The MHRA perspective on the new pharmacovigilance legislation

Mick Foy

MHRA, UK

Correspondence to:

Mick Foy,
MHRA, UK

Following an extensive period of drafting, consultation, negotiation, and re-drafting the new European Legislation came into effect in July this year. The new measures will be the biggest change to medicines legislation since the creation of the current European system in 1995. The background to the forthcoming changes dates back to 2003 when the European Commission decided to undertake an assessment of the pharmacovigilance system. Independent review and public consultation followed, as well as further work at the Commission, the European Medicines Agency (EMA) and EU member states, resulting in the publication of Regulation (EC) 1235/2010 and Directive 2010/84/EC on 31 December 2010.

The overriding purpose of the new package is to strengthen the public health system through better pharmacovigilance. All areas of post-marketing activities are subject to revision from ADR reporting, signal management, Periodic Safety Update Reports (PSURs), Risk Management Plans (RMPs) and Post Authorization Safety Studies (PASS).

As well as the public health angle the new legislation also seeks to improve efficiency by having improved decision-making processes, reducing duplication and making better use of IT through the use of centralized systems and standards.

However, not all of the new measures will come into effect immediately and a period of transition will apply in a number of areas.

Marketing Authorization Holders (MAHs) and other stakeholders should refer to the EC Implementing Measures and the Good Vigilance Practice Modules produced by the EMA and member states.

This article hopes to highlight areas of interest to medical writers, identifying what the major changes are and when they come into play.

Implementing Regulation

The European Commission, working with the EMA and member states, has developed Implementing Regulation to provide essential technical details on what must be done by the national competent authorities (NCAs), MAHs and the EMA on the introduction of the new legislation. A concept paper on these measures was made available from 8 September to 7 November 2011 for consultation; following this, the revised Implementing Regulation was drafted in discussion with member states and formally adopted and published in the official journal as Commission Implementing Regulation (EU) No. 520/2012 on 19th June.

The Implementing Regulation covers the following key areas in the pharmacovigilance process:

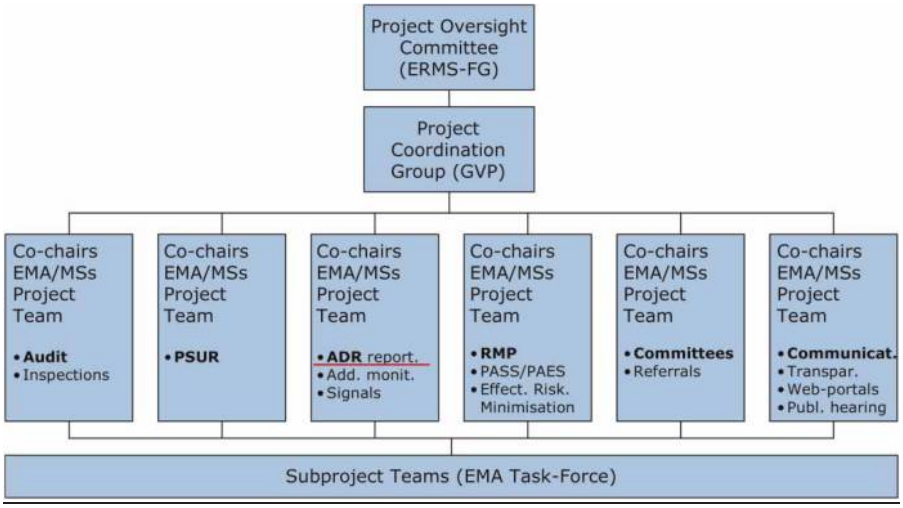
- Pharmacovigilance Master File System (PMFS)
- Quality Management System
- Use of terminologies
- Adverse drug reaction (ADR) reporting and individual case safety report (ICSR) standards
- Format and content of PSURs
- Format and content of RMPs
- Format and content of post-authorization studies
- Signal management responsibilities.

Good Vigilance Practice

Sitting beneath the Regulation, Directive and Implementing Measures are a set of Good Vigilance Practice (GVP) modules. The GVP modules replace Volume 9A and set out detailed, practical guidance on how MAHs and member states should meet the requirements. GVP is being developed according to the governance structure set out in Table 1; the

DOI: 10.1179/2047480612Z.00000000025

Table 1: GVP governance structure



concept is that the EMA and member states co-chair project teams to develop the guidance and report in to a project coordination group which in turn reports in to the European Risk Management Strategy Facilitation Group (ERMS-FG).

The first wave of GVP was released for consultation on 22nd February and adopted on 25th June, and covered:

- MODULE I Pharmacovigilance Systems and their Quality Systems
- MODULE II Pharmacovigilance System Master File
- MODULE V Risk Management Systems
- MODULE VI Management and Reporting of Adverse Reactions
- MODULE VII Periodic Safety Update Report
- MODULE VIII Post Authorization Safety Studies
- MODULE IX Signal Management.

Further waves are scheduled as follows:

III	Pharmacovigilance inspections	Q3 2012
IV	Pharmacovigilance system audits	Q3 2012
X	Additional monitoring	Q2 2012
XI	Public participation in pharmacovigilance	Q4 2012
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action, and planning of public communication	Q4 2012
XIII	Incident management (may be included in module XII: to be confirmed)	Q4 2012
XIV	Referral procedures for safety reasons (may be part of GVP or notice to applicants: to be confirmed)	Q3 2012
XV	Safety communication	Q3 2012
XVI	Risk-minimization measures: selection of tools and effectiveness indicators	Q3 2012

The MHRA is co-chair of Project Team 3, concerned with the development of GVP for ADR reporting, signal management, and additional monitoring. With regard to ADR reporting, it is known that centralized reporting to EudraVigilance will not be in place until after a period of transition while the functionality of the system is enhanced. This is likely to be in 2015 and until that time national arrangements will be in place. It is likely that some member states will not require national reporting and request MAHs send ICSRs to EudraVigilance, while others will have specific requirements for national, third country, and non-serious reports. The MHRA has specified that all UK ADR reports and serious third country reports are sent to the agency until the EudraVigilance functionality has been developed and audited. With regard to third country reports, our requirements will be kept under review as the Article 57 work takes shape and the EudraVigilance product dictionary is developed. MAHs should carefully review the GVP on ADR reporting to ensure the national requirements are clear.

There are other requirements for ADR reporting which MAHs need to prepare for that are set out in the GVP. These include the need to send non-serious reports, reports from patients, ADRs in post-authorization studies, and ADRs detected from digital media.

Another area subject to transition will be the reporting of ADRs identified in published literature. It was expected that the EMA would carry out monitoring and reporting to EudraVigilance on a

specified list of substances; however, this is now unlikely for some time and MAHs will need to continue reporting to NCAs as they currently do; again, GVP sets this out clearly.

Signal detection

One of the major public health developments with the new legislation is that signal detection and signal management is a legal requirement on all parties. The GVP on signal management clearly sets out the requirements on the EMA, member states and MAHs. The guidance largely follows CIOMS VIII with the concept of signal detection, validation, prioritization, evaluation, and communication. MAHs will need to have documented processes for signal detection that are appropriate to the level of reports received and the portfolio of products. This may be individual case review, statistical analysis, or a combination of both. There is clear guidance of what and when to communicate signals with the authorities and when to respond to requests.

For member states there are similar requirements; together with clear roles in monitoring EudraVigilance, every substance authorized or registered in the EU will be appointed as a lead member state which will be responsible for generating and validating signals from EudraVigilance and the subsequent notification.

The MHRA considers this a vitally important aspect of the new legislation but, at least in the UK, it will not be in place of current practices but complimentary to the national PV system.

Resources

While the EC impact analysis suggested minimum savings of €237 million per year, it is clear that some of the savings will not be realized immediately and the period of transition will be somewhat longer than perhaps initially expected. MAHs will need to consider the implications of the Implementing Regulation, GVP and Article 57 to ensure they are adequately resourced to meet the new rules.

Member states are also considering the resource implications; as we are now working within the new system it is becoming clear we need to fully understand the resources required, particularly people and IT investment.

Conclusion

As noted earlier, the new pharmacovigilance legislation is the biggest change to the European medicines regulations since 1995, and will deliver a much improved system for us to protect public health. The European Commission, EMA and member states have been working together over the past years to develop a comprehensive framework for us all to follow and this reaches across every area of the PV system. The above sets out just a few areas where the guidance is maturing; other aspects, such as PSURs, RMPs, PASS, and inspections will also need to be carefully considered by the industry. In addition, member states are also considering the implications for national reporting systems, the issues around public participation and communications, not to mention the new pharmacovigilance risk assessment committee, PRAC.

The work of the European regulatory network is intensifying and the challenges over the next few months will be significant. The rewards, however, in terms of an improved European pharmacovigilance system, promise to outweigh these challenges. The purpose of all of this activity is to benefit public health; this is what continues to drive us all.