

The Need for a New Pharmacovigilance Approach in the EU

Executive summary

Pharmacovigilance rules in the EU are found in a wide array of documents that are sometimes contradictory and often unclear. As such, the rules can be both complex and confusing. There is a need for a new approach to pharmacovigilance regulation in the EU that will allow pharmaceutical companies to focus their pharmacovigilance resources on safety evaluation activities instead of on complying with unclear and complex regulatory demands. Such an approach would be in the best interest of public health.

The legal framework needs to be improved. The legislation should contain clear and concise provisions that would simplify, strengthen and provide legal certainty to the EU legislative framework for pharmacovigilance. Burdensome national discrepancies throughout an enlarged European Union must be eliminated and national regulators should be prohibited from adding national requirements to those provided for in the European legislation applicable throughout the EU so as to avoid inconsistencies between the rules applied in different Member States. Such a prohibition should not, however, limit the powers of EU regulators to regulate across the EU and the EEA in the interest of public health.

Obligations that are currently unclear or ambiguous, in particular those that are laid down in the Commission guidance on pharmacovigilance, “Volume 9 – Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products” (‘Volume 9’), should be clarified and made more precise

The legislation should contain a single set of simplified rules for expedited and periodic reporting of adverse drug reactions (‘ADR’) in the EU and provide for a single reporting point for ADRs within the EEA. The reporting obligations can be further simplified by removing the “unexpected/expected” concept, and requiring the reporting of all serious cases when electronic reporting is implemented. The legislation should contain clear and flexible provisions regarding Qualified Persons (‘QPs’) responsible for pharmacovigilance that allow individual companies to appoint the number of QPs best suited to their respective organizations. Finally, it should also include consistent standards for inspections of company pharmacovigilance departments by the EMEA and EU Member State authorities.

Introduction

It is important from a public health perspective that pharmacovigilance rules are clear and unambiguous. Regulators, health care professionals, inspectors and pharmaceutical companies need to know exactly what rules apply and need to share a consistent interpretation of the rules. Currently, EU pharmacovigilance rules are found in a wide array of documents that are sometimes contradictory and often unclear. As such, the rules are both complex and confusing. In order to clarify the obligations, in particular in an enlarged EU with currently 25 Member States and 27 in the near future, there is a need for a new approach regarding how to regulate pharmacovigilance requirements. This paper sets out such a new pharmacovigilance approach that will rectify a number of the problems that currently exist in the EU pharmacovigilance system.

EU pharmacovigilance rules – complex and confusing?

EU pharmacovigilance rules are found throughout a range of legal and other texts including in a Council Regulation, EU Directives, EU guidances, national legislation, national guidances, and internationally agreed documents.

These various documents come in different degrees of clarity and have different legal effect. A Council Regulation provides the greatest legal certainty. It is adopted by the Council and the European Parliament based on a proposal from the European Commission. A Regulation is directly applicable in all EU Member States and the consistency of its application throughout the EU is guaranteed. Moreover, a Regulation is published in the Official Journal of the European Communities ('OJ') and is thus available in all official languages.

EU Directives are also adopted by the Council and the European Parliament based on proposals from the Commission. A Directive requires implementation through national legislation and is thus not directly applicable in all Member States. There are frequently discrepancies in national implementing laws and a uniform regime in all Member States cannot be guaranteed. A Directive is however published in the OJ in all official languages.

Commission guidances in the area of pharmacovigilance are published on behalf of the European Commission by the Enterprise Directorate General (DG Enterprise). The guidance on pharmacovigilance, "Volume 9 – Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products" ('Volume 9')¹ was drafted in consultation with the EMEA, experts from Member States and other interested parties. Although guidances do not have the same binding legal force as Regulations or Directives, they do

¹ Volume 9 – Pharmacovigilance: Medicinal Products for Human use and Veterinary Medicinal Products, p. 3, available at: <http://pharmacos.eudra.org/F2/eudralex/vol-9/home.htm>.

contain rules that pharmaceutical companies are expected to comply with, as evidenced in recent pharmacovigilance inspections.

Regulating pharmacovigilance through guidances leads to a number of problems related to legal certainty. For example, in Volume 9, the text itself contains a number of ambiguous provisions, some of which will be described below. A further problem is that Volume 9 is only available on the DG Enterprise website and only exists in English, which makes the rules even less accessible to non-native English speakers. The legitimacy of any new obligations imposed on pharmaceutical companies based purely on a guidance is also questionable in light of the lack of a proper legislative process.

Similar problems also arise from other Commission and EMEA guidances, for example the guidances related to the Clinical Trials Directive ('CTD').² Moreover, the approach to pharmacovigilance in the CTD is not harmonized with the pharmacovigilance requirements that apply to authorised products. Future legislation on pharmacovigilance should ideally cover pharmacovigilance during the full life cycle of human medicinal products and thus also supersede the CTD requirements for safety monitoring and reporting.

A further complicating matter is that national rules on pharmacovigilance exist side-by-side with the EU rules. Centrally authorised products can be subject to additional requirements at the national level. The result is a complex web of 25 different national pharmacovigilance rules in a variety of languages. Although these rules are often very similar, they are not uniform. There is also a significant duplication of effort that is evident at the national level. For example, the same safety data is still often assessed by multiple national authorities all working under different timeframes. This results in a significant burden on industry to answer similar questions at different points in time and may raise many false signals due to the repeated raising of suspected signals.

In addition to the EU and the national rules there is also a broader international effort to harmonise pharmacovigilance rules. The International Conference on Harmonisation ('ICH') produces guidelines on ways to achieve greater harmonisation of international pharmacovigilance rules. The Council for Organizations of Medical Sciences ('CIOMS') also produces publications and reports related to pharmacovigilance. Increased international harmonisation of pharmacovigilance rules is very important, but it potentially adds yet another level of complexity for regulators and pharmaceutical companies, in particular when the international rules are not fully implemented in the EU legal framework.

In short, the current EU pharmacovigilance rules are complex and can be confusing, which is a problem, in particular, for pharmaceutical companies.

² The implementation of the Clinical Trials Directive (Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of good clinical practice in the conduct of clinical trials on medicinal products for human use, OJ L 121, 1.5.2001, p. 34) is also inconsistent and might benefit from a more uniform legislative approach.

Legal issues arising from current EU pharmacovigilance rules

In this section we consider some concrete examples of problematic legal issues that arise from current EU pharmacovigilance rules.

Regulatory oversight and compliance

One result of the new pharmaceutical legislation is a shift toward tougher regulatory oversight. For example, recital 20 to Directive 2004/27/EC states that “[p]armacovigilance and, more generally, market surveillance and sanctions in the event of failure to comply with the provisions *should be stepped up*.”³ Article 104(9) of Directive 2001/83/EC, as amended, clarifies that “Member States shall take the necessary measures to ensure that a Marketing Authorisation Holder who fails to discharge these obligations is subject to *effective, proportionate and dissuasive penalties*.”⁴ In light of this, and an increasing number of pharmacovigilance inspections in the EU, it has become even more important to ensure that EU pharmacovigilance rules are clear.

Roles and responsibilities of the Qualified Person

The review of the pharmaceutical legislation introduces increased responsibility for the Qualified Person (‘QP’) responsible for pharmacovigilance. According to Article 21(a) of Regulation 2309/93 the QP is now responsible for “the establishment and maintenance” of a pharmacovigilance system. However, according to Article 23(2)(a) of Regulation 726/2004, as of 20 November 2005, he or she is responsible for “the establishment and *managing*” of such a system.⁵ This requirement is not consistent with other EU legal instruments, for example, Article 103 of Directive 2001/83/EC, as amended, still reads “establishment and *maintenance*.”⁶ It is not clear why different terms are used and what the practical implications of this inconsistency are.

In addition to the role of the QP being ambiguous, the number of QPs that are required per company is not clear either. The position taken by some regulators that there cannot be more than one QP in each company appears to be based on the text in Volume 9. This position, however, is very impractical for large multinational pharmaceutical companies that have considerable product portfolios (in some cases in excess of 150 products) and diverse business units.

³ Emphasis added.

⁴ Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67. Emphasis added.

⁵ Emphasis added.

⁶ Emphasis added.

The legislation should distinguish between the QP as a function and as a person and thus clarify that the function can be performed by as many persons as required.

Pharmacovigilance training requirements

EU pharmacovigilance rules are also not clear with regard to pharmacovigilance training requirements for staff. Volume 9 states that;

“The clock for expedited reporting starts as soon as one of the following has received the minimum information [...] required for the submission of an adverse report:

- any personnel of the marketing authorization holder – including sales representatives”.⁷

This provision has been interpreted by at least one competent authority to mean that **all** members of the company have a pharmacovigilance responsibility and that every staff member (including security staff and secretaries) should therefore receive effective training in pharmacovigilance requirements, regardless of their function. The relevant text of Volume 9 as quoted above does not impose any training requirements. It only requires pharmaceutical companies to comply with the clock start requirement. Consequently, flexibility should be retained in the method(s) used to comply with this requirement. A simple frequent reminder sent out by e-mail to all staff to report all adverse reports to the drug safety department should suffice.

Pharmacovigilance inspection standards

Finally, EU rules regarding pharmacovigilance inspections are not clear and there is an urgent need for clarity. Pharmacovigilance inspections are becoming routine in the EU. Yet, each Member State is responsible for its own pharmacovigilance inspections and each country has different rules and practices. There are currently no EU-wide clear and legally binding rules with regard to pharmacovigilance inspections. As a result, it is not always evident which documents inspectors can review, what the limits of the inspectors' powers are, and what rules apply with respect to the confidentiality of information resulting from an inspection. It is vital that these inspections are conducted based on a consistent set of standards.

EU pharmacovigilance rules at a crossroads – need for a new approach

The examples above demonstrate some of the problems associated with the way the current EU pharmacovigilance regime is regulated. The key problems include legislation that is complex, confusing, and that is primarily based on rules that lack legal certainty. These problems can be very burdensome for pharmaceutical companies and regulators, and are ultimately not in the interest of patients. The European Commission has recognised that “the

⁷ Volume 9, Section 1.2.2

current system of pharmacovigilance in the EU is complex and there is potential for duplication of efforts, as well as, for confusion of responsibilities.”⁸

In light of the above, there is a need for a new approach to regulating pharmacovigilance in the EU.

The Commission has now begun a process of reflection as to how to improve the EU pharmacovigilance system. It has commissioned the Fraunhofer Institute Systems and Innovation Research together with the Coordination Center for Clinical Studies at the University of Tuebingen to conduct an assessment of the current EU pharmacovigilance regime. The study documents the current system in terms of stakeholders, responsibilities, processes and resources; highlights strengths and weaknesses; and makes recommendations to the Commission (DG Enterprise) how to strengthen the system.⁹

The EU legislation should contain clear and concise provisions that would simplify, strengthen and provide legal certainty to the EU legislative framework for pharmacovigilance. National regulators should be prohibited from adding additional requirements to those provided for in the common legislation applicable throughout the EU so as to avoid inconsistencies between the rules applied in different Member States. Such a prohibition should not, however, limit the powers of EU regulators to regulate across the EU and the EEA in the interest of public health. Obligations that are currently unclear or ambiguous, in particular those that are laid down in Volume 9, should be clarified and made more precise.

The legislation should:

- contain a single set of rules for reporting adverse drug reactions ('ADR');
- provide for a single reporting point for ADR within the EEA;
- further simplify expedited reporting requirements by removing the “unexpected/expected” concept, thus requiring the reporting of all serious cases;
- require the submission of all serious ADR reports from within and outside the EU. The current differentiation of reporting requirements between EU and non-EU case reports, whilst understandable in managing the volume of reports, does not make sense from the perspective of “pharmacovigilance knows no boundaries.” The implementation of electronic reporting standards offers the opportunity for MAHs to submit all serious ADR reports from within and outside the European Union to Eudravigilance. That would promote efficiency and improve the important signal generation activities without imposing an additional workload burden for the regulatory authorities;

⁸ Assessment of the European Community system of pharmacovigilance – technical specifications, available at:
http://pharmacos.eudra.org/F2/pharmacos/docs/Doc2005/01_05/Technical%20specifications.pdf

⁹ Ibid.

- contain clear and flexible provisions regarding QPs that allow individual companies to appoint the number of QPs best suited to their respective organizations. In particular, the legislation should distinguish between the QP as a function and as a person and thus clarify that the function can be performed by as many persons as required; and
- include agreed consistent and transparent standards for inspections of company pharmacovigilance departments by the EMEA and EU Member State authorities.