EU pharmacovigilance legislation

Industry scrambles to meet the new rules

In an era where adverse drug reactions (ADRs) account for 5% of all hospital admissions and public confidence in the pharmaceutical sector is at an all-time low, medicines safety is at the top of Europe's legislative agenda. A direct outcome of this is the new pharmacovigilance legislation (Regulation (EU) No 1235/2010 and Directive 2010/84/EU), which comes into effect this July.[1,2]

According to the European Medicines Agency (EMA), the legislation's requirements represent the biggest change in the regulation of human medicines since 1995. The rules will affect both pre-marketing and post-marketing activities, and companies are already making major adjustments to their procedures, systems and resources in preparation. They are also bracing themselves for more fees – estimated to kick in around 2014 – to fund regulators' new pharmacovigilance tasks.

The legislation applies to all marketing authorisation holders (MAHs) and applicants, regardless of whether the products are nationally or centrally authorised.

Why the change?

The European Commission felt the need to strengthen the pharmacovigilance system in the wake of high-profile safety scares such as the global Vioxx (rofecoxib) recall in 2004 and after an independent review revealed a number of weaknesses in the framework. These included ambiguity surrounding pharmacovigilance roles and responsibilities, a lack of proactive and proportionate monitoring, duplicative reporting rules and poor transparency. To address these and other shortcomings, the commission proposed the new legislation, which was adopted in December 2010.

Though the law officially applies from 2 July for centralised authorisations and 21 July for national authorisations, some measures are being phased in beyond these deadlines – much to the relief of industry – because the necessary infrastructures will not be in place.

This is just as well, because companies still have a lot of unanswered questions. Indeed, at the end of a query-laden EMA workshop for small and medium-sized enterprises (SMEs) on 19 April 2012, Pharmacovigilance Working Party Chair June Raine concluded: "We need to provide more clarity [and] issue more Q&As on practical matters."

Industry requirements

While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product unless specific provisions apply.

One of the most controversial measures is Article 57(2) of the regulation, which requires MAHs to submit extensive information to the EMA on their products that are authorised or registered in the EU.

With this information, the agency will create and co-ordinate controlled lists of all the medicines on the EU market to help identify products in ADR reports – an activity that now only happens on an ad hoc basis.

The EMA's head of pharmacovigilance and risk management, Peter Arlett, told workshop participants, for example, that "Today we don't know what products on the market in the EU contain paracetamol. We do lists 'ad hoc' when a problem arises. Having up-front comprehensive lists of substances allows us to avoid the ad hoc process."

Because the details must be submitted using a new electronic format, companies will have to adjust their IT systems and collate this information in a new way. There is a broad range of information required, from a product's name to the structured substance information (SSI). The EMA, however, has responded to industry concerns about the feasibility of meeting these obligations in time by reducing the number of mandatory data elements that will be required by the July deadline; the SSI is one of these.

Another significant challenge for companies involves the submission and maintenance of pharmacovigilance system information, according to Matthias Heck, legal counsel for EU affairs at the European Confederation of Pharmaceutical Entrepreneurs (EUCOPE).[3]

By July 2015, MAHs will have to create a Pharmacovigilance System Master File (PSMF) to be maintained and updated on site, and potentially made available to regulators upon request. This will replace the current Detailed Description of the Pharmacovigilance System (DDPS), which applicants currently submit with their dossiers. They will instead have to submit with their dossiers a less detailed pharmacovigilance summary.

"The main difference is that we'll be asking for more information about the pharmacovigilance system rather than asking for information per product, reducing the burden", Joanna Harper of the UK Medicines and Healthcare products Regulatory Agency explained at the workshop.

Although in theory this should lighten the burden, it is still a major change for companies. If they have separate pharmacovigilance systems for different categories of medicinal products, each system will have to be described in a separate PSMF. Furthermore, MAHs will have to perform regular audits of their pharmacovigilance systems and record their findings in the PSMF. They will also have to put in place effective quality systems to ensure they can meet their pharmacovigilance obligations.

For all new products, the legislation requires companies to include with their marketing authorisation dossier a risk management plan (RMP) that is proportionate to the risk of the product. The RMP describes the pharmacovigilance activities and interventions, such as studies and reports, that the company has designed to identify, characterise, prevent or minimise risks relating to a product. Legally binding studies included in RMPs will cover both safety and efficacy. As a result, "there will be more studies required for new innovative products", said Dr Arlett.

A seventh EMA committee – the Pharmacovigilance Risk Assessment Committee (PRAC) – will be created to handle all aspects of pharmacovigilance and risk management. It

will thus assess RMP study protocols, such as those of post-authorisation safety studies (PASS) and post-authorisation efficacy studies (PAES) that may be required as a condition of marketing authorisation. These studies may also be required after a product's approval if deemed necessary.

As for reporting, the assessment of periodic safety update reports (PSURs) will now be more science-based. MAHs will therefore have to include in the PSUR a scientific evaluation of the product's risk-benefit balance based on all available data, including data from clinical trials and unauthorised indications. In addition, the reports will now have to contain cumulative data. PSUR submission timelines will be every six months during the first two years following the product's commercialisation, once a year for the following two years and at three-yearly intervals thereafter.

Mr Heck pointed out that although there are some simplifications to the EU PSUR rules (eg for certain product categories such as generics, they will no longer be routinely required), companies whose products are also marketed in non-EU countries may still have to meet more complex PSUR obligations elsewhere.

MAHs will be obliged to report electronically all suspected ADRs, whether they are spontaneous (eg reported by healthcare professionals or patients) or occur during post-authorisation studies. They will also be responsible for screening and reporting ADRs found in scientific and medical literature, in non-medical sources such as the lay press and via the internet and digital media. Companies will need to ensure there are mechanisms in place to collect and record all reports, as well as enable the traceability and follow-up of ADR reports.

Individual case safety reports (ICSRs), which are used to report one or more suspected adverse reactions to a medicinal product that occur in a single patient at a specific point in time, will need to be reported to authorities within 15 days for 'serious' ADRs occurring within and outside the EU. The legislation also introduces a new requirement to report within 90 days all 'non-serious' ADRs occurring within the EU, which could be "quite intense" from a staffing and financial perspective, noted Mr Heck.

Until the EMA's central ADR database, EudraVigilance, is fully functional, MAHs will have to report ICSRs for events occurring in the EU to their national competent authority; eventually they will be required to file the reports directly to EudraVigilance.

MAHs will also play a role in 'signal detection' to determine whether there are new risks associated with an active substance or a medicinal product, or whether risks have changed. To this end, they will need to monitor all available data and perform worldwide signal detection activities.

Impact on development costs

Reactions have been mixed with regard to the potential impact on drug development costs. European Association for Bioindustries (EuropaBio) healthcare biotechnology director Miriam Gargasi told *MedNous* in an email that the organisation was concerned about increased costs because "there are many opportunities for additional mandatory data requests by regulators after approval". However, she added, "it is difficult to estimate the exact impact". Mr Heck also said that it was hard to assess the financial impact, but early indicators suggest that costs will increase more than initially expected.

Alexandre Delacoux, executive director of European Biopharmaceutical Enterprises (EBE), is more optimistic. "Increased costs might appear on a case-by-case basis depending on increased scrutiny required. However, this is not a concern for EBE", he said.[4] He added that EBE members had already integrated the new requirements into their business models, noting that the rules would have to be "embedded in the R&D process as early as possible".

Speaking to *MedNous* during the workshop, Dr Arlett said that companies would have to start preparing "at least one to two years before they plan to submit their marketing authorisation applications". SMEs that do not have marketing authorisations yet would be wise to start planning particularly early, he noted, because they will have to reassure regulators (for the first time) that they have got a good pharmacovigilance system in place.

Sharing the regulatory burden

Preparing for the legislation will not only be taxing for industry. It has been a task of sisyphean proportions for the EMA and national authorities, as a considerable portion of the burden lies with the regulators.

Some of the EMA's more daunting hurdles include setting up the PRAC; preparing for the eventual processing of all EU PSURs; getting EudraVigilance fully operational so that all ADR reports can be submitted centrally (the aim is 2015); monitoring ADRs identified in scientific and medical literature and reporting them to EudraVigilance; and improving transparency (eg making more documents available to the public). In addition, the agency is preparing Good Pharmacovigilance Practices guidance that will replace the commission's Volume 9A of the Rules Governing Medicinal Products in the EU on pharmacovigilance.[5]

The commission is also working at full tilt. It is finalising an 'implementing regulation' that will explain the technicalities of the legislation and it has also introduced another set of pharmacovigilance proposals. The latter addresses additional weaknesses in the system that the commission identified after the 2009 withdrawal of Servier's Mediator (benfluorex); the corresponding legislation is expected to be adopted by July 2012.

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