Priority PASS

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European pharma companies are continuing to get to grips with revised pharmacovigilance legislation and the impact on post-authorisation safety studies (PASS), which must now take into account new good practice rules and updated requirements.

Regulatory agencies worldwide are increasing the pressure on pharmaceutical companies and other marketing authorisation holders for post-approval commitments focused on safety, with potentially large penalties for non- compliance. The European Union (EU) is a case in point. Recent changes in pharmacovigilance legislation in the EU promote more proactive approaches to measuring the efficacy and safety of medicinal products in the post- authorisation environment. In light of this development, pharma companies are seeing – and will continue to see – more obligations to conduct Post-Authorisation Safety Studies (PASS).

Legislative Overview

EU Regulation No. 1235/2010 and Directive 2010/84 were approved by the European Parliamentary system in December 2010. All pharma companies, regulatory agencies and other stakeholders had 18 months to implement the new requirements, with a deadline of July 2012. The Regulation and Directive were supported by Commission Implementing Regulation No. 520/2012, published in June 2012, which provides additional information and includes transitional timeframes for some elements of the new legislation.

The final layer of documentation that supports the legislation is the Good Pharmacovigilance Practices (GVP). This is a new concept in the EU and describes the expected operational application of the Regulation, Directive and Implementing Regulation. The GVP is being presented in 16 modules, which began to be published last year **(see Table 1)**.

GVP Module VIII

The content of Module VIII of the GVP is largely aligned with the requirements of the European Network of Centres for Pharmaceopidemiology and Pharmacovigilance (ENCePP) and the International Society of Pharmaceopidemiology (ISPE). It is not mandatory for an organisation to be registered with ENCePP to comply with GVP, although use of ENCePP-registered organisations will provide a level of reassurance to regulatory agencies.

A post-authorisation safety study is defined in the EU Directive 2010/84 as: 'Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures.'

This is a change from previous definitions, with the addition of the measurement of the effectiveness of risk management measures. The revised pharmacovigilance legislation reinforces the expectation that risk minimisation activities will be monitored for their effectiveness. It is anticipated the PASS will be a common tool utilised in this activity.

PASS may be interventional or non- interventional (observational). Interventional studies must follow the requirements outlined in the existing European Clinical Trial Directive (2001/20). The requirements described in GVP largely apply to non-interventional studies only. Studies are considered to be non-interventional when the product is used within the terms of the marketing authorisation, there is non assignment of patients to a particular therapeutic strategy, and there are no additional diagnostic or monitoring procedures.

A common area of discussion is the use of interviews, questionnaires, and/or blood tests. In GVP these are not considered interventional, but practical experience shows that some European agencies continue to consider them to be so.

Table 1. Overview of good pharmacovigilance practices

Module no.	Module title	Status at time of publication
I	Pharmacovigilance systems and their quality systems	Published (June 2012)
II	Pharmacovigilance system mast file	Published (June 2012)
III	Pharmacovigilance inspections	Published (December 2012)
IV	Pharmacovigilance audits	Published (December 2012)
V	Risk management systems	Published (June 2012)
VI	Management and reporting of adverse reactions to medicinal products	Published (June 2012)
VII	Periodic safety update report	Published (June 2012)
VIII	Post-authorisation safety studies	Published (June 2012)
IX	Signal management	Published (June 2012)
X	Additional monitoring	Consultation closed
XI	Public participation in pharmacovigilance	Consultation pending (Q2 2013)
XII	Continuous pharmacovigilance, ongoing benefit-risk evaluation, regulatory action and planning of public communication	Consultation pending (Q2 2012)
XIII	Unassigned	Not applicable
XIV	International cooperationv	Consultation pending (Q2 2013)
XV	Safety communication	Consultation closed
XVI	Risk minimisation measures: Selection of tools and effectiveness indicators	Consultation pending (Q2 2013)

The result: the same study may be interventional in some countries, but not in others, This presents challenges for the study sponsor in identifying which regulatory requirements to adhere to and how to manage conflicts that may arise.

EU PAS register

The recommendation is to includ information regarding both interventional and non-interventional studies in the EU PASS Register, the electronic register for PASS. This is currently under development by the European Medicines Agency, and will be an evolution of the current ENCePP register. Also recommended is to include the study protocol, any substantial protocol amendments, process reports and the final study report.

PASS conduct

GVP Module VIII also provides guidance on the conduct of PASS, including research contracts with investigators, the development of the protocol, management of substantial amendments to the protocol, requirements for progress reports, and preparation of the final study report. Suggested formats and contents for these documents and the use of ENCePP checklists and additional guidance are described and recommended.

Furthermore, GVP emphasises the importance of continuous pharmacovigilance activities throughout the conduct of PASS. Study sponsors are expected to monitor the data being generated at frequent intervals to identify any change to the current knowledge of the benefit- risk profile of the product. This is typically performed at monthly

or quarterly intervals by a cross-functional group involving physicians, clinical research staff and pharmacovigilance personnel.

Adverse events

A key impact of the revised pharmacovigilance legilation is the management of adverse events. While adverse events occurring in interventional clinical studies continue to follow traditional processes, the adverse event management within observational studies has become increasingly complex **(Figure 1)**. Adverse events observed in studies based on retrospective record review do not require submission to regulatory agencies outside of the final study report. However, studies based on primary data collection now need to collect all adverse events (related and unrelated to study drug, serious and non-serious). All serious related adverse events need to be submitted to regulatory agencies within 15 days, including events that are both expected and unexpected.

Of more impact, however, is the new requirement to submit non-serious adverse events to regulatory agencies on an expedited basis. This does not affect non-serious adverse events occurring in a site outside the EU, but those non-serious adverse events occurring in a site within the EU require expedited submission within 90 days. Consequently these events need to be made available to the responsible pharmacovigilance department promptly to enable the submission process. The requirement to submit non-serious adverse events with in 90 days is currently in a transition phase.

Six countries in the EU required this as of July 2012, but it will be required for all EU countries by 2016.

Consideration needs to be given to management of these requirements across studies that have sites both in and outside the EU. One strategy is to apply the same adverse event collection processes across the study, collecting non-serious adverse events across all sites to forward to the relevant pharmacovigilance group. However, this may cause a significant resource burden for the investigator, the clinical research personnel and the pharmacovigilance personnel. Another strategy is to customise the adverse event collection process across the sites, only collecting non-serious adverse events from the EU sites. This process has logistical issues with differing requirements for different sites.

Once these hurdles have been overcome, the study completed and the study report submitted to the relevant regulatory agencies, there is one final requirement: GVP recommends that final manuscripts are forwarded to regulatory agencies within two weeks of first acceptance for publication. This has caused concern in the pharma industry about potential infringement of legal agreements with journals and the potential for accidental distribution of an article before publication.

The implementation of GVP in the EU has a significant impact on both European and global PASS. Consideration to GVP requirements should be given to both ongoing PASS studies and those currently in the planning stage.

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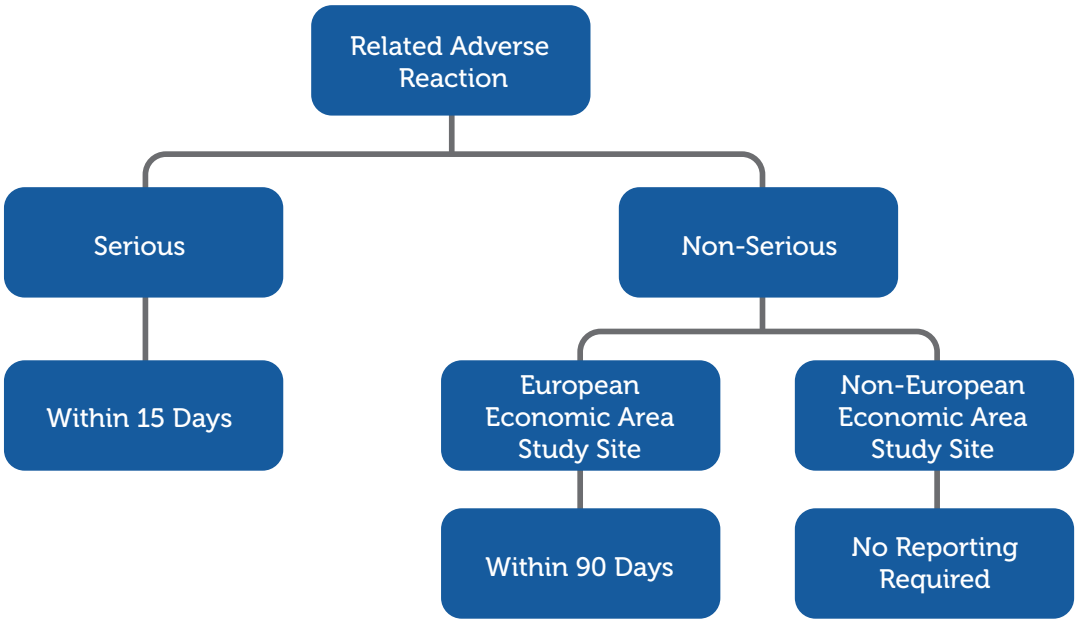
Figure 1. Adverse event expedited submissions requirements for Observational PASS



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