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Strengthening and Rationalizing Pharmacovigilance in the EU: Where is Europe Heading to?

A Review of the New EU Legislation on Pharmacovigilance

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Abstract

Amendments to the European pharmacovigilance legislative framework are expected to come into force in 2011, following the adoption of the proposed amendments to Directive 2001/83/EC on the community code relating to medicinal products for human use (hereinafter referred to as the Directive) and to Regulation (EC) No. 726/2004 laying down community procedures for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMA) [hereinafter referred to as the Regulation]. The Regulation shall apply 18 months after publication in the *Official Journal of the European Union*. The amendments to the Directive and the Regulation will induce changes in the EU in terms of evaluation of risk associated with medicinal products as well as the framework on how the EU takes harmonized regulatory action on drug safety. In this review, the text agreed between the European Parliament and

Council is examined and compared with the pharmacovigilance legislative framework currently in force. We argue that the new legislation has improved numerous uncertainties in current legislative framework and provides for the following: (i) clear roles, responsibilities and obligations for the key responsible parties; (ii) rationalization of EU decision making on drug safety issues in order to deliver measures that are equally and fully implemented for all relevant products across the community with a view to preventing unnecessary patient exposure to risks; (iii) strengthening medicine safety transparency and communication so that the understanding and trust of patients and health professionals in the safety of medicines will improve, as well as the penetration of key warnings; (iv) strengthening companies' pharmacovigilance systems, allowing companies to improve their systems constantly while reducing administrative burden; (v) ensuring the proactive and proportionate collection of high-quality data relevant to the safety of medicines through risk management and structured data collection in the form of Post-Authorization Safety Studies (PASS), together with rationalized single-case and periodic reporting of suspected adverse drug reactions (ADRs); (vi) involvement of stakeholders in pharmacovigilance through direct patient reporting of suspected ADRs and inclusion of patients and healthcare professionals in decision making; and (vii) simplification of the current community pharmacovigilance procedures with consequent efficiency gains for both the pharmaceutical industry and medicines regulators.

For the first time, companies can be made legally liable to carry out PASS and Post-Authorization Efficacy Studies. The amendments to the Regulation and to the Directive will strengthen the European network on pharmacovigilance. A Pharmacovigilance Risk Assessment Committee (PRAC) based at the EMA will be set up, which will be responsible for all matters related to pharmacovigilance at an EU level. Three European databases will be strengthened (EudraVigilance, EudraPharm and the European Pharmacovigilance issues Tracking Tool) as well as the setting up of an EU safety portal to better inform the public on all safety issues being discussed at an EU level. Public hearings at the PRAC will improve transparency in the decision-making process, whilst details and results of all PASS agreed to by the PRAC will also be made publically available.

Pharmacovigilance is the science of, and activities relating to, the detection, assessment, understanding and prevention of adverse effects of marketed medicines; specifically, taking action to increase the products' benefits and reduce their risks. This is achieved by monitoring the use of medicines in normal conditions of use to identify previously unrecognized adverse effects or changes in the patterns of adverse effects; assessing the benefits and risks of medicinal products to take a decision on what action, if any, is necessary to improve the safe use of medicinal products; providing information to the public and healthcare professionals to optimize the safe and effective use of medicines; and assessing the impact of any action taken. It is imperative that pharmacovigilance is carried out by both industry and regulators since notification and reporting of suspected adverse drug reactions (ADRs) arising with the use of medicinal products, by healthcare professionals and consumers, is an essential source of new information for the achievement of these objectives.

Not all hazards can be identified under the limited and restricted environment of testing in clinical trials, before a medicinal product is marketed. Since patients, consumers and indeed some

healthcare professionals have expectations that medicinal products available are 'safe', they are, from time to time, surprised when regulatory action is taken to restrict their use, introduce new warnings in the product information, or withdraw medicines as a result of the emergence of new data regarding safety issues affecting the positive benefit-risk assessment of the product.

Information collected during the premarketing phase of a medicinal product is inevitably insufficient in compiling a complete safety profile of a product, as animal testing is sometimes not necessarily predictive of human safety. Data from clinical trials are limited by various factors, including their (sample) size and duration. Furthermore, conditions of use differ during clinical trials from those encountered during normal clinical practice. Information about rare but serious ADRs, chronic toxicity, use in special groups (such as children, the elderly or pregnant women), or drug interactions could not be available for all of the medicinal products, thus emphasizing the need for ongoing surveillance.

In December 2008, the European Commission (EC) launched legislative proposals for a European Regulation and a Directive to strengthen and rationalize pharmacovigilance in the EU.[1,2] Following a public consultation procedure,[3] proposals for amending the Regulation and the Directive, in those aspects relating to pharmacovigilance, were drawn up based on a system of measures to decrease bureaucracy associated with the regulatory process of carrying out pharmacovigilance and to introduce legislative tools so that harmonized action on drug safety across the EU can be taken. The aim of this review is to present the structure and functions of the new proposed pharmacovigilance system in the EU, which is expected to have a major impact on the EU regulators (and competent authorities of accession countries [such as Croatia and Turkey]) and on the pharmaceutical industry.

1. Literature Search Methodology

To identify relevant literature, we performed an EU Council Public Register, EU Parliament Public Register, EU Committee of Regions Public Register, EUROPA (EC) and Eur-Lex search (2005–September 2010). We used the search term 'pharmacovigilance' and included all documents written in English.

2. Regulatory Background

Since the thalidomide case of the early 1960s, there has been a steady evolution of drug regulation in the EU.[4] This process started with the initial introduction of side effect reporting schemes in some European countries and the first EC medicines legislation in the 1960s to the setting up of the European Medicines Agency (EMA) in the mid 1990s and the revised pharmaceutical legislation in 2004.[4] In January 2005, the EC awarded a contract for an assessment of the community system on pharmacovigilance entitled ''Assessment of the European Community System of Pharmacovigilance'' to a joint bid from Fraunhofer Institute Systems and Innovation Research and Coordination Centre for Clinical Studies at the University of Tubingen (KKS-UKT).[5] The contractors were independent non-governmental organizations with considerable experience in conducting projects for the EC. In November 2005, the Fraunhofer Institute for Systems and Innovation Research report on the ''Assessment of the European Community System of Pharmacovigilance'' was published.[6] Based on the recommendations of the independent contractors, in 2006 the EC launched a public consultation on the current system for pharmacovigilance in the EU. Based on the feedback received from the public consultation, in February 2007 the EC concluded that a revision of the EU's pharmacovigilance system was required.[7]

On 10 December 2008 the EC tabled legislative proposals (a Directive and a Regulation)[1] to amend the European legislation on pharmacovigilance. The aim was to achieve a consolidated regulatory framework for the management of risk associated with medicinal products (inclusive of innovative medicines such as advanced therapies medicinal products. The proposed European Regulation and Directive on pharmacovigilance are expected to come into force in 2011, following publication in the *Official Journal of the European Union*. The

Regulation shall apply from 18 months after publication.[8-10]

During negotiations on the text of the Regulation and Directive between the EC, the Council and the Parliament, surprisingly few key provisions were altered.[8,11] Examples include (i) the proposed amendments of the Council to have a member and an alternate member from each of the EU Member States on the Pharmacovigilance Risk Assessment Committee (PRAC); and (ii) the new direction taken that the Committee for Medicinal Products for Human Use (CHMP) will have to rely on the pharmacovigilance assessments made by the PRAC both pre- and postmarketing. The CHMP is the main scientific committee of the EMA for the benefit-risk assessment evaluation of medicinal products. It is an important decision-making committee and is responsible, among other things, for giving opinions on applications for centralized marketing authorizations for medicinal products and on scientific advice on the development of medicines. Under the current legislative framework, the CHMP does not have to rely on assessments made by the Pharmacovigilance Working Party.

Further provisions that will be introduced include the setting up and maintenance of a repository for Periodic Safety Update Reports (PSURs), the referral to the PRAC instead of referring to the CHMP for community interest referrals arising from pharmacovigilance data, and the legal basis for regulators to request any information about the volume of sales or prescriptions of the medicinal product concerned.

2.1 Aims and Objectives of the Regulation and Directive

The overall aim of the legislative proposals is to improve the postmarketing safety of approved medicinal products in the EU. The specific objectives put forward by the EC in the legislative proposal are summarized below.

- Clear definition of roles, responsibilities and obligations for responsible parties.
- Introducing a clear EU decision-making process on drug safety issues with a view to preventing unnecessary patient exposure to risks that are fully implemented for all relevant products across the community.
- Increasing the transparency through public hearings held during the decision-making process at an EU level to improve the trust of patients and healthcare professionals in the safety of medicines.
- Reducing the administrative burden on companies' pharmacovigilance systems.
- Ensuring the proper risk management through the recording of high-quality spontaneous ADRs and structured data collection in the form of PASS.
- Widening the legal definition of adverse events to capture medication errors as well as enabling direct patient reporting of suspected ADRs.
- The inclusion of patients and healthcare professionals in the decision-making process.
- Simplification of the EU pharmacovigilance procedures to increase efficiency gains for both the pharmaceutical industry and medicines regulators.

The Regulation and Directive establish a number of new provisions, structures and procedures in order to achieve their objectives.

3. Key Provisions

3.1 Rationalize and Strengthen Pharmacovigilance in the EU

The proposed amendments to the current legislative framework by the EC are intended to rationalize and strengthen pharmacovigilance in the EU in terms of protecting the public health of patients/consumers by clearly defining the roles, responsibilities and obligations for responsible parties; reducing the administrative burden on companies' pharmacovigilance systems, and ensuring proper risk management through the recording of high-quality spontaneous ADR reports and structured data collection in the form of PASS; and the simplification of the EU pharmacovigilance procedures to increase efficiency gains for both the pharmaceutical industry and medicines regulators. How will the new pharmacovigilance Regulation and Directive achieve this? Based on a safety concern by the competent authorities,

pharmaceutical companies will be requested to conduct a PASS at any time during the life cycle of a medicinal product following the granting of the marketing authorization, which will be included as a condition within the marketing authorization. The role of the EMA in the area of pharmacovigilance is further developed, especially with respect to management of EudraVigilance (the EU pharmacovigilance database) and the data-processing network. The new Directive and Regulation on pharmacovigilance[9,10] require that, apart from information on ADRs in humans, arising from use of the product within the terms of the marketing authorization (i.e. normal conditions of use), spontaneous reports will also be utilized to capture information on the use of the medicinal product outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors. The EudraVigilance database shall be modified to cater for this legislative requirement.

In order to co-ordinate safety issues better across the EU, a European safety web portal will be created and maintained by the EMA where key safety information on medicines for human use will be published. The safety web portal will be used to host information on additionally monitored medicinal products in the EU, issue information on public hearings on safety issues at the EMA and host links to safety portals maintained by each Member State.

Another important provision in the amended directive will be that a Member State may delegate any pharmacovigilance task to another Member State; this information will be made public by both the delegating Member State and the EMA.

A PRAC, based at the EMA, will be responsible for leading the scientific opinion on any question relating to the pharmacovigilance of medicinal products for human use that will occur at any stage of the pre- and post-licensing procedure.[9-11] However, for the sake of consistency and continuity of the assessments, the final responsibility for the benefit-risk assessment of medicinal products for human use should remain with the CHMP of the EMA for centrally authorized medicinal products, and with the authorities competent for the granting of national marketing authorizations. Fees shall be introduced for providing assessment of community pharmacovigilance procedures, PSURs, PASS protocols and risk management systems. All medicines authorized subject to the requirement to conduct a PASS, or subject to conditions or restrictions with regard to their safe and effective use, will be listed and will be identifiable on the European safety portal as intensively monitored medicinal products.

Under the new provisions, Marketing Authorization Holders (MAHs) will have to keep a 'pharmacovigilance system master file' and to provide a risk management system for each new medicinal product authorized, which should be proportionate to both the identified and the potential risks. The creation of the pharmacovigilance system master file will replace the detailed description of pharmacovigilance submitted in module 1.8 of a marketing authorization application. The European database on marketing authorizations in the EU (EudraPharm) will be populated by industry in contrast to the current regulatory framework under which Member States are responsible for communication of this information. The proposed amendments to the Directive include a decrease in regulatory burden for generic companies to prepare and submit PSURs. The aim is to free resources in industry to focus more on pharmacovigilance activities.

3.2 Pharmacovigilance Risk Assessment Committee

The amended Regulation establishes a new scientific committee of the EMA, the PRAC, which must be set up within 18 months of the Regulation coming into force. Committee membership will include one member and one alternate member appointed by each Member State, five members and their alternates appointed by the EC, on the basis of a public call for expressions of interest, after consulting the European Parliament, one member and one alternate to represent healthcare professionals appointed by the EC, on the basis of a public call for expressions of interest, after consulting the European Parliament, and one member and one alternate

member to represent patient associations appointed by the EC, on the basis of a public call for expressions of interest, after consulting the European Parliament.[9,10] The EMA, National Agencies and the EC are expected to cooperate to ensure that the final composition of the Committee, including members and alternate members, cover those scientific areas relevant to pharmacovigilance and risk assessment of medicinal products for human use. The members, who will be appointed for a renewable period of 3 years, may be accompanied by other relevant experts at the Committee meetings. The members, alternate members and experts must not have any financial or other interests in the pharmaceutical industry that could affect their impartiality. Specific rules for conflict of interest exist for other Committees of the EMA. The PRAC will have a number of important responsibilities, and its effective functioning will be pivotal to the regulatory success in the implementation of the Regulation and Directive. The tasks of the PRAC are summarized as follows:

- assessment of pharmacovigilance data submitted during all pre- and post-authorization activities at the EMA;
- assessment of PSURs;
- assessment and agreement of risk management plans (RMPs);
- impose, through the EC, temporary measures to be implemented by Member States to protect patients if the PRAC considers that a product may not be safe anymore or that a product will not provide any significant therapeutic benefit;
- assess and either endorse or object to protocols of PASS to be carried out in more than one Member State;
- the creation and maintenance of a single frequency date for the submission of PSURs by MAHs;
- establishing and making public a list of medicinal products for human use under additional monitoring.

The PRAC is expected to meet every month for 3–4 days. Members will need to devote adequate time to prepare prior to meetings since the workload involved is not to be underestimated.

3.3 Setting Up and Maintenance of a List of Medicinal Products for Human Use Under Additional Monitoring

New provisions will provide for the EMA, in collaboration with the Member States, to set up and maintain a list (that shall be made public) of medicinal products for human use subject to additional monitoring. The list shall include the names and active substances of medicinal products authorized in the EU that contain either a new active substance or are new similar biological products, or have been specifically requested to be included by either the EC or the Member States, following consultation with the PRAC. The list shall include an electronic link to the product information and to the summary of the RMP.

Furthermore, all medicinal products that are listed by the EMA as subject to additional monitoring will be required to include a statement in the summary of product characteristics (SmPC) indicating that "This medicinal product is under additional monitoring. All suspected adverse reactions should be reported to <name and web-address of the national competent authority that issues the marketing authorisation>." This applies irrespective of the indication.[8-11]

4. Discussion

4.1 Rationalizing the Decision-Making Process

The predefined upgrade of the Pharmacovigilance Working Party at the EMA to a Committee is crucial to correct functioning of the Regulation and Directive to achieve these goals and objectives. New legislative procedures in the amendments to the Directive will give a legal basis so that modifications to key safety profiles, as well as suspensions and revocations of marketing authorizations to medicinal products on the EU market, can be made possible irrespective of whether the medicinal product was authorized through a national or EU procedure (Decentralized, Mutual Recognition or Centralized). This is a major step forward in the decision-making process.

In the current system, recommendations by the Pharmacovigilance Working Party on the safety of medicinal products authorized in the

EU, and the investigation of adverse reactions to enable effective identification, assessment and management of risk, at any phase in the product life cycle, are not implemented by Member States in a harmonized manner. This leads to the situation where in one Member State a warning might be present on the product information of a medicinal product but not in another. The proposed legislation also introduces a major streamlining of roles in the EU for pharmacovigilance referrals, where the CHMP will be responsible for adoption of an opinion if a procedure involves a centrally authorized medicinal product, and the Co-ordination Group for Human Mutual Recognition and Decentralized Procedures (CMD[h]) for procedures that do not involve centrally authorized products. This is a major change in direction from the current system where the CHMP, and consequently the EMA, is responsible for adopting an opinion on all community referrals on pharmacovigilance-related issues.

4.2 Decreasing Bureaucratic/Procedural Burden

The new legislative amendments introduce numerous measures that will decrease bureaucratic/procedural burden for the pharmaceutical industry and regulators (EMA and national agencies). These measures include the electronic submission of PSURs by MAHs, the creation of a repository at the EMA for PSURs where National Competent Authorities and their delegates to EMA committees can access these reports over the Internet (through the European Pharmacovigilance issues Tracking Tool), and the possibility for MAHs of generic products not to submit PSURs. There will be a simpler and clearer ADR reporting system as ADRs will be transmitted electronically to the European pharmacovigilance database (EudraVigilance). Importantly, EudraVigilance will be made available to all National Competent Authorities and they can carry out signal detection on any dataset (EU/non-EU and at Member State level). Other measures include the establishment and operation of the pharmacovigilance system by the MAHs, and the content and maintenance of the pharmacovigilance system master file. An additional major step is the legal power for any Member State to delegate its responsibility at the Pharmacovigilance Committee to another Member State.

4.3 Protecting Public Health

Proper management and recording of spontaneous ADR reports comprises a critical pharmacovigilance tool useful in identifying unexpected side effects or indicating whether certain adverse effects occur more commonly than previously believed, or whether some patients are more susceptible to ADRs than others. Such findings can lead to changes in the marketing authorization of the medicine, e.g. restrictions in use, changes in the dose of the medicine and introduction of specific warnings or side effects in the SPC. In order to achieve this, the proposed legislation will strengthen the EudraVigilance database and its data warehouse (the EMA's signal detection software) as the sole EU database, containing individual case summary reports (ICSRs) originating from either clinical trials or as spontaneous reports (EU as well as non-EU). The legislation will also direct National Competent Authorities and MAHs to accept ICSRs sent to them by patients, carers, families and consumers as well as healthcare professionals (nurses, doctors, pharmacists, etc.). The definition of an adverse drug event will be broadened to also incorporate medication and administration errors. This is expected to be very useful for Member States, which will be able to capture potential medication errors associated with medicinal products. In our opinion, the widening of the definition of an ADR to include and capture adverse events from off-label use and abuse, as well as the introduction of the possibility that the public can also submit ADR reports to the competent authority, is envisaged to strengthen spontaneous reporting systems. At present, only a few Member States accept direct reporting from the public but, where it exists, it seems that the system has not overburdened the competent authority.[11] However, since the new system proposes that all ADRs (and not just serious ones) are reported to EudraVigilance, we expect that,

taken together, these changes might further affect the resources of competent authorities, especially the smaller EU agencies. This is not entirely unexpected since a report issued by the European Parliament shows that both companies and Member States have failed to meet the current requirement to report ADRs within 15 days, with Member States being the worst 'offenders', reporting 50% of reports late.[11] Importantly, all ADRs will be reported to the EudraVigilance database by competent authorities and companies. This means that information on all ADRs will, for the first time, be centralized in one place in the EU; thus, it is expected that EudraVigilance will become a valuable research tool for all.

The new legislation will also strengthen the EudraPharm database, so that it contains all information on authorized medicinal products in the EU, by directing MAHs to submit all information on their marketed medicinal products. Other measures in the legislation will increase the transparency of the EU decision-making process since public hearings will be allowed to take place at the PRAC, improving the trust of patients and healthcare professionals in the safety of medicines. The legislation will also provide for the setting and maintenance by the EMA of an EU web safety portal to host all relevant key safety issues on medicines, as well as the obligation for EU Regulators to audit their pharmacovigilance systems on a 2-yearly basis and to report the results to the EC.

It is of note that, from a public health point of view, new provisions (proposed by the EC and the European Parliament) in the legislation will provide for a black symbol preceding the statement ''This medicinal product is subject to additional monitoring'' in the SmPC for intensively monitored medicinal products. Furthermore, for all medicinal products, a standard text shall be included explicitly asking health professionals to report any suspected adverse reaction in accordance with the national spontaneous reporting system. These provisions are expected to provide a significant benefit to public health by increasing the penetration of safety warnings, thereby reducing the potential risks and promotion of national spontaneous reporting systems.

One very important change in the current framework that is expected to have a major impact on industry, as well as regulators, is the legal power for regulators to be able to request PASS as part of conditions of marketing authorizations, and therefore legally binding on the company. These non-interventional PASS will be initiated, managed or financed by the MAH, and will involve the collection of data from healthcare professionals or patients. Such studies will not be promotional and payments shall be restricted to compensation. Furthermore, draft protocols will be agreed upon or rejected by either the competent authority if the study is carried out in one Member State or to the PRAC if the PASS is to be carried out in more than one Member State. In addition, companies will also have the obligation to submit the abstract of the study results to the PRAC, which may make this public and may make recommendations for the product labelling. Such recommendations for the product labelling will be legally binding and shall be taken into account by regulatory authorities and the MAH. However, irrespective of these provisions, it is our opinion that the scope of the new legislative provisions is limited. This is because Directive 2001/83/EC defines PASS as a study carried out within the terms of a marketing authorization of a medicinal product. Therefore, studies investigating the use of the medicinal product outside the terms of a marketing authorization need to be submitted as a 'clinical trial' in line with the Clinical Trials Directive (Directive 2001/20/EC).

Another important change in the current framework that is expected to have a major impact on industry as well as regulators is the central assessment by the PRAC of PSUR or any safety issue arising from pharmacovigilance data for all medicinal products in the EU (both nationally and centrally authorized). The new legislation will provide for the EMA to set up and maintain a repository for PSURs and the corresponding assessment reports. These will be accessible to the EC, national competent authorities and committee members. Such provisions are expected to alleviate the current workload on competent authorities to file and assess PSURs, since compe-

tent authorities have often been overwhelmed by the sheer volume of PSURs they have received in the past, with the result that many have gone unread.[11] Furthermore, the new provisions will avoid duplicate assessments being carried out by Member States on the same PSUR. The new legislation will also change the structure of PSURs to contain (i) summaries of data relevant to the benefits and risks of the medicinal product, including results of all studies with a consideration of the potential impact on the terms of the marketing authorization; (ii) a scientific evaluation of the benefit-risk balance of the medicinal product; (iii) all data relating to the volume of sales of the medicinal product and any data in possession of the MAH relating to the volume of prescriptions, including an estimate of the population exposed to the medicinal product; and (iv) the current line listings of ADRs currently being submitted by MAHs. Consequently, the new legislation will introduce a significant shift in the manner in which PSURs are prepared by MAHs since the legislation will require a scientific evaluation of the benefit-risk balance of the medicinal product. Important to note is that for holders of marketing authorizations for medicinal products authorized in line with Articles 10 (1) or 10a of Directive 2001/83/EC, new provisions will enable PSURs for such products to be submitted only in specific cases, such as when listed as a condition in the marketing authorization or when requested by a competent authority on the basis of concerns relating to pharmacovigilance data. These provisions are expected to decrease burden on generic manufacturers to prepare PSURs that are required routinely by the current legislative provisions. However, we would like to point out that although generic manufacturers might want to benefit from the new legislative provision not to submit PSURs to the PRAC for assessment, should regulatory action be taken on medicinal products following the assessment of a PSUR submitted by an originator company, the non-submission of a PSUR for assessment by generic manufacturers might preclude them from being able to be heard during the regulatory decision-making process. New legislative procedures will make the PRAC recommendations on the maintenance, variation, suspension or revocation of the marketing authorization concerned legally binding.[8-10]

In addition to the numerous provisions on pharmacovigilance, the new legislation also provides for the PRAC to be involved during the centralized procedure drug approval phase (pre-authorization), where the CHMP is directed to rely on the scientific assessment and recommendations of the PRAC in order to agree and monitor risk management systems for all medicinal products for human use inclusive of advanced therapy medicinal products.[8] It is our opinion that this provision could limit the CHMP's flexibility in reaching consensus when arriving at an opinion on the benefit-risk of a medicinal product if the risk management system is modified during the drug approval process very late in the day during the procedure. This is because agreement with the PRAC on the modification to the risk RMP cannot be achieved during the plenary sessions at day 210 of the centralized procedure; therefore, such a limitation on the CHMP could potentially affect the drug approval process.

On the other hand, new legislative provisions will provide for the CHMP to be able to request Post-Authorization Efficacy Studies (PAES) to be conducted by MAHs as a condition of the marketing authorization. The legislation, however, does not contain measures aimed at avoiding unnecessary trials, which could be particularly important in view of ethical concerns about involving certain vulnerable groups in clinical trials.

The new legislation will also affect the manner in which the EMA handles safety referrals. Under the current system, EU-wide regulatory action on safety issues can be achieved procedurally through the initiation of different referral procedures set by Directive 2001/83/EC. To date, safety referrals can be initiated under article 36 (which provides for Member States to vary, suspend, or withdraw marketing authorizations to protect public health), article 107 (as a result of the evaluation of pharmacovigilance data), as well as article 31 (in specific cases where the interests of the community are involved). New legislative provisions will now provide that article 36 will be deleted since amendments to article 107 will incorporate the provisions of the current article 36.[8-10]

Overall, it is felt that most of the provisions put forward by the EC in its proposal have been endorsed following the co-decision legislative procedure. This was not unexpected because the EC's draft proposal set to resolve the following issues in the current legislation:

- EU referrals/opinions that are unclear as well as overlapping;
- the inconsistent implementation by Member States of adopted wordings on safety by the EMA's Pharmacovigilance Working Party;
- the mistrust of major stakeholders in the EMA setup that the CHMP is not only adopting opinions for approving new medicinal products, but is also responsible for taking post-approval regulatory actions on drug-induced safety issues;
- the unclear responsibilities of MAHs and National Competent Authorities as well as lack of clear standards for the authorities and industry, where the lack of clarity leads to non-compliance and difficulties with enforcement;
- the current complex ADR reporting rules, depending on the authorization route, report origin (EU/non-EU) and seriousness, thus resulting in extensive duplication of reporting;
- the unclear legislative provision on medication error reporting as well as the lack of a clear legal basis for patient reporting across the EU;
- duplicate reporting and lack of standardization of PSURs.

5. Conclusions

Once the Regulation and Directive on the pharmacovigilance of medicinal products for human use come into force, it will mark the beginning of a new chapter in drug safety. Taken together, the new legislative framework on pharmacovigilance will affect all of its stakeholders. It will entail a heavy workload for some of its interested parties and, in some areas at least, a steep learning curve. The EMA will have to set up and maintain a web portal, restructure its databases and set up the PRAC with its rules for procedures and mandates. The EMA will also have to co-ordinate the centralization and assessment of PSURs and PASS, as well as the review and assessment of pharmacovigilance signal, and organize public hearings in relation to discussions at the PRAC. The latter activity is a completely new activity at the EMA and will definitely be seen as a learning curve. MAHs will benefit from clearer requirements with respect to submissions for PSURs and detailed description of pharmacovigilance, but will have to provide for the possibility of conducting PASS as well as PAES as conditions of marketing authorizations. It is our opinion that Member States will be affected positively by the new legislative provisions. Although it will entail a heavy workload for all EU member states, this is especially the case for small Member States because these need to get the required resources in place (inclusive of expertise, which in small member states can be difficult to find) to implement risk management programmes at a national level. The centralization and access of PSUR submissions, as well as the strengthening of EMA databases that Member States have access to, will free up resources so that national competent authorities can fulfil their pharmacovigilance obligations more effectively. Finally, the EU will have a comprehensive set of tools to achieve the goal of patient protection by strengthening the safety monitoring ('pharmacovigilance') of medicines. A stocktake on the conduct of pharmacovigilance tasks by the Member States carried out by the EC will be made public 3 years after these new regulations come into force and every 3 years thereafter.

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