand (2) the links between the two systems of regulation and liability. The two problems are somehow related.

Several studies on the functioning of the regulatory regime of pharmaceutical safety in the EU reach the conclusion that, even though it isn't perfect, such a regime is accepted, quite harmonised (especially after the adoption of the EC Directive 2001/83), and quite effective in ensuring pre- and post- marketing surveillance[108].

(1) As regards tort law, however, harmonisation of pharmaceutical products liability in Europe remains chimeric, for two substantial reasons. The first and most obvious one is the presence of special regimes specifically put in place in this field by some Member States, especially Germany and Spain[109].

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104 This claim is stressed by Philipson T.J., Sun E.C., Goldman D., "The effects of Product Liability Exemption in Presence of the FDA"; and see also Philipson T.J.- Sun E. , "Is the Food and Drug Administration Safe and Effective?"; Green M.D., "Statutory Compliance and Tort Liability: Examining the Strongest Case".

105 It would be hard to claim with certainty that this is the case due the specific facts of the judgement in question, and to the swinging attitude of the Supreme Court in preemption rulings, as discussed *supra*.

106 *Restatement (Third) of Torts: Products Liability*, § 6(c): "A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients."

107 Substantial as it provides a negligence regime, but the specific rule is way more producer-friendly in the US, since, as already recalled, the relevant section of the Restatement provides that: "A prescription drug or medical device is not reasonably safe due to defective design if the foreseeable risks of harm posed by the drug or medical device are sufficiently great in relation to its foreseeable therapeutic benefits that reasonable health-care providers, knowing of such foreseeable risks and therapeutic benefits, would not prescribe the drug or medical device for any class of patients".

108 For a comprehensive discussion see Feldshreiber P., *The Law and Regulation of Medicines*, Oxford University Press, 2008. It must be noted, however, that the system is still regionally shaped. And this creates a series of problems as regards the ability of such a system to confront with the globalization of the production and testing process.

109 Germany: *Gesetz uber den Verkehr mit Arzneimitteln,* 1976; Spain: *Ley 22/1994, Sobre Responsabilidad Civil Por Danos Causados por Productos Defectuosos*

The second reason is that the implementing process of the EC Directive 374/1985 on Product Liability has been long and complex, and the outcomes are still not entirely clear, due to the reluctance of the Member States to retrieve from their judicial and doctrinal interpretations of the subject in favour of a centralised model that is, at least in some cases, less favourable for the consumer (like in France or in Italy). With its rulings of year 2002[110] the European Court of Justice attempted to put an end to the debate by stating that the model provided by the Directive, despite the literal wording of article 13[111], has to be considered the only general system of product liability in the EU, and that parallel regimes can survive only if they provide liability systems of a different type, or special liability systems relating to specific types of products. That means, as a consequence, that the ruling of the ECJ in the case *Commission vs UK*, on the proper meaning of the development risk defence, has to be considered the valid interpretation of the defence across Europe in the application of the Directive. So in the Member States in which pharmaceutical cases undergo the Directive's regime, a producer will be held to the Directive's standard, whereas in Member States having a special regime, the producer will be held to such a different standard, and there is more. In Member States applying general tort law provisions to specific products (such as pharmaceuticals), the standard the producer will have to reach will change again. A hypothetical example might help to understand the issue.

A German firm produces a pharmaceutical product and has a marketing authorisation that permits the firm to market such a product in Germany, Italy and England. A year later, consumers suffer damages from the consumption of the product. In Germany, plaintiffs will be able to obtain full compensation under the *Arzneimittelgesetz* by simply proving that they suffered damages from the pharmaceutical[112]. The producer will be responsible on a strict liability basis. Besides, in England, the producer will be able to defend himself, if he proves that the damage came from a development risk, as interpreted by the Court of Justice. That means that knowledge of the risk (if it existed at the moment the product entered the market) was not reasonably and objectively accessible and obtainable for the producer[113]. Finally, in Italy, if we assume the applicability of Article 2050 cc[114] to this type of claims[115],

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110 Case C-52/00 Commission vs France [2002] ECR I-3827; and Case C-183/00 *Gonzàlez Sànchez vs Medicina Asturiana SA* [2002] ECR I-3901.

111 Directive 374/85/EC, article 13: "The Directive shall not affect any rights which an injured person may have according to the rules of contractual or non-contractual liability or a special liability system existing at the moment when this Directive is notified."

112 *Arzneimittelgesttz § 84.*

113 This interpretation suggest a substantial analogy with the negligence regime that is provided by Section 6 (c) of the *Restatement Third on Torts.*

114 Art. 2050 of the Italian civil code provides: "Chiunque cagiona danno ad altri nello svolgimento di un'attività pericolosa, per sua natura o per la natura dei mezzi adoperati, è tenuto al risarcimento, se non prova di avere adottato tutte le misure idonee a evitare il danno".

115 Which can be the case if we consider that general tort law rules can be applied as special liability rules for specific types of products (as pharmaceuticals are), see case Cass civ., 29 April 2005, n.8981: "Posto che la disciplina della responsabilità da prodotti difettosi *si affianca e non si sostituisce alla disciplina codicistica sulla responsabilità per danno* [...] il produttore risponde dei danni cagionati dal vizio di progettazione del suo prodotto qualora siano provati la sua colpa nella causazione dell'evento, ed il nesso causale tra il vizio della cosa ed il pregiudizio."

the plaintiff will be able to chose who to sue: the German producer, or the Italian supplier. Furthermore, for the producer (or supplier) to avoid liability the burden of proof is harsher than under the Directive's provision, since the defendant has to show he took "all appropriate measures to avoid the damage", in the way such a provision is interpreted by the courts[116]. Clearly the outcomes of these three imaginary lawsuits could be different, showing different attitudes towards consumer safety across the EU. So, again, is pharmaceutical products liability harmonised in the EU? the answer is no, and it doesn't seem that such a trend is likely to change.

(2) The second question goes with the first. How are the regulatory and the litigation systems linked? There are two interesting provisions in the EC Directive 2001/83 on pharmaceutical safety.

The first one is in article 25: "Authorisation *shall not affect the civil and criminal liability* of the manufacturer and, where applicable, of the marketing authorisation holder."

The second is in article 61.4: "The fact that the competent authority do not refuse a marketing authorisation pursuant to paragraph 2 or a change to the labelling or the package leaflet pursuant to paragraph 3 *does not alter the general legal liability* of the manufacturer or as appropriate the marketing authorisation holder."

What is "the general legal liability of the manufacturer"? To which regime of civil liability does Directive 2001/83 refer itself? Aims of systemic coherence would suggest that it refers to the Product Liability Directive, which was intended to cover "all movables", therefore including pharmaceuticals. That is the case for example in the UK. But here rises a problem of linkage between the two regimes. The Product Liability Directive, given the defence provided by Article 7(e), limits its effects to the moment the product enters the market. The relevant knowledge to be considered to assess a producer's liability, is the knowledge available at that moment. The ECJ made this point clear in its ruling against France[117] (the implementing legislation of which rendered the development risk defence available only to the producer that could prove a ten years monitoring after the product entered the market)[118]. The consequence is that the Directive's regime of product liability cuts out the whole pharmacovigilance post-marketing period that will therefore fall into the boundaries of a different liability regime, in case of damages, obeying to different rules (such as negligence). It has been pointed out that such an outcome is paradoxical[119]. Liability rules, which are supposed to play a role *ex-post* in risk management are bound to the *ex-ante* state of knowledge, whereas regulation (with the pharmacovigilance system) is taking care of the *ex-post*, while regulation is typically meant to prevent adverse events (and therefore

116 The producer has to show positively that he took all possible measures and techniques to avoid the damage, even the most advanced and abstractly possible ones, no matter the costs or the hardness of the feasibility; for a discussion see Recano P., *La responsabilità civile da attività pericolose*, CEDAM, 2001, pp. 200-210.

117 Case C-52/00 Commission vs France [2002] ECR I-3827.

118 Such a legislation was overruled in the above mentioned case, explicitly because the two fields were meant to be kept separated.

119 Cafaggi F.*, The institutional framework of European Private Law*, pp. 191 and following.

plays its role mainly *ex-ante*)[120]. In other words, for pharmaceutical products, the Product Liability Directive doesn't seem to work. And in the light of enhancing consumers safety, such a fragmentation goes to the detriment of both the access to justice and the level of protection (if damages occur outside the boundaries of the Directive and the consumer has to sue in negligence, he will have to prove the fault of the defendant, which is, as it has been deeply discussed by lawyers and scholars, extremely difficult)[121]. Basically, in countries where pharmaceuticals undergo the discipline of the Product Liability Directive, the link between regulation and liability provides a shape shifting liability regime, depending on the timing of the damage and of the related knowledge.

In Member States such as Germany or Spain, however, the relevant liability regime will definitely be the special regime put in place by national laws (such as the *Arzneimittelgesetz*). Therefore, a producer will be held to a standard of strict liability, with no defence, all along the regulatory process (both *ex-ante* and *ex-post*). Such a regime renders *de facto* any regulatory compliance by the manufacturer valueless, and this might discourage producers from any innovative research, as well as encourage non virtuous behaviour, such as *moral hazards*[122]. In those countries, the link between the two systems consists in the latter (liability) erasing the former (regulation) in cases of damages caused by pharmaceuticals.

The most interesting scenarios are those of countries that apply general tort law provisions as special product liability regimes for pharmaceutical products. That is the case in Italy. We believe that the application of Article 2050 cc as interpreted by the courts is the most effective among those we have analysed, being our first goal the protection of consumers without unreasonably sacrificing the interests of the producers (whose incentives to innovate are deeply influenced by the related risks). First, in any case of damages caused by pharmaceuticals, the Italian judicial model of pharmaceutical product liability ensures the applicability of the same regime regardless to the timing of the damage and of the related knowledge (contrary to those countries where pharmaceuticals undergo the discipline of the Directive). Secondly, there is no development risk defence (which implies a 'negative proof' that the state of knowledge wasn't such as to enable the existence of the defect to be discovered, with all the uncertainties related to the "state of knowledge" brought in by such a defence), but a burden of proof, upon the producer, to positively demonstrate he took all appropriate measures to avoid the damage, including even those only abstractly possible, no matter the costs or the feasibility[123]. Such a provision fits quite well with the pharmacovigilance system, as it ensures the possibility of a cross-fertilisation

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120 Cafaggi F., *The institutional framework of European Private Law*, pp. 191 and following.

121 A few words to recall the origins of product liability in the US and the EU. In both scenarios, the first concern was to shift the burden of proof from the claimant to the defendant, in order to balance the asymmetric distribution of information and economic means. For an overview see among others Ponzanelli G., *La responsabilità civile - Profili di diritto comparato*, Il Mulino, 1992.

122 As stated by Wandt M., "German approaches to Product Liability".

123 See Italian cases: Cass civ., 29 April 2005, n.8981; Tribunal of Venice, 14 February 2005; Tribunal of Rome, 20 April 2002, *Diritto e Giustizia*, 2002; Cass civ. 27 July 1991 n.8395, *Rep. Foro It.*, 1992; Cass civ. 15 July 1987 n.6241, *Foro It*, 1988.

between the litigation and the regulatory system, the latter being likely to get enriched by the outcomes of litigation[124]. Therefore, such a regime has the potential to avoid the risk of a loss of knowledge. On the other hand, regulatory compliance wouldn't loose its value (as it happens in Germany), since an undiscoverable damage (as interpreted by the courts in the application of Article 2050 cc) wouldn't imply liability for the producer.

Conclusions

The link between liability and regulation remains weak[125]. As for the European Union, there are no clear regulations or even guidelines on how the two systems should positively interact in order to reach an optimal level of consumer protection. Moreover, if we focus on tort law it must be recalled that product liability claims are extremely occasional in the EU. A serious investigation on the issue of access to justice is needed here, since at the moment there appear to be substantial obstacles, namely the cost of litigation, and the absence of collective actions. The Vioxx case provides a good example: in the US a massive class action led to a settlement worth 4,8 billion dollars. Individual cases have been started in the EU as well, but on a dramatically smaller scale, and there is no access to clear data regarding such settlements. As for what concerns the current situation in the United States it in uneasy to draw precise conclusions. Criticisms to the doctrine of preemption have been raised along the paper. Was the doctrine to be considered overruled after *Wyeth*, the situation in both sides of the ocean would be still unsatisfactory in light of the "negligence" nature of the liability rules provided by both the *Restatement Third* and the Product Liability Directive as interpreted by the ECJ.

As suggested in the Introduction, production and testing of new drugs are nowadays highly globalized phenomena. However, we have observed in the paper that rules are still focused on national or regional areas. Regulators are struggling to confront with such an issue. The increasing number of bodies involved across the world in the approval process of a new drug, combined with the incomplete international harmonisation of the relevant regulatory guidelines, generate a non-negligible level of uncertainty. A possible answer to such uncertainty could be found in the regulatory role of tort law rules. We believe that a good beginning in linking the regulation and the liability systems, towards a better availability of relevant knowledge, might be to give to the law of tort an autonomous role in identifying the proper conduct to adopt in the borderline field of what can be known and what can't be known.

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124 See among others Green M.D., "Statutory Compliance and Tort Liability: Examining the Strongest Case" at 482 ("Sometimes it is the tort system that uncovers instances of non-compliance with FDA regulatory standards, rather than the FDA itself."); and generall Viscusi K., *Regulation through Litigation*.

125 See Cafaggi F., *The institutional framework of European Private Law*, pp. 191 and following, according to whom such a topic is still poorly analysed and understood.