Focus

A review of the European risk management strategy for medicinal products for human use

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Abstract
The environment for developing medicinal products is becoming increasingly risk-averse as regulatory agencies across the world focus significant resources on measures intended to improve the safety of medicinal products. In Europe, risk management systems for medicinal products for human use build on existing pharmacovigilance systems, making more efficient use of limited resources to deliver excellence. Risk management plans are an important element of the European risk management strategy, and guidance is starting to emerge. The goal is to deliver a European risk management system greater than the sum of its parts. This article reviews the European risk management strategy and progress on its implementation.

Introduction
Following a series of highly-publicised product withdrawals in the late 1990s due to safety concerns, regulatory agencies and the pharmaceutical industry were criticised over the adequacy of measures taken to protect public health. In response to this public pressure, the environment for developing medicinal products is becoming increasingly challenging. Guidance on risk management plans is now available and sponsors are required to proactively investigate and document potential drug safety issues throughout the lifetime of the product.

In July 2002, following the withdrawal of cerivastatin, the Heads of Agencies agreed to a mandate for an Ad hoc Working Group to consider the action needed to strengthen pharmacovigilance systems so that all medicines, approved Nationally or Centrally, could benefit from the same high standards of safety monitoring. In January 2003, the Ad hoc Working Group agreed to the following five elements of a European risk management strategy:

1. A revised mandate for the Pharmacovigilance Working Party (PhVWP)
2. A pharmacovigilance resource survey across the Member States
3. Improving utilisation of limited pharmacovigilance resources
4. Strengthened pharmacovigilance communications and information exchange
5. Guidance on risk management plans.

Objectives of the European risk management strategy
The European approach to risk management builds on the strengths of the existing European Union pharmacovigilance systems and focuses on areas for improvement. As the legal framework for pharmacovigilance in the EU requires each Competent Authority (CA) to deliver pharmacovigilance at a national level, each CA plays an important role in the effectiveness of the European system. The Heads of Agencies recognised that a new European strategy was needed to bring improvements in pharmacovigilance through co-ordinated pan-European systems.

A mandate for a European risk management strategy (ESRM) was agreed upon in order to:

- Build on National Competent Authorities’ (NCAs) resources and expertise and incorporate the European Medicines Agency’s (EMEA) role in the coordination of the supervision of products authorised in the Community
- Support consistent, robust decision making
- Ensure accessible information on safety, including information exchange between NCAs
- Reduce duplication of work
- Be demonstrably effective in protecting public health.

The model for excellence in pharmacovigilance, developed in the UK, has been adopted. Five key elements are said to be essential. Three of these are process-related (best evidence, robust scientific decision making and effective tools to protect public health). The remaining two elements, scientific outcome measures and audit, underpin these processes, recognising that excellence cannot be achieved by process alone.

Five elements of the European risk management strategy and progress to date
In May 2005, the Heads of Agencies Ad hoc Working Group issued a progress report on the implementation of the European risk management strategy.
1. Revised mandate of the Pharmacovigilance Working Party

Robust decision making is an essential part of the model for pharmacovigilance excellence. The Ad hoc Working Group, in collaboration with the Committee for Medicinal Products for Human Use (CHMP), has developed a revised mandate for the PhVWP, setting out new responsibilities, which include:

- Evaluation of potential drug safety signals arising from spontaneous reporting
- Provision of advice on quantification of risk
- Advising on risk management plans
- Setting standards for procedures and methodologies to promote good vigilance practice
- Promotion of communication and exchange of information between the EMEA and CAs.

2. A pharmacovigilance resource survey across the Member States

Three surveys were conducted in 2002 and 2004 among all EU Member States, including the 10 countries that joined the EU in 2004. The surveys showed that staff resources were limited, with the capability of the network focused in a small number of Member States, with the majority of time spent on National products. Also, there was a heavy reliance on spontaneous reporting with the processing of paper-based Periodic Safety Update Reports (PSURs) forming a significant portion of the workload.

3. Improved utilisation of limited pharmacovigilance resources

Given the limited resources available for pharmacovigilance, reducing duplication of effort is a priority. A work-sharing process has been developed to reduce the duplication of effort on PSURs. In addition, an Ad hoc Working Group on the synchronisation of PSUR submissions has been established. More work needs to be done on developing the “reference” or “lead” Member State principle for development of risk management plans and communication materials. The legal basis of such an arrangement needs further consideration also.

EudraVigilance is the EU data processing network and management system containing suspected adverse reactions to medicines licensed across the EU. The system is intended to be an important tool in the European risk management strategy, with a view to facilitating the conduct of pharmacovigilance at an EU level. However, implementation problems have been experienced and delays have occurred.

4. Strengthened pharmacovigilance communications and information exchange

On September 12, 2003, Confidentiality Arrangements were finalised between the European Commission, the EMEA and the FDA to promote cooperation and transparency between the United States and the EU. The Confidentiality Arrangements allow the European Commission, the EMEA and the FDA to exchange information as part of the regulatory processes, pre- and post-approval. The aim of the Confidentiality Arrangements is to strengthen communication between regulatory authorities and to reinforce public health promotion and protection. Implementation will be in a step-wise approach, including procedures for information exchange and audits to assess benefit. These Confidentiality Arrangements will allow open dialogue between regulators on safety issues and should facilitate the development of global risk management plans.

5. Guidance on risk management plans

In November 2005, the EMEA issued a guideline on risk management systems for medicinal products for human use. A risk management system is defined, in this case, as “a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions.”

An EU Risk Management Plan (EU-RMP) is required to identify the risks associated with a product, to clarify the safety profile of a product and to minimise risk to patients in clinical use. An EU-RMP may need to be submitted at any stage of a product’s lifetime and should be included in Marketing Authorisation Applications for new chemical entities, biotechnology products, new dosage forms, new routes of administration, new indications and new patient populations, or at any time on request from a Competent Authority (CA) or on the initiative of the Marketing Authorisation Holder. The location in the dossier is still to be confirmed.

An EU-RMP consists of three elements: a safety specification; a pharmacovigilance plan and an evaluation of the need for risk minimisation activities. If additional risk minimisation activities are required, the EU-RMP will need to contain a risk minimisation plan.

The EU-RMP should be updated and submitted to the CA as important new safety information becomes available, or with the PSUR, unless other requirements have been agreed to as a condition of the Marketing Authorisation.

Safety specification

The safety specification should be a summary of the important identified risks, important potential risks and important missing information. It should also identify potentially at-risk populations and outstanding safety questions that warrant further investigation to fully characterise the risk-benefit profile of the medicinal product.

The safety specification will help industry and regulators identify the need for specific pharmacovigilance methods, including data collection methods, and will facilitate construction of the pharmacovigilance plan.

Elements of the safety specification might include non-clinical findings not adequately addressed by clinical data, limitations of the clinical safety database, populations not studied, adverse events, identified and potential interactions including food-drug and drug-drug interactions and pharmacological class effects.

For each element listed in the safety specification, the important identified risks, the important potential risks and the important missing information should be documented. A pharmacovigilance plan and an evaluation of the need for risk minimisation activities can then be prepared, based on this list.

Focus continued…
The pharmacovigilance plan is based on the risks and potential risks identified in the safety specification and should propose actions to address the safety concerns identified. For medicinal products where no special safety concerns have arisen, routine pharmacovigilance activities should suffice. In situations where these may be inadequate, more formal data collection practices should be included, such as outline protocols for post-approval safety studies or increased monitoring in clinical trials.

A key concept in the development of pharmacovigilance plans is safety milestones. The plan should document time points and events, for example when exposure to the product has reached a pre-defined level, when results of safety studies are available, or when the product has been marketed for a certain period of time. The pharmacovigilance plan is a living document and must be amended and updated as safety information becomes available and safety milestones are reached.

**Evaluation of the need for risk minimisation activities**

For each safety concern identified, an evaluation of the need for risk minimisation activities should be provided. It is possible that risk minimisation activities could be limited to routine activities such as ensuring appropriate warnings are included in the product information, or by careful use of labelling and packaging to reduce medication errors. In some cases, additional risk minimisation activities will be required.

**The risk plan**

The risk plan describes the activities to be carried out to reduce the risks associated with an individual safety concern, and should include both routine and additional activities. The latter might include communications to healthcare professionals and the public, distribution control, treatment protocols, treatment guidelines and restrictions and conditions within the Marketing Authorisation. Each additional risk minimisation activity should have a section detailing how its effectiveness in reducing risk will be assessed.

Risk communication is an important tool in risk management and risk minimisation. Patients and healthcare professionals need accurate and timely information about the risks associated with medicinal products so appropriate treatment decisions can be made. Further guidance on risk communication is being developed.

The effectiveness of risk minimisation activities should be assessed, and these assessments should be included in the EU-RMP as it is updated.

**Discussion**

For many products, risk management activities can be adequately handled through the labelling and routine safety monitoring; therefore risk management may become a formalisation of routine development activities. However, risk management planning should be considered at an early stage in the product’s lifetime and built into development plans. The sponsor must actively identify and evaluate emerging safety signals to facilitate discussions with regulators to develop and maintain suitable risk management plans.

In order to develop appropriate risk management plans, increased dialogue will be required earlier with regulatory agencies and adequate time should be allowed in development plans for these discussions.

While the sponsor should actively attempt to identify risks prior to approval, significant delays in drug development should be avoided. Approval of a Marketing Authorisation Application does not mean that a drug is without risk, and risk management activities should continue throughout the lifetime of the product. The risk-benefit assessment should also reflect the benefits as well as the risks.

At Step 2 of ICH E2E: Pharmacovigilance Planning in November 2003, it was recognised that ICH participants had been developing risk management guidance in isolation and harmonisation was necessary.

The ICH guideline 10 is intended to aid industry and regulators in planning pharmacovigilance activities in preparation for the early post-marketing period of a new drug. The focus of the guideline is on the safety specification and pharmacovigilance plan, consistent with the European strategy. As risk management is an ICH topic, it should be possible to develop a global risk management plan for a product that may be tailored to account for legislative differences between regions, if necessary.

Further guidance will be necessary to ensure that regulators apply a consistent approach to the content and detail of risk management plans and to products in the same class.

EU enlargement brings new challenges to risk management activities. A greater degree of infrastructure and IT systems will be required to implement pan-European systems and processes for pharmacovigilance activities and it will be interesting to see how implementation progresses at the European level.

**Conclusion**

The regulatory environment is becoming increasingly risk-averse and regulatory agencies across the world are dedicating significant resource to risk management activities. The sponsor is required to proactively investigate potential drug safety issues throughout the lifetime of the product, starting early in development.

For many products, risk management activities can be adequately handled through labelling and routine safety monitoring. If properly implemented, there should be minimal impact on the conduct of global drug development and commercialisation activities.

Risk management is an ICH topic which should facilitate development of risk management plans with global utility, tailored to meet the specific needs of each region.

The approach to risk management from European regulators is to examine current pharmacovigilance systems to assess their strengths and identify areas for improvement. Progress has been made on the five initial priorities for action. The PhVWP has a revised mandate, including specific risk management activities, the survey of EU pharmacovigilance resources has been carried out, arrangements for sharing regulatory information are now in place and guidance on risk management plans is available.
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