

New European legislation on pharmacovigilance

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The European Parliament and the Council of the European Union have recently adopted Regulation (EU) No 1235/2010¹ and Directive 2010/84/EU² concerning the pharmacovigilance of medicinal products for human use. These and other European institutions have been laying down rules on the subject for decades, but this is the first time they have enacted legislation specifically and (almost) exclusively regulating pharmacovigilance. This paper analyzes the context, causes, objectives, key points and challenges of the new legislation.

1. The meaning of pharmacovigilance

Despite rigorous studies and trials carried out before the approval of a new medicinal product, relatively little is known about its benefits and risks until the medicine is marketed and widely used, because the circumstances of clinical practice differ notably from those of premarketing testing.³ 1) Clinical trials often involve a limited number of patients. This usually precludes identifying rare –but sometimes serious– adverse effects. 2) The duration of clinical trials is often much shorter than the expected length of treatment in clinical practice. Adverse drug reactions appearing after exposure for prolonged periods or only long after exposure are, consequently, improbable to be detected before being put on the market. 3) Clinical trials usually involve relatively healthy patients, who may not be entirely representative of the future target population (the medicine's consumers). 4) The treatment of patients involved in clinical trials is usually limited to only one drug. It is therefore unlikely to identify adverse drug–drug interactions before marketing. In short, the full safety (and efficacy) profile of medicinal products for human use can be known only after they have been placed on the market.⁴

¹Regulation (EU) No 1235/2010 of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products (Official Journal of the European Union L 348 of 31 December 2010).

²Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use (Official Journal of the European Union L 348 of 31 December 2010).

³J.R. Laporte and M.D. Rawlins, Pharmacovigilance, *Pharmaceuticals Policy and Law* 1 (1999), 49–59.

⁴Recital 2 of the Preambles of Regulation (EU) No 1235/2010 and Directive 2010/84/EU.

For all of these reasons, it is very important to set up pharmacovigilance systems. They must be designed to continuously monitor the use of marketed medicinal products, in order to detect, as soon as possible, noxious and unintended reactions to them, to verify whether their risk-benefit balance is still favourable and to adopt appropriate regulatory decisions with the aim of protecting public health and other public (e.g. environmental)⁵ interests as well. Pharmacovigilance can be defined as a set of activities undertaken to collect, process, store, assess and transmit information on the risks and benefits of medicinal products, in order to maintain, vary, suspend or revoke their marketing authorisation, and to make other regulatory decisions relating to the use of the aforementioned products.

2. The growing importance of pharmacovigilance

Postmarketing surveillance of medicines has become more and more important over the years. Since European institutions laid down rules on the subject first in 1965, every major reform of pharmaceutical legislation has boosted and strengthened pharmacovigilance systems. Two main factors could explain this development.

On the one hand, the social benefits of pharmacovigilance activities have increased. As some prominent sociologists have noted, we live in a “risk society”⁶ – a society increasingly exposed to widespread, massive and extremely uncertain risks, where people are to a greater extent aware of them, and more and more conscious that those risks are created and could be mitigated by the human hand. Ours is thus a society increasingly preoccupied with safety. In particular, the risks associated with medicines are perceived larger than ever, and this is not a misconception at all. Some recent developments have posed new and serious threats to drug safety: globalization of pharmaceutical markets, online drugstores, fake medication, augmentation in the number of consumers of medicines, growth in the per capita consumption of medicinal products, etc.

On the other hand, the social costs of pharmacovigilance have considerably decreased. It is also said by renowned sociologists that we are living in the age (or the society) of information.⁷ Communication and information technologies have experienced spectacular growth and development over the last decades, and will probably still progress during the next ones. This has made a huge impact on several activities, especially on those greatly involving the management of information, as is the case of pharmacovigilance. Monitoring the safety and efficacy of medicines has become more and more efficient over time. New technologies have offered and

⁵See Articles 1.28, 8.3(ca) and 8.3(g) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁶U. Beck, *Risk Society: Towards a New Modernity*, Sage Publications, London, 1992; A. Giddens, *Risk and Responsibility*, *Modern Law Review* **62-1** (1999), 1–10.

⁷See, e.g., the trilogy of M. Castells, *The Age of Information*, volumes I (2009), II (2009) and III (2010), Wiley-Blackwell, Oxford.

will probably still offer many facilities to substantially improve both the quantity and the quality of information relating to costs and benefits of medicines. They allow all the stakeholders to collect more and better data, and to store, retrieve, evaluate and exchange it with much less time, effort and other valuable resources.

3. Key points of the 2010 reform

3.1. More pharmacovigilance

Regulation (EU) No 1235/2010 and Directive 2010/84/EU have expanded and strengthened European pharmacovigilance systems in many ways. The amendment of the definition of “adverse reaction” is one of them. This term plays a key role, insofar as the main goal of pharmacovigilance is to “prevent, detect and assess adverse reactions to medicinal products placed on the market”.⁸ The extent of its definition consequently determines the scope of most pharmacovigilance rules. Article 1.11 of Directive 2001/83/CE, in its original version, defined it as, “a response to a medicinal product which (. . .) occurs at doses *normally used* in man for the prophylaxis diagnosis or therapy of disease or for the restoration, correction or modification of physiological function”. Literally interpreted, this clause seems to exclude adverse responses originated by abnormal uses of medicinal products. Directive 2010/84/EU has broadened the definition of that term –and therefore the scope of many pharmacovigilance duties– to ensure that it now covers noxious and unintended effects resulting not only from the authorized use of a medicine at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including misuse and abuse of the product.

The now explicitly imposed duties concerning the follow-up of reports of suspected adverse reactions⁹ can also serve as an example of the legislative purpose to improve the quality of pharmacovigilance.

Moreover, pharmacovigilance is substantially strengthened by requiring “additional monitoring” for some medicinal products which pose abnormally high risks: medicinal products with a new active substance, medicinal products authorised in exceptional circumstances or subject to certain conditions, biological medicinal products, etc.¹⁰

Another example is the requirement to conduct authorisation safety or efficacy studies. The previous legislation provided for the possibility of carrying out only *safety* studies,¹¹ and did not clarify whether they would be voluntary or compulsory,

⁸Recital 2 of the Preambles of Regulation (EU) No 1235/2010 and Directive 2010/84/EU.

⁹See Articles 102(e), 107.4, 107a.1 and 107a.2 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

¹⁰See Article 23 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

¹¹See Article 1.15 of Directive 2001/83/EC, in its original version.

nor the conditions under which they would be required. Directive 2010/84/EU and Regulation (EU) No 1235/2010, on the contrary, have empowered the relevant authorities to impose on the marketing authorisation holders the obligation to perform post-authorisation studies. These studies would relate not only the safety of medicinal products but their efficacy as well, and would be required at the time of the granting of the marketing authorization or later.¹² The European Parliament gave the following justification for this provision:

“By widening the scope of post-authorisation studies, this gives national competent authorities more freedom to determine the kind of study which is most useful. At the moment, most drugs are subject to some kind of post-authorisation safety study as an extra safety precaution. However, although safety monitoring happens through the life of a drug, efficacy is only checked once, at the time of authorisation. There should be the possibility to monitor drug efficacy post-authorisation as well, in real world populations and real-life conditions”.¹³

Unlike the safety of medicinal products, their therapeutic effectiveness can normally be sufficiently tested and proved through pre-approval studies. For that reason, pharmacovigilance focuses on adverse reactions. However, marketing authorisation may be granted –because the risk-benefit balance of the considered medicinal product is positive– despite the fact that there is more uncertainty on the therapeutic effects of the medicine than is normally the case. In these exceptional circumstances, post-authorisation efficacy studies should be performed to sufficiently reduce such uncertainty. Moreover, the use of the product in real-life conditions might reveal that its therapeutic effects are not exactly as expected.

Those legislative acts, however, have not fully clarified all the circumstances under which the marketing authorization might be obligated to conduct the studies. Such omission is problematical. Post-authorisation studies can generate very valuable information concerning both the safety and the efficacy of medicinal products, but also represent a considerable burden for the marketing authorisation holders, because of the costs of carrying out these studies. The lack of rules specifying the conditions under which such studies may be required –or the lack of precision of those rules– gives the competent authorities discretionary power, which poses a threat to authorisation holders: the less –or the less concrete– the rules, the wider discretion the authorities have and the more the risk of abuses pharmaceutical firms bear.

According to Directive 2001/83/CE (as amended by Directive 2010/84/EU), marketing authorisation may be granted subject to certain conditions in exceptional

¹²See Articles 21a and 22a of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

¹³Committee on the Environment, Public Health and Food Safety, Report on the proposal for a directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2 June 2010 (A7-0159/2010, Amendment 20, pages 17 and 18).

circumstances: “when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety of the medicinal product under normal conditions of use, for objective, verifiable reasons and must be based on one of the grounds set out in Annex I”. The performance of a safety or efficacy study may be one such condition.

Those studies may be also required in normal circumstances. The accuracy of the rules laid down to determine these circumstances –and the discretion left to competent authorities to require post-approval studies– depends in fact on whether the considered study concerns either the safety or the efficacy of the medicinal product, and on whether the obligation to perform it is imposed at the time of granting the marketing authorisation or after that.

The obligation to conduct post-authorisation efficacy studies may be imposed: a) at the time of the granting of a marketing authorisation, only, “where concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed”;¹⁴ and b) after the granting of a marketing authorisation, “when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly”. In both cases, the aforementioned obligation shall be based on the delegated acts adopted by the European Commission¹⁵ to determine the situations in which post-authorisation efficacy studies may be required.¹⁶ This legal clause notably reduces the margin of discretion left to the competent authorities to impose such an obligation.

Safety studies may be required: a) at the time of the granting of a marketing authorisation;¹⁷ and b) after its granting, “if there are concerns about the risks of an authorised medicinal product”.¹⁸ The European legislature has neither further clarified in which “normal” circumstances a post-authorisation efficacy study may be required, nor empowered the Commission to determine them. The competent authorities therefore enjoy a broad discretion in imposing the obligation to perform such studies.

The creation of the Pharmacovigilance Risk Assessment Committee (PRAC) also serves the purpose of making the post-approval surveillance of medicines more robust. Unlike the Committee for Medicinal Products of Human Use (CMPHU) and the coordination group established by Directive 2001/83/EC, PRAC is a body specialized in pharmacovigilance. Some of its members are appointed by Member States and some others by the Commission, “on the basis of their relevant expertise in pharmacovigilance matters and risk assessment of medicinal products for human use, in order to guarantee the highest levels of specialist qualifications and a broad

¹⁴See Article 21a(f) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

¹⁵See Articles 21a(f) and 22a.1(b) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

¹⁶See Article 22b of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

¹⁷See Article 21a(b) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

¹⁸See Article 22a.1(a) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

spectrum of relevant expertise”. One of the members should represent health care professionals, and another, patient organisations.¹⁹ PRAC is the “main adviser’s main adviser” of the European Union regulatory authorities on pharmacovigilance issues. PRAC is responsible for providing scientific assessment and recommendations to CPMHU and the coordination group on any concerns relating to pharmacovigilance processes and on risk management systems, and for monitoring the effectiveness of those systems.²⁰ The mandate of PRAC covers all aspects of the risk management of the use of medicinal products for human use. This includes all matters relating to the detection, assessment, minimisation and communication of the risk of adverse reactions, having due regard to the therapeutic effect of such products, the design and evaluation of post-authorisation studies and pharmacovigilance audit.²¹ CPMHU should rely on such advice,²² although it may adopt an opinion which differs from it,²³ as long as it explains in detail the scientific grounds for the difference.²⁴

3.2. *More information technology*

As said above, new information and communication technologies are instrumental in order to strengthen pharmacovigilance systems and make them more rational, simple, efficient, transparent and cooperative. The Eudravigilance database and data processing network, which has been functioning since December 2001, plays a crucial role in achieving those goals. Directive 2010/84/EU and Regulation (EU) 1235/2010 aim to maintain, reinforce and further develop this online database as the single –or at least the main– point of receipt, storage and exchange of information concerning the safety of medicinal products for human use authorised in the European Union.

According to those legislative acts, Eudravigilance has to contain information on suspected adverse reactions in human beings arising from use of medicinal products.²⁵ However, it would be more consistent with the objective of pharmacovigilance activities –to verify whether the risk-benefit balance of medicines remains positive– if Eudravigilance were to contain information not only on the safety of those products but on their (lack of) efficacy as well.

The new legislation has defined in broader and more accurate terms the conditions under which different stakeholders may have access to information contained

¹⁹See Article 61a of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

²⁰See Article 56(1)(aa) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010. The tasks of PRAC are detailed in Articles 10a(a), 23.2, 23.4, 23.5, 24.2, 25a, 28.3, 28.4, 28a.2 and 28b.2 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

²¹Article 61a.6 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

²²See Article 5(2) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

²³See Recital 10 of the Preamble of Regulation (EU) No 1235/2010.

²⁴Articles 28.4 and 28b.2 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010, and Articles 107g.2, 107g.3, 107k.2, 107k.3 and 107q.2 of Directive 2001/83/EC, as amended by Directive 2010/84/EU, explicitly impose this explanation duty in some cases.

²⁵Article 24.1 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

in Eudravigilance. There shall be three levels of openness of this database: a) *full* accessibility, for competent authorities of the Member States and for the European Medicines Agency (EMA) and the Commission; b) accessibility for marketing authorisation holders to the extent *necessary* for them to comply with their pharmacovigilance obligations; and c) *appropriate* accessibility for the public, including patients and healthcare professionals; the EMA shall work together with all stakeholders, including research institutions, healthcare professionals, and patient and consumer organisations in order to define such an “appropriate level of access”; in any case, the information shall be made publicly accessible in an aggregated format together with an explanation of how to interpret the data, while guaranteeing data protection.²⁶

In order to avoid duplication of work and therefore to save resources, suspected adverse reactions which occur in the European Union have to be reported by marketing authorisation holders and Member States only to Eudravigilance,²⁷ which must be configured so that the reports can be immediately forwarded to the Member State on whose territory the reaction occurred.²⁸

By monitoring Eudravigilance, mainly through the application of data mining techniques, stakeholders can identify safety problems more efficiently. For that reason, Regulation 1235/2010/EU imposes, on the EMA, the obligation to monitor the data held on the abovementioned database with the aim of determining whether there are new risks or whether risks have changed and whether those risks have an impact on the risk-benefit balance of medicinal products.²⁹

The medicines web-portals are also important tools to achieve certain pharmacovigilance goals, especially to enhance the level of transparency of the system and to allow the participation of the public in it. EMA, in collaboration with the Member States and the Commission, have to set up and to maintain a European medicines web-portal for the dissemination of information on medicinal products authorized in the Union.³⁰ In addition, the European medicines web-portal must serve as a mechanism that allows, helps and encourages the public (in particular, patients and health professionals) to participate and to cooperate in some pharmacovigilance processes – for instance, by submitting valuable information that authorities and other stakeholders should take into account. That web-portal must contain, for example, information on how to report suspected adverse reactions to national competent authorities and how to submit information and participate in public hearings regarding urgent procedures.³¹

²⁶See Article 24.2 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

²⁷See Article 107.3 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

²⁸See Article 24.4 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

²⁹See Article 28a.1(c) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

³⁰See Article 26.1 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

³¹See points (f) and (i) of Article 26.1 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010, and Articles 107c.7, 107j.1, 107j.2 and 107l of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

Each Member State also has to set up and maintain a national medicines web-portal which must be linked to the European one and contain similar information.³² Moreover, Member States have to ensure that patients and health professionals may report suspected adverse reactions through the national medicines web-portals or through alternative reporting methods.³³

3.3. *More efficiency. Simplification, coordination, differentiation*

From the economic efficiency (i.e., rationality) point of view, the quantity and quality of pharmacovigilance should depend on its social costs and benefits. Stakeholders should invest in monitoring medicines until the social marginal return of the investment (the increasing probability in preventing certain adverse reactions to medicines or their lack of efficacy times the magnitude of the harm caused by these reactions or that lack of efficacy) equals its social marginal costs.

It must be noted that those social benefits (and consequently the optimal level of pharmacovigilance) are mainly a function of two variables. The first one is the existing uncertainty about the adverse reactions and the therapeutic effects of the medicinal product: the more uncertainty that exists, the more likely it is to improve the knowledge on its safety and efficacy and to prevent damage. The second one is the severity of the potential harm: the more serious it may be, the larger the expected returns of pharmacovigilance are. The intensity of pharmacovigilance activities should hence be proportionate to the aforementioned uncertainty and to the harm that adverse reactions to medicines or their lack of efficacy might cause.

That efficiency principle has inspired some of the past reforms of the European pharmaceutical legislation. For instance, marketing authorisations were valid only for five years and were renewable for the same periods as well. Every five years, on application of the authorisation holder, the competent authority had to verify through a formal (and costly) procedure whether the risk-benefit balance of the considered medicinal product was still showing to be positive or not, and to make an explicit decision in that regard.³⁴ That rule was modified in 2004. Now marketing authorisations need to be renewed after an initial five years. And once renewed they shall be valid for an unlimited period, unless the competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with one additional five-year renewal.³⁵ The old rule is probably less efficient than the current one. The rationale of this latter is as follows. Once a medicinal product is authorised and placed onto the market, the uncertainty of its safety and efficacy (and consequently the social benefits of monitoring it) tends to decrease. As time goes by, unexpected adverse reactions to that medicine are less and less likely to be discovered, and carrying out a formal procedure to renew the authorisation becomes less and less useful.

³²See Article 106 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

³³See Articles 102(b) and 107a.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

³⁴See, for example, Article 24 of Directive 2001/83/EC.

³⁵See paragraphs 2 and 3 of Article 24 of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

The 2010 legislative reform has also tried to ameliorate the efficiency of pharmacovigilance processes in many ways. As mentioned above, Eudravigilance has made it possible to simplify the reporting of suspected adverse reactions, thus avoiding unnecessary duplication of work. Marketing authorisation holders, for example, must report those reactions exclusively to Eudravigilance, which shall automatically forward them. In order to ensure that Member States do not fall into the temptation of saving their own resources by imposing inefficient burdens on others, Directive 2010/84/EU has explicitly stated that, “unless there are justifiable grounds resulting from pharmacovigilance activities, individual Member States shall not impose any additional obligations on marketing authorisation holders for the reporting of suspected adverse reactions.”³⁶

The obligation of marketing authorisation holders to submit periodic safety update reports has been simplified and rationalized as well. These reports have to be submitted electronically (only) to the EMA,³⁷ which must make them available to the national competent authorities.³⁸ And it is no longer necessary that those reports contain a detailed listing of all suspected adverse reactions,³⁹ because the individual case reports must have been directly submitted to Eudravigilance previously. Now they shall contain all data relating to the volume of sales of the medicinal product, any data in possession of the marketing authorisation holder relating to the volume of prescriptions, an estimate of the population exposed to the medicinal product, summaries of data relevant to the benefits and risks of the medicinal product, and a scientific evaluation of its risk-benefit balance.⁴⁰

The efficiency of pharmacovigilance activities can be (and in fact has been) ameliorated by means of coordination. For example, where medicinal products that are subject to different marketing authorisations contain the same active substance or the same combination of active substances, the frequency and dates of submission of the periodic safety update reports may be amended and harmonised to enable a single assessment to be made in the context of a periodic safety update report work-sharing procedure and to set a Union reference date from which the submission dates are calculated.⁴¹ A single assessment of periodic safety update reports has also to be performed for medicinal products authorised in more than one Member State,⁴² and in order to avoid duplication of effort the coordination group must try to reach agreement on the regulatory action to be taken by Member States.⁴³

The system can also be more efficient by enacting different rules for different cases. The level of pharmacovigilance should be adjusted in proportion to the magnitude

³⁶See Article 107a.6 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

³⁷See Article 107b.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

³⁸See Article 107b.2 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

³⁹See Article 104.6 of Directive 2001/83/EC, in its original version.

⁴⁰See Article 107b.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴¹See Article 107c.4 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴²See Article 107e of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴³See Article 107.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

of risks posed by each medicinal product. The following example can serve to illustrate this point. Until 2010 there was a rigid scheme for periodic safety update reports regarding all medicinal products. Those routine reports had to be submitted in principle every six months for the first two years following initial placement on the market, then once a year for the following two years, and thereafter at three yearly intervals.⁴⁴ The trouble was that those intervals were sometimes too long for some medicines and too short for others.

Now there is more flexibility. Routine reporting is not required for some medicinal products whose safety and therapeutic effects are already relatively well known: generic ones, homeopathic ones, medicinal products containing an active substance for which well-established use has been demonstrated, and traditional-use registered herbal medicinal products. Nevertheless, the relevant authorities may require periodic safety update reports for such medicines on the basis of concerns relating to pharmacovigilance data or due to the lack of periodic safety update reports relating to an active substance after the marketing authorisation has been granted.⁴⁵ In the remaining cases, the frequency with which such reports are to be submitted must be specified in the marketing authorization,⁴⁶ and may be modified afterwards on request of the marketing authorization holder.⁴⁷ The old frequencies scheme is still applicable to the marketing authorisations which were granted before 21 July 2012, although the authorities may change the frequency under certain conditions.⁴⁸

The possibility of relaxing the requirements of labelling and packaging can serve as another example of efficiency through differentiation. Member states may, under certain conditions, grant an exemption to the obligation that certain details appear on the labelling and in the package leaflet. This may be done when the medicinal product is not intended to be delivered directly to the patient, or where there are severe problems in respect to its availability.⁴⁹

The new European legislation has also improved the efficiency of pharmacovigilance by imposing the obligation to carry out some tasks on the parties which can perform them at the lowest cost. Let's illustrate this point with the following example. Under previous legislation, marketing authorization holders had to report suspected serious adverse reactions of which they can reasonably be expected to have knowledge.⁵⁰ Insofar as individual case reports published in the worldwide scientific literature are considered to be reports of which the marketing authorisation holders can reasonably be expected to have knowledge, these parties had to maintain

⁴⁴See Article 104.6 of Directive 2001/83/EC, in its original version.

⁴⁵See Article 107b.3 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴⁶See Article 107c.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴⁷See Article 107c.6 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴⁸See Article 107c.2 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁴⁹See Article 63.3 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁵⁰See Article 104.3 of Directive 2001/83/EC.

awareness of possible publications by periodically accessing a widely used systematic literature review and reference data base,⁵¹ and to submit the reports published there. That legal provision led to countless duplicated reports, because many marketing authorisation holders had the same requirement for reporting the same cases published in the literature, regarding medicines containing the same active substance or the same combination of active substances.

To solve this problem, the new European legislation has, on the one hand, obliged the EMA: a) to monitor selected medical literature for reports of suspected adverse reactions to medicinal products containing certain active substances; b) to publish the list of active substances being monitored and the medicinal literature subject to this monitoring; and c) to submit relevant information from the selected medical literature to Eudravigilance.⁵² On the other hand, the new legislation has exempted marketing authorisation holders from the requirement of reporting the suspected adverse reactions recorded in the aforementioned listed medical literature.⁵³ The new legal rule is obviously far more efficient than the previous one.

Also delegation enables the improvement of efficiency, when the delegated authority can carry out the considered task at a lower cost than the delegating one. For that reason, the new legislation has allowed Member States to delegate any of the pharmacovigilance tasks entrusted to them to another Member State subject to a written agreement from the latter.⁵⁴ In this way, both States can benefit from existing economies of scale in performing certain pharmacovigilance activities.

3.4. More transparency

A pharmacovigilance system can be qualified as transparent insofar as any person (e.g., competent authorities, stakeholders and the general public) may access to all the information available in this system on the safety and efficacy of certain medicinal products, and on the corresponding pharmacovigilance activities. Several social benefits come from a high level of transparency.

Transparency prevents violations of the Law as it increases the probability of these infringements being detected and the offenders being punished: “Sunlight is said to be the best of disinfectants; electric light the most efficient policeman”.⁵⁵

Insofar as information on pharmacovigilance refers to governmental activities, its openness to public scrutiny enables citizens to monitor the performance of civil servants and politicians, to hold them accountable, to eventually revoke their mandates at election times, and to ensure they satisfy public interest, i.e. the interests of the citizens. Transparency is a necessary condition of accountability and democracy.

⁵¹ See point I.4.3.2 of the European Guidelines on Pharmacovigilance for Medicinal Products for Human Use (September 2008).

⁵² See Article 27 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁵³ See Article 107.2 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁵⁴ See Article 103 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁵⁵ L. D. Brandeis, *Other People's Money*, 1932, p. 92.

To be informed on the safety and efficacy of marketed medicinal products enables competent authorities, marketing authorisation holders, health professionals and consumers to prevent harm caused by those products. To the extent that they do not have information about the risks and benefits of a medicine, they cannot take appropriate measures to minimize such risks and maximize those benefits in order to optimally protect public (or their own) health.

The provision of information to interested parties (e.g. marketing authorisation holders, healthcare professionals and patients) allows them to cooperate and participate in pharmacovigilance activities. For example, if health professionals and consumers are appropriately informed on their right (or eventually duty) to report certain adverse reactions, the probability of this data being reported by them will likely increase.

Transmission of information can produce new and better information. The recipients of information can assess, contrast, review, criticise, correct and amend it. They can give their own opinion or make data known that nobody else knew about until then. For instance, by accessing the available information on safety and efficacy of all medicines, pharmaceutical firms can review, rectify, redirect and improve their own research and development lines, thus saving many resources.

In addition, transparency can enhance the trust of citizens in the governmental management of risks.⁵⁶ It can increase social acceptance of the decisions adopted by the relevant authorities on controversial and sensitive matters which is often the case when dealing with pharmacovigilance issues.

Not surprisingly, the European Court of Human Rights has stated that these rights may compel the State to enable the people to have access to all relevant and appropriate information which would allow them to assess any risk to which they were exposed.⁵⁷ In particular:

“The positive obligation to take all appropriate steps to safeguard life (. . .) entails above all a primary duty on the State to put in place a legislative and administrative framework designed to provide effective deterrence against threats to the right to life (. . .).

This obligation indisputably applies in the particular context of dangerous activities, where, in addition, special emphasis must be placed on regulations geared to the special features of the activity in question, particularly with regard to the level of the potential risk to human lives. They must govern the licensing, setting up, operation, security and supervision of the activity and must make it compulsory for all those concerned to take practical measures to ensure the effective protection of citizens whose lives might be endangered by the inherent risks.

⁵⁶See P. Slovic et. al., *The Perception of Risk*, Earthscan, London, 2000, p. 321.

⁵⁷Judgments of 19 February 1998 (*Guerra and others v. Italy*, 14967/89, paragraph 60), 9 June 1998 (*McGinley and Egan v. United Kingdom*, 21825/93 and 23414/94, paragraph 101) and 19 October 2005 (*Roche v. United Kingdom*, 3255/96, paragraphs 162 et seqq.).

Among these preventive measures, particular emphasis should be placed on the public's right to information, as established in the case-law of the Convention institutions. The Grand Chamber agrees with the Chamber (. . .) that this right, which has already been recognised under Article 8 (. . .), may also, in principle, be relied on for the protection of the right to life, particularly as this interpretation is supported by current developments in European standards (. . .).⁵⁸

In fact, European pharmacovigilance systems have become increasingly more transparent since 1965. And the 2010 reform of pharmaceutical legislation has followed this trend, which can be seen in many points.⁵⁹

National medicines web-portals will probably play a key role in order to enhance the transparency of pharmacovigilance activities within the European Union. The EMA, in collaboration with the Member States and the Commission, has to set up and maintain a European medicines web-portal for the dissemination of information on medicinal products authorized in the Union.⁶⁰ As a minimum requirement the web-portal shall make information accessible to the public on the following: the names, professional qualifications and declarations of interests of the members of the CPMHU, the PRAC and the coordination group; agendas and minutes from their meetings; conclusions of assessments, recommendations, opinions, approvals and decisions on pharmacovigilance issues taken by those Committees, the coordination group, the national competent authorities or the Commission; the initiation and some other aspects of urgent procedures; a summary of the risk management plans for medicinal products authorized through the centralized procedure; the list of medicines subject to additional monitoring; a list of the locations where pharmacovigilance system master files are kept and contact information for pharmacovigilance enquiries,

⁵⁸Judgment (Grand Chamber) of 30 November 2004 (*Önerlydiz v. Turkey*, 48939/99, paragraphs 89 and 90).

⁵⁹See, for example, Articles 21.3 (public availability of the marketing authorization, package leaflet, summary of the product characteristics, conditions and deadlines for the fulfillment of those conditions), 21.4 (public availability of the assessment report, including a summary written in a manner that is understandable to the public), 59.1 (package leaflet), 102(d) (timely information on pharmacovigilance concerns relating to the use of medicinal products), 103 (publication of the delegation of tasks between Member States), 106 (national medicines web-portals), 106a (public announcements regarding information on pharmacovigilance concerns in relation to the use of medicinal products), 107c (publication of reference dates and frequencies of submission of periodic safety update reports), 107j (public announcements of the initiation of urgent procedures, public hearings), 107i (publication of final assessment conclusions, recommendations, opinions and decisions), 107q (publication of agreements on actions to be taken by Member States), 108b (publication of a report on the performance of pharmacovigilance tasks by Member States) and 123(4) (publication of a list of medicinal products for which marketing authorisations have been refused, revoked or suspended, whose supply has been prohibited or which have been withdrawn from the market) of Directive 2001/83/EC, as amended by Directive 2010/84/EU. See also Articles 23 (publication of a list of medicines subject to additional monitoring), 24 (access to Eudravigilance), 26 (European medicines web-portal), 28 (publication of final recommendations, opinions and decisions) and 29 (publication of a report on the performance of pharmacovigilance tasks by the EMA) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁶⁰See Article 26.1 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

for all medicines authorised in the European Union; reference dates and frequency of submission of periodic safety update reports; protocols and public abstracts of results of the post-authorisation safety studies; information on how to report suspected adverse reactions to national relevant authorities, and how to submit information and to participate in public hearings regarding urgent procedures, etc.⁶¹

Each Member State also has to set up and maintain a similar national medicines web-portal which shall be linked to the European one. By means of those national web-portals Member States have to make the following publicly available as a minimum requirement: public assessment reports, together with a summary thereof; summaries of product characteristics and package leaflets; summaries of risk management plans; the list of medicinal products subject to additional monitoring; and information on the different ways of reporting suspected adverse reactions to medicinal products to national competent authorities by healthcare professionals and patients.⁶²

Another important legal novelty concerns the information to be contained in the summary of product characteristics and in the package leaflet. For medicinal products subject to additional monitoring, the summary of product characteristics and the package leaflet have to include a black warning symbol, the statement, “This medicinal product is subject to additional monitoring”, and an appropriate standardised explanatory sentence.⁶³ This information allows healthcare professionals and the general public to easily identify medicinal products subject to additional monitoring as such, and to take a proactive approach towards them.

For all medicinal products, a standard text must be included in the summary of product characteristics expressly asking healthcare professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system.⁶⁴ Correspondingly, a similar standard paragraph has to be inserted in the text of the leaflet of all medicines expressly asking patients to report any suspected adverse reaction to his or her doctor, pharmacist or healthcare professional or directly to the national spontaneous reporting system. The information should also specify the different ways of reporting available (electronic reporting, postal address and/or others).⁶⁵ This information will probably encourage and facilitate both professionals and patients to report such suspected adverse reactions.

⁶¹ See Article 26.1 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁶² See Article 106 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁶³ See Article 11 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁶⁴ See Article 11 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁶⁵ See Article 59.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU. This provision was introduced by the European Parliament, in its Report on the proposal for a directive of the European Parliament and of the Council amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use, 2 June 2010, Committee on the Environment, Public Health and Food Safety of the European Parliament (A7-0159/2010, Amendments 16 and 23, pages 15 and 20).

Additionally, the European legislature has improved the regulation of some information procedures, like, for example, public announcements relating to pharmacovigilance concerns.⁶⁶

The new legislation, however, has some questionable aspects. There are issues which could arguably have been regulated in a more efficient and consistent way. It must be noted, for instance, that the European medicines web-portal has to contain more information than the national ones. For example, Member States are not obliged to make public the names, professional qualifications and declarations of interests of the members of the national committees which provide scientific advice to the national competent authorities in pharmaceutical issues. We cannot see the reason for this and for other differences between the European level of transparency and national ones.

There is thus neither a good reason (at least apparently) for discriminating between post-authorisation *safety* studies and post authorisation *efficacy* studies in order to make them publicly available through the European medicines web-portal. Regulation (EU) No 1235/2010 has inconsistently guaranteed public access only to certain information about the former ones.

It is also difficult to understand why marketing authorization holders, healthcare professionals and the general public may not access the repository for periodic safety reports set up and maintained by the EMA. Regulation (EU) No 1235/2010 provides that this repository has to be accessible (only) to the Commission, the national competent authorities, the Pharmacovigilance Risk Assessment Committee, the Committee for Medicinal Products for Human Use and the coordination group.⁶⁷ The rest of the interested parties should have at least restricted access to that repository.

3.5. More cooperation and participation of stakeholders

The cooperation of all involved parties (competent authorities of the European Union and of the Member States, marketing authorisation holders, healthcare professionals, patients and the general public) in the pharmacovigilance systems can also produce many social benefits.

All of them are well placed to collect and transmit valuable information on the efficacy and safety of medicinal products. If all of them may participate in the pharmacovigilance system and pool such data, they could all use this information to make better decisions in order to minimize the risks of medicines and maximize their benefits.

Moreover, the participation and cooperation of all of the stakeholders could also strengthen the trust of all of them in the pharmacovigilance system. It could increase the social acceptance of the decisions adopted by all of them, in particular by the competent authorities, on pharmacovigilance matters.

⁶⁶See Article 106a of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁶⁷See Article 25a of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

Cooperation is sometimes compulsory. This usually occurs when it is valuable enough and the obliged subject does not have enough incentives to willingly cooperate. This is, for instance, the case of the obligations imposed on marketing authorisation holders to report suspected adverse reactions and to submit periodic safety update reports. Cooperation can also be voluntary. There is then a right, not a duty, to cooperate. The submission of information by patients can serve as an example to illustrate this.

Those cooperation rights occupy an important place in the European Union law. The Court of Justice has stated that the, “observance of the rights of the defence is, in all procedures initiated against a person which are liable to culminate in a measure adversely affecting that person, a fundamental principle of Community law which must be guaranteed even in the absence of any rules governing the procedure in question”.⁶⁸ Particularly, “the principle of the right to a hearing is a general principle of law whose observance is ensured by the Court of Justice. It applies to any procedure which may result in a decision by a Community institution perceptibly affecting a person’s interests”.⁶⁹ According to article 41.2 of the Charter of Fundamental Rights of the European Union, the right to good administration includes, inter alia, “the right of every person to be heard, before any individual measure which would affect him or her adversely is taken”, and, “the right of every person to have access to his or her file”.

The 2010 Reform of the European pharmaceutical law has substantially strengthened the rights of patients to participate in pharmacovigilance procedures. There are two major improvements in this direction. The first one is the direct reporting of suspected adverse reactions by patients. Patient reporting had already been incorporated into the pharmacovigilance systems of several countries, and the experience has been widely positive to date. There is no evidence that patient and physician reports differ in their quality. Both of them tend to submit different information. Patient reports have identified new suspected adverse reactions that had not previously been submitted by healthcare professionals. Patients’ descriptions of suspected adverse reactions to certain medicines have identified some symptoms which those professionals have been unable to describe correctly in their reports. It also seems that patients may report such reactions more quickly. There is, nevertheless, a drawback, although not a very serious one: patient reports are initially more time consuming to process.⁷⁰

⁶⁸See, for example, Judgments of 13 February 1979 (*Hoffmann-La Roche v. Commission*, 85/76, paragraphs 9 et seq.), 10 July 1986 (*Belgium v. Commission*, 234/86, paragraph 27), 14 February 1990 (*France v. Commission*, C-301/87, paragraph 3) and 5 October 2000 (*Germany v. Commission*, C-288/96, paragraph 99).

⁶⁹See, for example, Judgments of 23 October 1974 (*Transocean Marine Paint Association v. Commission*, 17/74, paragraph 15) and 10 July 2001 (*Ismeri Europa v. Court of Auditors*, C-315/99 P, paragraph 28).

⁷⁰See A. Blenkinsopp, P. Wilkie, M. Wang & P. A. Routledge, Patient reporting of suspected adverse drug reactions: a review of published literature and international experience, *British Journal of Clinical*

Until now, the European legislation provided for reporting only by marketing authorization holders and healthcare professionals. Now all Member States must allow, facilitate and encourage patients to report suspected adverse reactions directly to the relevant authorities.⁷¹ They must even offer patients the possibility of reporting through web-based formats and through alternative formats.⁷² Patients have therefore a right to choose the way of reporting.

This method of collecting information is also facilitated and encouraged by means of making both the request to report suspected adverse reactions and how to submit them public. As mentioned above, this information has to be included in the package leaflet of all medicines⁷³ (which is still probably the most effective tool to inform patients about such products) and in the medicines web-portals that the EMA and the Member States shall set up and maintain.⁷⁴

The second substantial improvement in this area is the participation of the public (independent of marketing authorisation holders and healthcare professionals) in certain pharmacovigilance procedures, in particular with regards to the urgent ones conducted by the EMA in order to suspend, revoke or modify a marketing authorisation, to refuse its renewal or to prohibit the supply of a medicinal product.⁷⁵ All of those people have a right to submit any information relevant to the procedure to the competent authorities. If the urgency of the matter permits and it is appropriate on justified grounds particularly with regard to the extent and seriousness of the safety concern, public hearings may be held. To facilitate and ensure the exercise of this right, the initiation of the urgent procedure has to be announced through the European medicines web-portal, and the announcement must specify the issue being addressed and how the information may be submitted. The European medicines web-portal must also indicate how to participate in such public hearings.

The new regulation, nevertheless, arguably has some flaws. For example, the public has not been granted a right to participate in pharmacovigilance non urgent procedures (e.g., of signal detection)⁷⁶ or in urgent procedures conducted by only one Member State. And Member States just “may” (not must) publicly announce the initiation of urgent procedures on their national medicines web-portals.⁷⁷ Those provisions and omissions are at least questionable.

Pharmacology 63(2) (2007), 148–156; L. Aagaard, L.H. Nielsen, E.H. Hansen, Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006, *Drug Safety* 32(11) (2009), 1067–1074.

⁷¹See Article 102(a) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁷²See Article 102(b) of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁷³See Article 59.1 of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁷⁴See Articles 106(e) of Directive 2001/83/EC, as amended by Directive 2010/84/EU, and Article 26.1(f) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁷⁵See Article 107j of Directive 2001/83/EC, as amended by Directive 2010/84/EU, and Article 26.1(i) of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁷⁶See Article 107h of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁷⁷See Article 107j of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

3.6. More Europe

One of the most important and persistent trends in the development of the European pharmacovigilance systems is the centralisation of the main regulatory tasks. Initially, Member States retained all the powers to execute the European pharmaceutical legislation. Council Directive 65/65/EEC of 26 January 1965, on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products, did not confer administrative powers to the European Community authorities. It just tried to approximate the rules national competent authorities had to apply, in order to safeguard public health while removing some disparities between national provisions that hindered the development of the pharmaceutical market within the Community.

Since then, the administrative competences conferred to the European Union (or Community) authorities in order to control the pharmaceutical market have greatly increased. Every major reform of European legislation in this area has extended them. European Union authorities have, on the one hand, important regulatory powers. The Commission decides on the granting of marketing authorisation of some medicinal products, and on their renewal, maintenance, variation, suspension or revocation. On the other hand, European Union authorities perform relevant coordination and information tasks. The EMA, for instance, maintains the Eudravigilance database and data collecting network, which plays a central role in pharmacovigilance, coordinates multiple pharmacovigilance activities of the national authorities, provides Member States and even other involved parties scientific and technical support, advice and information relating the safety of medicinal products.

This move towards centralisation could plausibly be explained on the grounds of efficiency. In a decentralised (or national) system of authorising and monitoring of medicinal products, Member States duplicate work, because each of them has to verify exactly the same. All of them have to analyze whether the risk-benefit balance of a medicine is currently favourable. This risk-benefit balance is substantially the same in all European countries. National differences (i.e., with respect to traditional dietary habits, average height and weight of the population, social perception of certain risks, etc.) within the European Union are usually not large enough to justify divergent national assessments and decisions on the marketing authorisation of a medicine and on its renewal, maintenance, suspension or revocation. On the contrary, those national differences are becoming smaller and smaller. A decentralised system has the advantage of national authorities being in a better position than European ones to know their own peculiarities in order to adopt optimal decisions. Nevertheless, insofar as such peculiarities do not have a big influence on the correctness of those decisions, the benefits of the decentralisation are probably low.

The disadvantages of such decentralisation are, on the contrary, substantial. This is especially so when the medicinal product is authorised in more than one Member State. The procedural costs are then multiplied by the number of authorising Member States. And, since assessing the risk-benefit balance of medicines is usually an

extremely difficult task, it is likely that different Member States adopt divergent decisions on the same issue, thus undermining the principles of legal certainty and equal treatment, and giving rise to legal claims made by the stakeholders.

The 2010 legislative amendments follow the pattern of centralising information, coordination, assessment and regulatory tasks. This fact can be illustrated with several examples. By reinforcing Eudravigilance as the single point of receipt of pharmacovigilance information on medicinal products, by making this database more accessible to all competent authorities and stakeholders, by providing the setting up of a repository for periodic safety update reports and the corresponding assessment reports so that they are fully and permanently accessible to those authorities, and by providing the creation of a European medicines web-portal, the 2010 reform has also strengthened the position within the pharmacovigilance system of the organization entrusted with the management of those information tools: the EMA.

The mandate of the coordination group has been notably enlarged to include the examination of questions regarding pharmacovigilance and variations of marketing authorisations of *all* medicinal products approved by Member States.⁷⁸ Formerly, it was empowered to examine (only) issues related to marketing authorisations of a medicinal product approved in *two or more* Member States.⁷⁹ The creation of PRAC, which has to provide scientific advice on pharmacovigilance matters regardless of whether the concerned medicinal product was authorised through the centralised or non-centralised procedure, has greatly strengthened the role of the European Union in assessment tasks.

The aforementioned possibility of harmonizing frequency and dates of submission of periodic safety update reports to enable a single assessment within the European Union further exemplifies that centralizing trend. And it must be highlighted that any regulatory measure (i.e., of maintenance, variation, suspension or revocation of the marketing authorisation concerned) following such a single assessment has to be adopted by a Union procedure leading to a harmonized result.⁸⁰

4. Developments and challenges

In spite of its very recent reform, there are still some shortcomings and areas for further improvement in the European legislation on pharmacovigilance. For example, as explained above, the transparency of the system and the involvement and participation of healthcare professionals, patients and the general public may arguably be ameliorated.

⁷⁸See Articles 27, 31.1, 107c, 107e, 107g, 107k and 107q of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

⁷⁹See Article 27.1 of Directive 2001/83/EC, as amended by Directive 2004/27/EC.

⁸⁰See Article 107g of Directive 2001/83/EC, as amended by Directive 2010/84/EU.

There are also some important issues the 2010 reform has hardly tackled. An illustrative example is personal data protection. The processing of sensitive personal data concerning health is at the core of all pharmacovigilance processes. Even though this poses many serious problems, neither Regulation (EU) No 1235/2010 nor Directive 2010/84/EU have paid much attention to them. Only one of their Articles is devoted to these matters. And it merely states that EMA, “shall ensure that healthcare professionals and the public have appropriate levels of access to the Eudravigilance database, while guaranteeing personal data protection”.⁸¹ It is said in the Preamble of those norms, however, that they shall apply without prejudice to the European Union legislation on personal data protection, and additionally that:

“In order to detect, assess, understand and prevent adverse reactions, and to identify and take actions to reduce the risks of, and increase the benefits from, medicinal products for the purpose of safeguarding public health, it should be possible to process personal data within the Eudravigilance system while respecting Union legislation relating to data protection. The purpose of safeguarding public health constitutes a substantial public interest and consequently the processing of personal data can be justified if identifiable health data are processed only when necessary and only when the parties involved assess this necessity at every stage of the pharmacovigilance process”.⁸²

The European Data Protection Supervisor issued a very negative opinion on the (proposals for the) new legislation on pharmacovigilance. According to it, the simplified reporting system and the strengthening of the Eudravigilance database lead to increased risks for data protection, especially when it involves patients’ direct reporting. The Supervisor made several recommendations in that regard (i.e., introduction of a decentralised and indirect reporting system whereby communication to the European web-portal is coordinated via the national web-portals),⁸³ most of which have not been finally incorporated into the legislation.

Some of the problems posed by the new legislation could be solved, at least to a certain extent, by means of its transposition and implementation. But others will require the legislation to be amended. And it is possible that we will not have to wait a long time for this to happen. The same social and technical phenomena which have led to the 2010 reform (i.e., globalization, progress of the information and communication technologies, etc.) will probably further develop and still push the European legislature in the same direction.

⁸¹ Article 24.2.VI of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁸² See Recital 33 of the Preamble of Directive 2010/84/EU, and Recital 23 of the Preamble of Regulation (EU) No 1235/2010. See also Recital 23 of Regulation (EC) No 726/2004, as amended by Regulation (EU) No 1235/2010.

⁸³ Opinion of 22 April 2009 (COD/2008/0257).

There is especially wide room for improvement with respect to regulatory harmonization of pharmacovigilance.⁸⁴ The same circumstances that have caused the Europeanisation of pharmacovigilance systems inside the European Union are also determining (and will still probably determine in the near future) the convergence of these systems with outside ones. Given that pharmaceutical firms are increasingly seeking authorisation of the same products in several regions (mainly in Europe, North America and Japan) and medicinal products produce similar effects on the people from all those regions, international regulatory harmonisation of pharmacovigilance would reduce its costs and enhance its efficiency.⁸⁵

⁸⁴See, mutatis mutandi, J. L. Valverde, The need of one International Statute for Medicinal Products, *Pharmaceuticals Policy and Law* **9** (2007) 271–272; J.L. Valverde, Toward a global legal statute for medicinal products, *Pharmaceuticals Policy and Law* **9** (2007) 273–315; Y. Juillet, Internationalisation of regulatory requirements, *Pharmaceuticals Policy and Law* **9** (2007) 369–382.

⁸⁵See L.B. Faden and C.P. Milne, Pharmacovigilance activities in the United States, European Union and Japan: Harmonic Convergence or Convergent Evolution?, *Food and Drug Law Journal* **63** (2008), 683–700. See a description of the U.S.A pharmacovigilance system in V. Eng, Drug Safety: It's a learning process, *Saint John's Journal Legal Commentary* **24** (2009), 159–199.