Consolidation of Safety Surveillance by Risk Management Strategies: A Status Analysis

Introduction
Safety surveillance has evolved into a continuing process during the whole drug life cycle, both in the development phase and the post-marketing period. Policy-makers and regulatory bodies have instigated proactive safety assessments during drug development by mandating the manufacturers to submit risk management plans (RMPs) along with the marketing authorisation application. The RMP lays out a schematic platform on which the pharmacovigilance plan and risk-benefit analysis are characterised for any drug. Here we discuss how the current risk management principles are woven to shape up a progressive safety profile for a drug, alongside setting a road map for risk minimisation and efficacy evaluation.

Regulatory Framework on Risk Management
A risk management plan (RMP) must identify or characterise the safety profile of the medicinal product(s) concerned, indicate how to characterise further the safety profile of the medicinal product(s) concerned, document measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those interventions and document post-authorisation obligations that have been imposed as a condition of the marketing authorisation. From 2005, a new European legislation has authorised regulatory agencies to require drug companies to submit, along with their application for marketing authorisation, a risk management plan comprising detailed commitments to post-marketing pharmacovigilance. The EMA proposed Regulation and Directive of December 2008 concerning pharmacovigilance proposes, among many other measures, more widespread use of risk management systems, particularly if there are concerns about risks affecting the risk–benefit balance of an authorized product and which should be proportioned to the risks. According to the proposal, if concerns exist about the safety of a drug authorised for exceptional circumstances, a marketing authorisation can be granted provided that post-authorisation studies are conducted.

The FDA Amendments Act, signed into law in September 2007, has set forth risk identification, evaluation, and mitigation objectives for the FDA regarding post-market drugs. Risk evaluation and mitigation strategies (REMS) are risk management plans that use risk minimisation strategies beyond the professional labelling to ensure that the benefits of certain prescription drugs outweigh their risks. The REMS can be needed before or post approval and each REMS is unique for a single drug or a class of drug as determined by the FDA. This led pharmaceutical companies to incorporate greater attention to drug safety into their pre-market approval processes as well as post-marketing surveillance. The approval holder can propose a modification to submitted REMS or the FDA has the authority to require submission of a proposed modification to a REMS to ensure that the benefits of a drug outweigh its risks.

Risk Management Principles
The safety profile of any investigational drug at the time of authorisation is based on the data from clinical trials, where the drug is tested on a targeted population for a particular indication. The risk management plans are designed to plan the pharmacovigilance activities based on pharmacological principles of specific issues identified from pre- or post-authorisation data. The overall objective of risk management is to ensure that the benefits of a particular medicinal product (or a series of medicinal products) exceed the risks by the greatest achievable margin for the individual patient and for the target population as a whole. In the EU, as well as complying with the legislation, the primary document and process for risk management adheres to the principles in the International Conference for Harmonization (ICH) Guideline E2E on Pharmacovigilance Planning. The RMP is a dynamic, stand-alone document which should be updated throughout the life-cycle of the products. The core elements of RMP include safety specification, pharmacovigilance plan and risk minimisation. These elements operate with the objective to identify, clarify, evaluate and minimise the risks associated with the drug use. To impart a stronger safety surveillance, the RMPs have included additional pharmacovigilance activities that go beyond spontaneous reports, such as post-authorisation safety studies (PASS) or post-authorisation efficacy studies (PAES), or monitoring safety aspects of ongoing clinical trials. The EMA RMP has been criticized for poor risk communication plan and limited transparency, while the pharmacovigilance activities were also found inadequate to ascertain the observed risks in certain RMPs, thereby demanding more stringent pre-marketing evaluation.
The FDA identifies risk management as an iterative process designed to optimise the benefit-risk balance for regulated products throughout the product life cycle. The FDA utilises the term REMS, which is defined as a required risk management plan that uses tools beyond the prescribing information (the package insert) to ensure that the benefits of certain drugs outweigh their risks. The FDA REMS is built on the core elements of medication guide, communication plan, elements to assure safe use (ETASU) and implementation system. The FDA has also published several guidance documents like recommended approach for communicating important drug safety information to the public, pharmacovigilance planning at the time of licence application, and quality risk management to provide regulators and industry with principles and tools for risk management as a basis for consistent risk-based decisions throughout a product’s life cycle.

A pragmatic approach is needed to plan a risk management strategy or programme as each medicinal product is unique and demands a customised road map to attain risk management objectives. Safety surveillance by evaluating reported adverse events, detecting and managing safety signals and implementing interventions to minimise risks are the core aspects while designing the strategy. The strategy of risk management has shifted from solely post-marketing to complete product life cycle during the past decade, and is currently witnessing a transition towards systematic epidemiology. Typically, these programmes are designed by staff from the central office of the MAH in conjunction with the requesting health authority. For globally marketed products, however, it is often staff at the affiliate offices who are actually responsible for programme implementation. Labelling in the form of package insert, summary of product characteristics and investigator brochure are considered as cornerstone for risk management. Evaluation of the effectiveness of drug risk-minimisation measures is mandatory for both REMS in the United States and risk management plans in the European Union (EU-RMPs). Risk-minimisation programmes can be challenging to implement because implementation may need to occur at multiple levels and be conducted by multiple parties. Traditional risk interventions include labelling changes, black box labels and dear doctor letters. For complex risk minimisation programmes, an additional level of implementation may involve engaging with third-party vendors to build specific programme infrastructure (e.g., central data collection repositories, patient service ‘hubs’ and quality monitoring systems). Active dissemination efforts, which feature multiple communication methods targeting multiple audiences and involving peer-to-peer human interaction, have been empirically proven to be more effective than passive strategies, such as printed pamphlets or informational websites, alone.

Current Risk Management Strategies
The stakeholders of the risk management process include marketing authorisation holder (MAH), competent authority, healthcare professionals and patient. Pharmaceutical companies are attempting to address the challenges of on-market drug risk management within complicated and often highly-charged business, social and political contexts.

A comparison of the current sets of FDA and EMA risk management guidance documents indicated that they are driven by similar objectives with regard to the identification, monitoring, and minimisation of risk and as a consequence lead to similar data needs. However the methodologies to monitor the risk minimisation activities are quite different.
For most companies, the EU-RMP serves as a global reference document for risk management activities.

Both REMS and RMPs provide positive guidance for identification, monitoring, and minimisation of risk to patient safety, while no qualitative or quantitative specifications are yet available to relate risks and benefits of a drug\(^1\). The EMA has conducted the Benefit-Risk Methodology project since 2010 which is now in the pilot phase of implementation, while the FDA started to develop a structured framework for benefit-risk assessment from 2009 and currently the FDA plans to use a staged approach in implementing the benefit-risk framework in the human drug review process.

**Conclusion**

Risk management is a proactive iterative process, which has evolved to relate risks, benefits and cost-effectiveness of medicinal products. Real-world epidemiological studies on databases of automated insurance claims, electronic medical records and registries have gained significance for safety surveillance in the recent years. The fundamentals of the risk management process remains the same, while the tools utilised for achieving the objectives are transforming with time. The additional pharmacovigilance activities mandated by the risk management plans have further strengthened the safety surveillance methods during the drug development and post-approval phases.

**References**

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