

NEW FRONTIERS OF PHARMACEUTICAL LAW YOUNG RESEARCHERS WORKSHOP*: A SUMMARY

by

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The *Dipartimento di Studi giuridici* of the Università del Salento, Lecce, in association with *Opinio Juris in Comparatione* and the British Institute of International and Comparative Law (BIICL), Product Liability Forum, held on May 6th–7th, 2010 the Young Researchers Workshop “New frontiers of pharmaceutical law”. The Workshop was intended to stimulate the debate and promote Young Researchers’ ideas and work on pharmaceutical law topics such as ethical issues, market approval processes, civil liability (product liability and compensation schemes), antitrust and intellectual property. The discussion highlighted how this legal field, which originally stems from general principles of private and public law, is now experiencing a thorough process of specialization and partial isolation, only partially mitigated by the globalization of the pharmaceutical market.

This Workshop was opened by Dr. Duncan Fairgrieve, Director of the Product Liability Forum of the BIICL. Through the lense of comparative law (both horizontal and vertical), the speaker addressed the audience on the relationship between civil liability and *ex ante* regulation tools, highlighting the coordination problems that give rise to the risk development defense and US-style preemption in pharmaceutical law.

Stemming from these ideas, Marco Rizzi’s presentation entitled “Regulating risks in pharmaceutical law: the need of an optimal interplay between products safety and products liability” opened the first panel of the workshop, dedicated to the connections between health regulation and policy. Rizzi called for a theoretical model of pharmaceutical products safety in which regulation and liability operate complementarily, as they are supposed to achieve the same goal of protecting consumers. He proposed a move forward from the traditional separation between public and private law (a suggestion that many other participants will share along the debate), and a reshaping of pharmaceutical law around the empirical necessities of patients. “Relevant knowledge” is deemed to be the key notion in this respect. The analysis started with some comparative remarks about the divergences and similarities between the U.S. and the European drugs regulatory and liability regimes.

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As for the former, the discussant highlighted how the International Conference on Harmonization is trying to soften the differences between the two legal orders. However, a complete harmonization is still a long way off, and this is even more the case for tort law, because of the differences still existing between the European Member States legal regimes despite the implementing of the EC Directive no. 374/1985. To make an important example, U.S. do not apply the European concept of “development risk”, but rather make reference to the vague notion of “state of the art”.

In the second part of his presentation Marco Rizzi made the case for bridging a tighter link between regulation and product liability, and expressed his concern for the opposite direction that the U.S. legal system is rather taking in this respect. He showed how the “preemption” doctrine - that is the idea that FDA approval of labeling preempts conflicting or contrary State law - has been gaining momentum in the area of drugs litigation, at least until the 2009 U.S. Supreme Court decision in the case *Wyeth vs Levine* apparently – but not in the discussant’s opinion – overruled it.

However, Marco Rizzi’s claim was that both scenarios, the European and the American, still consider the two regimes separate rather than complementary. The discussant concluded by mentioning the Italian regime as an example of a system that might work properly in making them interact. Article 2050 of the Italian Code, in fact, seems to protect effectively consumers without unreasonably sacrificing the interests of the producers.

Starting from the influenza A H1N1 case, Anniek de Ruijter’s paper gave a detailed insight of the role that public health policies play within the EU political and constitutional system. In particular, the Author highlighted the constitutional implications of the European response to the pandemic emergency, getting to the conclusion that Europe relied excessively on informal instruments of cooperation and denied parliaments a proper role of control, therefore violating the basic principles of a democratic order.

In the first part of her discussion, the Author described the creation of a European institutional system for the protection of EU citizens’ health. The speaker started from the 1998 Treaty of Amsterdam reforming the EC Treaty Article 152, under which institutional networks for the surveillance and control of communicable diseases could finally be implemented. Always in 1998 the European Network for Communicable Diseases moved its first steps and ended up covering two main pillars: surveillance network and the European Early Warning and Response System, whose scope was alerting national health authorities in Member States whenever an international outbreak required European coordination. The last phase of the process was the extension of the Health Security Committee mandate (created in 2001 after the September 11th terrorist attack) to cover generic health emergencies and to prepare a united European response in case of a flu pandemic.

In the second part of the relation the Author addressed the history of the EU response to the 2009 pandemic, paying a more specific attention to how the European regulations on vaccines were adapted to the emergency, both from the point of view of the authorization procedures and product liability.

Finally, the legitimacy of the whole EU emergency procedure came into question. The informal structure of the Health Security Committee was deemed to violate the *rule of law* and democracy principles, as the Committee members, responding to the sole respective national health departments, had the power to create and propose extensive measures with an extreme impact on the lives of EU citizens without being subject to any effective legal constraint. As the Speaker pointed out, the same decision of declaring that a pandemic was ongoing was taken on the complete discretion of the Committee: neither the National nor the European Parliament could play any role in this respect. What is more striking, the European procedures in case of outbreak of communicable diseases might also seriously impact on citizens' fundamental rights: emergency measures might restrict the free movement of people and goods, and the exchange of information between national health systems might result into a violation of patients' right to privacy; even the decision to prioritize certain groups for vaccination might have constitutional implications with regard to the right to access health care. For all of these reasons, the H1N1 pandemic experience represents an important opportunity to reconsider the whole European response to epidemic threats.

Following Marco Rizzi's opinion, Francesco Quarta as well strongly advocated for a deeper involvement of private actors in monitoring the costs connected to drug prescriptions.

The discussant started from highlighting the tight connection that links drug costs to what is traditionally considered the main purpose of tort law, that is making the victim whole: tort victims, in fact, at least those resulting with health damages, are likely to use damage awards mainly to buy medicines or to cover other medical expenditures. Nonetheless, centralized systems like Italy *de facto* exclude private citizens from playing any role in the control of drugs costs; this is not the case in the US, where the Department of Justice incentives private parties to bring suits against drug companies whenever they detect anticompetitive conducts, such as raising pharmaceutical prices by promoting off-label use. What is more important, these so called "qui-tam" plaintiffs may be able to recover up to 25 % of the obtained proceeds.

Therefore, the Author assumed that these "Private Attorney General" actions might be profitably exported to Europe without any risk of violating the European legal tradition. He concluded by making the case for a complete reconsidering of the public/private divide, and expressing his hope that the democratic emergency that often brings Parliaments to outsource regulation to alleged "independent agencies" could rather be overcome by reconsidering the intersection of private litigation and public goals.

The second Panel of the Workshop, entitled “Specific issues in pharmaceutical law”, was opened by Dr. Peter Feldschreiber from the MHRA, who gave an in-depth and thorough presentation on “Causality in medicine law” from the dual perspective of scientific and legal causation.

In the first paper of the session Isabelle Chivoret addressed the topic of causality in product liability cases, and used the French case law on damages deriving from vaccines against Hepatitis B as an example of how Courts might weigh scientific evidence differently in establishing causal connections between conducts and torts. The Author reported a contrast on the point between the French *Cour de Cassation* and *Conseil d’Etat*: while the first in 2003 relied on the absence of scientific certainty about the nexus between the vaccine and the disease to exclude the responsibility of pharmaceutical companies, the second used factual presumptions based on a case-by-case analysis to get to the opposite solution. The Author supported the position expressed by the *Cour de Cassation*, and expressed her belief that causation should reflect scientific knowledge and should not be based on purely empirical presumptions.

The public/private divide that was already at the centre of Francesco Quarta’s analysis on “private attorney’s actions” and Marco Rizzi’s proposal on the regulation of risks in pharmaceutical law, came back to the fore with Francesca Ferrari’s presentation dedicated to nanomedicine issues.

Francesca Ferrari’s work addressed three main points: first, she explained what nanomedicine is and what kind of legal questions it gives rise to; second, she argued that nanomedicine is a typical situation where a precautionary approach is needed, and draw a comparison between this field and the European legislation on GMO (genetically modified organisms), arriving at the conclusion that the European system is overly grounded on regulatory functions; third, she criticized this solution as not taking into full account the necessity of a proper balancing between prevention and compensation in the social acceptance of the new risks.

The Author at first pointed her attention on the fact that, despite the new challenges connected to the practice, there is still no piece of legislation explicitly dedicated to nanomedicine on the European level. This happens because nanomedicine is incorrectly referred to as a new enabling technology and not as a new model of healthcare tool, without considering that nanoproducts are expected to blur the rigid distinction between drugs and medical devices. Moreover, even if the risks connected to the practice are still uncertain, this was not enough for Europe to adopt in this case as well, under the precautionary principle, the pre-market approval regulation already in force in the GMO field. The discussant’s explanation for that was that nanomedicine issues cut across too many disciplines and industrial sectors, making it impossible to arrange a comprehensive set of specific rules. This means that nanomedicine is, and in the future is likely remain, regulated through dispositions already in place for other sectors, as long as they are sufficiently flexible to be adapted to its specificities. Is this the only possible solution? The Speaker replied with a clear no. What is missing here is a clear liability rule that

permits to overcome the risk that the development risk defence, under the EU Products Liability Directive, broadens too much its scope of action. The Speaker's conclusion was that precautionary actions cannot be reduced to a choice among different legal solutions, but should rather be seen as a complex framework that takes into account all the possible conflicts that might arise in the area.

Also addressing the general issue of regulation of uncertain risks, Albina Mulaomerovic focused on pharmacovigilance in Canada, noting the non-compulsory nature (at least for professionals) of this "phase IV". From a comparative perspective, she questioned whether such a voluntary practice is in line with other models (such as that of the EU), while advocating a revisiting of the federal law.

Opening the third panel dedicated to IP and Competition Law issues, Anna Lisa Bitetto's contribution dealt with the controversial practice of parallel imports in the pharmaceutical sector, that is, following the Discussant's definition, «the unauthorized distribution across borders of goods protected by intellectual property rights in the receiver nation».

Parallel imports present highly controversial features both from a legal and an economic perspective. EC law has traditionally contrasted firms trying to prevent parallel imports from distributors, as this is likely to result in a partitioning of the European market contrary to the principles set by the EC Treaties. Furthermore, it is unclear from an economic point of view whether parallel imports, by reducing prices for retail distribution, do actually enhance the welfare of consumers, or rather disincentivise R&D investments to their detriment. The Author gave short account of the different economic positions on the point and went on to make extensive reference to EC case law, and mainly to the *Bayer*, *Glaxo*, and *Syfiat* cases. Finally, the Author quoted an analysis on the economic impact of parallel pharmaceutical trade in the European markets, showing that there is no evidence of a "race to the bottom" of prices, but rather a "convergence to the top"; she concluded by signalling the importance of balancing incentives for innovation with free access to drugs, especially for the needs of underdeveloped countries.

Chiara Sammarco's work was focused on the effects of purchasing medicines through tendering procedures as a way to stimulate dynamic competition in the pharmaceutical market.

As can be gleaned from an Austrian Institute of Research survey on the topic, a significant number of EU members use tendering as a procedure for purchasing medicines. As for Italy, pharmaceuticals are purchased through public tenders in order to reach two goals: to ensure the needs of hospitals are met and to deliver drugs to patients in home care or discharged from hospitals. In both cases, the aim is to ensure the maximum availability of pharmaceuticals at the lowest price. The German case also deserves a more specific mention, as Germany is the only country where the public price of drugs is fixed by private companies and not by public regulatory entities.

The Discussant went on by mentioning the four factors that might be taken into account in order to make tendering in the pharmaceutical sector more efficient: transparency, maximum participation, attention to the composition of tender lots and to the sums awarded for contracts.

As for transparency, the Author highlighted the trade-off between enforcing non discriminatory procedures and avoiding parties to collude, as it might happen when the conditions offered are clearly stated and known to the other participants.

The composition of tender lots was deemed to represent the problematic core of the practice. Advice from the Italian Competition Authority (AGCM) suggested that tendering objects shall be neither expanded nor artificially restricted, and should be carefully designed in technical and economic terms but without making reference to any specific brand or patent (regarding the Italian case, some useful guidelines can be found in the case law, and mainly in a 2003 Emilia Romagna Regional Administrative Court decision¹). The Speaker's conclusion on the point was that including in the same lot a homogeneous class of drugs does not represent the most appropriate tool in order to stimulate competition, as it might create all-inclusive and undistinguished containers of medicines with different efficiency and innovation potentialities.

Finally, the Discussant suggested that lowest price should not represent the only criteria for determining the award, especially for in-patent drugs, which require a thorough and extensive comparative selection.

Panel III ended with Antonio Del Sole's presentation entitled "The legal protection of biotechnological inventions". The Discussant focused his contribution on the EC regulations referring to the patentability of biotechnological inventions, by making a more specific reference to the EC Directive 98/44/EC and to the Directive Chapter II, covering "Scope of protection" issues. What is at stake here is whether a biotechnological genetic patent protects all the possible uses of the patented genetic sequence, or rather the sole specific purpose the patent was originally allowed for. The text of the Directive looks rather obscure in this respect, as Articles 8 and 9 and Article 5 seem to point respectively in the two opposite directions indicated above. However, in the Author's opinion Article 5 should prevail and therefore biotechnological patents should be kept "purpose-bound", as the AG conclusions in the case C-428/08, *Monsanto Technology LLC v. Cefetra BV and others* further confirmed. The opposite solution would be in contrast with what the Discussant called the "exchange principle" between the inventor and society, according to which the legal order protects (for a limited amount of time) the inventor's exclusive right on the patented product, and the inventor in exchange acknowledges to the scientific community the opportunity of studying and further implementing his discovery.

¹ TAR Emilia Romagna no. 549/2003.

A presentation from Dr. Agnese Querci entitled “Clinical trials on vulnerable human subjects” opened the fourth and last session of the Workshop, dedicated to “Professions and bioethics”.

The starting assumption of the Discussant’s analysis was that clinical trials should be differentiated according to parameters such as the ability of persons involved. Trials on people affected with mental or physical disabilities might therefore be problematic because of the patients’ incapacity of expressing a free and informed consent; in the case of minors, consent might be given by the parents and the minor together, but a proper balance between the two seems hard to establish. However, the necessity to conduct such trials might still arise in emergency situations.

In this respect, the EC Directive 2001/20/EC allows the inclusion in clinical trials of incapacitated adults with the only condition of the legal representative’s consent: the Italian d. lgs. No. 211/2003, instead, adds a “state of necessity” requirement (the therapy is needed in order to save the life or avoid critical damages to the person involved). Moreover, the long time that is needed to designate the guardian under Article 408 of the Civil Code further enhances the rigidity of the Italian solution. In the Speaker’s opinion, another option would be listing by law those who can allow trials in case of emergency (consort or partner *more uxorio*, relatives) following the legislation on legal transplants. The cases of minors, pregnant women and vaccine testing should be regulated specifically. As a final remark, the Discussant restated the importance of letting patients freely express their consent to tests in the best possible way, without any undue psychological influence and not just in the absence of physical constrictions.

Luca Nocco and Benedetta Guidi focused their attention on the legal and medico legal aspects of the debate concerning the off-label prescription of drugs, that is «the administration of a registered medicine or medical device that is not included nor disclaimed in the product information». The two discussants’ long analysis addressed a large amount of topics: among them, we remember the Italian case law regarding the doctors’ professional autonomy, with a more specific reference to the liability issues connected to the prescription of drugs; the reasons that justify the off-label prescription of medicines; the so-called Italian “Di Bella” case; the Italian rules and procedures on off-label prescriptions; some comparative remarks between the Italian and the American case.

Off-label use of drugs is regulated in Italy by two pieces of legislation, law no. 94/1998 and law no. 244/2007. The two provisions are not easy to reconcile: the first requires off-label employments to be in compliance with common knowledge and scientific opinions, while the second adds the availability of favourable data deriving from phase two clinical experimentations. Recommendations from the Italian National Bioethics Committee make the point even more unclear: not only may a doctor be authorised, but he may even be bound to use off-label prescriptions in state of necessity, whenever there might be a realistic possibility of using therapies already known and accepted by medical science. The medical deontological code as well, in its last 2006 version, only states that non conventional

practices must be held under the direct professional responsibility of medical doctors. An expressed and informed consent from the patient is also generally required.

The Discussants moved on to describe the scarce Italian case law on the topic. According to a 1997 decision from the Private Law Division of the *Corte di Cassazione*, new therapies should be allowed only after careful clinical experimentations. However, in 2008 the Criminal Law Division tackled the issue more broadly, stating that doctors may be held liable for off-label prescriptions whenever they do not accurately evaluate the patient's physical conditions, and, what is more important, whenever they suggest treatments which are not useful in curing the specific disease they are called on to evaluate: the odd conclusion is that off-label treatments are allowed as long as they obtain better results than on-label ones.

As for the U.S. case, the Authors assumed that off-label prescription of drugs is generally acknowledged both by the Federal Drugs Administration and by the Courts. According to a widespread opinion, U.S. doctors are not even required to inform patients that treatment is off label, as failure to inform does not constitute malpractice in itself. In any event, doctors would not be held liable for failure to warn about any undemonstrated risks, even those they should have been aware of.

The conclusion is that the Italian system leaves far less freedom to physicians in prescribing off-label treatments. However, the Discussants' belief was that «freedom to prescribe drugs cannot transform itself in an unrealistic ambition, based on experimentalism and empiricism, with the tendency to lead to a culpable complaisance».

The fourth session continued with the Aurélie Mahalatchimy's presentation dedicated to issues regarding advanced therapy medicinal products (ATMP), that is to say medicinal products based on human genes, cells and tissues. The main scope of the analysis was to explore the problematic relation between the topic and the general bioethics principles, and more specifically to describe how the EU institutions, despite not being competent to regulate ethical standards as such, handle such controversial issues on a legislative level with the aim of creating a more complete political union.

The Speaker started from giving a detailed account of the European legal framework related to the topic. As medicinal products, ATMP are covered by the EC Directive 2001/83/EC, but also by the more specific EC Regulations no. 1394/2007 and no. 726/2004. Furthermore, the EC Directive 2004/23/EC regulates various activities connected to tissue and cells, such as their donation, procurement, testing and distribution.

The analysis went on by describing the ethical role the European Parliament tried to play during the process of adoption of the aforementioned Directives. In particular, some of the parliamentary amendments aimed at banning human cloning research, or at least to provide Member States with an explicit right to prohibit the use of particular cells, such as germ cells, foetal and embryonic cells.

Furthermore, the Parliament proposed that all uses of particular tissues and cells should respect some minimum quality and safety standards.

However, the Commission rejected most of the EP proposals, and especially the one on the prohibition of research of human cloning, as it supposedly felt outside the scope of the EC Treaty Article 152 on human health protection. As a consequence Member States are left with a wide action margin, which means that, according to the subsidiarity principle, States can prohibit every use of human tissues and cells, with the only limit being that legal measures shall not represent «*a means of arbitrary discrimination or a disguised restriction on trade between Member States*» (proportionality principle).

However, this is not to say that ethical aspects are completely out of the reach for the EU legislation. The main reference is to be made to the EU Charter of Rights and to the principle stated therein of human dignity, but also to the principles of voluntary and unpaid tissue and cell donations, consent, non profit basis of procurement of tissues and cells that are all expressed as recommendations in the Directive 2004/23/EC. Furthermore, ethical assumptions infiltrate binding and non binding norms indirectly related to ATMP, such as the decisions for the adoption of European support programmes for scientific and technological research, or even the Article 3 of the Directive 98/44/EC on the legal protection of biotechnological inventions, which denies the patentability of those products whose commercial exploitation would be contrary to the “public order” or “morality”. The Speaker’s conclusion is that the effect of such provisions should not be underestimated, as it is likely to play an important role in what she called the European “governance by dominium”.

Some interesting comparative remarks with the Italian case described by Luca Nocco and Benedetta Guidi can be taken by Francisco Miguel Bombillar Saenz’s paper about the Spanish legislative regulations on the “compassionate exemption” in the use of drugs.

The formula refers to three different medical treatments that may save the life of patients suffering from severe diseases and not having a satisfactory therapeutic alternative: *a*), “compassionate use” of drugs, that is using drugs in the clinical research stage even without being part of the clinical trial; *b*), “foreign drugs”, that is access to drugs approved in other countries other than Spain; *c*), “off-label” use, that is access to drugs used in conditions other than those provided in their data sheet. The three practices are now covered by the Spanish Royal Decree 1015/2009, enacted in June 2009 with the aim of speeding up procedures and guaranteeing safety to patients. Until that moment, Spanish patients in the above-mentioned condition had to follow a long and painful three-steps procedure: after they had given their informed consent to the treatment, the doctor, the Centre Director and the AEMPS (the Spanish Medicines Agency) were competent to approve or refuse the compassionate use for every single case, each of them repeating evaluations that, in the Author’s view, should have been left to the patient’s discretion (e.g. the benefit/risk connection of a given treatment). The new legislation, instead,

provides patients with two different and patient-friendly procedures: individual access authorizations and temporary use permits.

The second appears as the most relevant option, as it exonerates medical centres from applying for individual clearances for each patient *«in cases of drugs that are at an advanced stage of clinical research (...), whenever it is planned to be used on a significant group of patients»* (article 9 RD 1015/2009), under the conditions established by the AEMPS. AEMPS is also entitled, under article 13 of the Decree, to use recommendations in the off-label use: in this respect, the Agency shall consider, between the other factors, whether the use *«entails a significant health care impact»*, that is, as the Author critically pointed out, whether it increases public pharmaceutical expenditure.

Finally, the Author explained how the new automated procedures provided for the submission of applications will supposedly speed the process up further. He concluded by giving some remarks on the administrative law issues connected to the topic, paying a more specific attention on how patients might challenge a denial from the AEMPS under the doctrine of “legitimate interest”.