

POST AUTHORIZATION SAFETY STUDIES (PASS); UPDATED EU REGULATIONS

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New regulations requiring improved safety reporting in post-marketing studies have been introduced in the last decade, mainly as a result of high-profile product recalls. These new regulations are designed to ensure that medicinal products are monitored for long-term safety and effectiveness in more extensive patient populations. This article will provide a review of the recent updates in this field as well as address how the most recent EU regulation published at the end of 2010 will change post-authorisation studies in the future.

On 31 December 2010, the European Commission (EC) published in the *Official Journal of the European Communities* Regulation (EC) No 1235/2010 ("the Regulation") and Directive 2010/84/EC ("the Directive") amending as such pharmacovigilance Regulation (EC) No 726/2004 concerning medicinal products authorised through the centralised procedure (including advanced therapy medicinal products under Regulation (EC) No 1394/2007) and Directive 2001/83/EC concerning medicinal products authorised through the national, decentralised and mutual recognition procedure. The Regulation entered into force on January 1st, 2011 and will be applicable from July 2nd, 2012 onwards. The Directive entered into force on January 20th, 2011 and the Member States shall adopt and publish the laws, regulations and administrative provisions necessary to comply with this Directive by July 21st, 2012 at the latest. As a key change, the Regulation and Directive require the Marketing Authorisation Holder (MAH) to conduct post-authorisation studies on safety and/or efficacy, either at the time of authorisation or during the post-authorisation phase. Such studies aim at collecting data for the assessment of the safety and/or efficacy of the medicinal product in everyday medical practice.

Following the new pharmacovigilance legislation, a Marketing Authorisation (MA) may be conditionally granted, with a requirement that the MAH conducts post-authorisation efficacy studies in case concerns relating to some aspects of the efficacy of the medicinal product are identified and can be resolved only after the medicinal product has been marketed. After authorisation, the Competent Authority (CA) may oblige the MAH to conduct a post-authorisation efficacy study in case the understanding of the disease or the clinical methodology indicates that previous efficacy evaluations might have to be revised significantly. The requirements concerning e.g. risk management systems and post-authorisation safety studies (PASS) are tailored for individual medicinal products and are made proportionate to the specific risks of the medicinal product. In order to increase transparency and communication the protocols and abstracts of the results of PASS will be published by the European Medicines Agency (EMA) on the Agency's web-portal. Since the new legislation provides harmonized guidance and procedures for the supervision of PASS, it is likely that such studies will be more frequently requested by the CAs in the future.

A REVIEW OF RECENT INITIATIVES IN MONITORING POST-APPROVAL DRUG SAFETY

In November 2004, the International Conference on Harmonisation (ICH) issued guidelines on pharmacovigilance planning¹ aimed at creating a more proactive approach towards the identification and quantification of safety concerns after marketing of a medicinal product in the three ICH regions (EU, Japan and the US). The ICH guideline on pharmacovigilance planning was adopted in the EU, including additional requirements, in November 2005 by requiring the submission of an EU Risk Management Plan (RMP) as a part of a marketing application for all new chemical entities. In the EU RMP, it is mandatory to describe the safety profile of the medicine and to propose the pharmacovigilance measures taken to study additional safety concerns during use of the drug in the real-world setting. Volume 9A of European guidelines² provides further guidance on RMPs in Europe, including the conduct of PASS.

Outside of the Volume 9A regulation, the EMA has been conducting other efforts to promote risk management and safety

initiatives. In November 2007 a two-year program was launched for further development of the European Risk Management Strategy (ERMS) initiatives in order to implement a more proactive approach to risk management that encompasses the entire lifespan of a drug. As part of the ERMS initiatives, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) project was initiated. The project's goals include facilitating multi-centre, independent post-authorisation studies focusing on safety and on benefit/risk balance, using available expertise and research experience across Europe^{3,4}.

The US also heightened focus on drug safety and risk management which has resulted in significant changes for the pharmaceutical industry during the post-approval phase of drug development. In July 2009, the Food and Drug Administration (FDA) released a draft Guidance implementing section 505(o) of the Federal Food, Drug, and Cosmetic Act, a powerful new law authorizing the FDA to require post-marketing studies and clinical trials for drug and biological products found to raise safety concerns. Studies that the FDA requires sponsors to conduct, or which sponsors agree to conduct after FDA has approved a product for marketing, are respectively referred to as Postmarketing Requirements (PMRs) or Postmarketing Commitments (PMCs). The requirement of such studies must be based on scientific data and is limited to certain specific purposes, including assessment of a known serious risk related to the use of the drug involved, assessment of signals of serious risk related to the use of the drug and identification of an unexpected serious risk when available data indicates the potential for a serious risk. The draft FDA Guidance indicates that new drug applicants will have input on the design and conduct of all studies, however such input is purely discretionary, as the FDA is given authority to impose PMRs unilaterally, and can pursue legal action against non-compliant manufacturers for unapproved marketing or misbranding of drugs⁵.

PASS – A CRITICAL TOOL IN SEARCHING FOR 'MISSING INFORMATION'

According to the Directive 2010/84/EU, the new definition of a post-authorisation safety study is “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”⁶. However, previously, a post-authorisation safety study was defined in Article 1(15) of Directive 2001/83/EC as “a pharmaco-epidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorization conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product”. One may therefore conclude that the amended definition of PASS aims to cover not only on-label, but also off-label studies, thus implying that any new safety information, based on the studies conducted outside the scope of the MA, ought to be communicated to the CAs and will be taken into account in the risk/benefit analysis of the product.

Depending on the type of the study, the medical objective and the size of the patient population to be observed, PASS can be conducted either as clinical trials of phase IV (falling under the scope of the Directive 2001/20/EC) or as non-interventional (observational) studies. Unlike clinical trials, observational research provides data on how marketed products are actually being used in the real world without the restrictions of a controlled environment. In accordance with legal requirements, PASS may be requested by CAs either as a commitment at the time of authorisation or in the post-authorisation phase, for identifying previously unrecognized safety concerns. For certain medicinal products, applicants may receive a MA under the condition that they perform additional monitoring. In such cases the MA will be compulsorily varied to include the obligation as a condition of the MA and the risk management system has to be updated accordingly. The proposed Article 28 of Directive 2001/84/EU sets out the rules that will apply to any PASS falling outside the scope of Directive 2001/20/EC.

Volume 9A provides guidance on PASS, and refers to “principally those non-interventional post-authorisation safety studies where there is a known safety issue under investigation and/or when the numbers of patients to be included in the study will add significantly to the existing safety data for the product(s)”, creating ambiguity in further defining of what does and what does not constitute PASS. Inconsistent interpretation of the PASS definition within and between companies resulted in various outcomes, varying from under- to over-reporting, including inadequate company oversight and tracking of PASS, non-inclusion of relevant study updates and reports in RMPs/Periodic Safety Update Reports (PSURs) and the FDA annual reports, or the opposite - MAHs taking the conservative approach and including every post-marketing study in RMPs/ PSURs or generation/reporting of data irrelevant to safety. These misconceptions of PASS resulted in significant unnecessary work for MAH and CAs. In order to address the request of CAs in the most competent and efficient manner, careful analysis and definition of the study objectives, typically requiring a pharmacoepidemiology expertise, is of utmost importance.

A variety of data collection methods may be used to evaluate the safety of authorised products. The study methods in this field, including cohort, case-control, cross-sectional studies, patient registries and randomized clinical trials, continue to develop. Involvement of experts with a strong understanding of both strengths and limitations of automated databases and observational data (e.g. misclassification, channeling bias, confounding by indication) is essential to ensure appropriate study design and analysis so that incorrect or premature conclusions do not drive decisions about product safety. The study design needs to be tailored to particular products and safety concerns, where different principles are applied in a variety of situations. Any specific safety concerns to be investigated should be identified in the protocol and explicitly addressed by the proposed methods. A recent study showed that at the moment of regulatory approval, 40% of PASS proposals were classified as a short description or a commitment without further information, precluding an ad-

equate scientific assessment. The lack of a protocol makes it impossible to assess the feasibility of the proposed PASS during decision making, which increases the risk that the required safety information will not be forthcoming.

To ensure proper design all protocols should be evaluated by the Pharmacovigilance Risk Assessment Committee or CA of the member state where the study will be conducted (in case the study is only performed in one country). For proper conduct, the studies cannot be performed where the act of conducting the study promotes the use of medicinal product, and payments to healthcare professionals for participating in non-interventional safety studies must be restricted to compensation for time and expenses incurred only. The MAH shall monitor the data generated and consider its implications for the risk-benefit balance of the medicinal product concerned. Timely submission of PSURs,

RMPs, annual (or more frequent) study progress reports and final reports is essential.

CONCLUSION

In today's environment, simple risk communication in the form of product labeling (Package Insert or Summary of Product Characteristics) to meet regulatory needs is often insufficient. Obtaining and maintaining MA for products is becoming increasingly difficult. As more risk management and safety studies are required for approval and become an integral part of active surveillance efforts, the quality of data generated from these studies is going to be more closely monitored and high-quality programs will be the expected norm.

Post-authorisation safety studies offer an important new tool to actively study safety concerns in the real world setting. Detailed planning and comprehensive

study protocol increase the likelihood of the PASS providing the necessary safety information. The need for individualized tailored PASS, depending on the type of drug, should be supported by the proposed data source. The MA applicant is advised to clearly assess its validity and evaluate the proposed methodology.

ABOUT SGS

Medical and pharmacovigilance expertise, combined with highly qualified SGS personnel across different departments (Data management, Statistics, Clinical Trial Management, Medical and Regulatory Affairs) can favourably impact the decision-making process and support the MAH in delivering high quality results. The talent, expertise and knowledge that exist within the SGS Life Science Services can help our clients to create the most effective plan for ensuring product safety.

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