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Risk management of pharmaceuticals in the EU and US - trends and analysis

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Risk management is a process for identifying, characterising, evaluating, monitoring, communicating and mitigating risks that may arise from the normal conditions of use for a medical product. It has been widely recognised as an appropriate tool for ensuring that marketed products continue to meet a positive benefit/risk balance. The process seeks to ensure that following an appropriate risk assessment, certain risk minimisation activities or interventions are carried out so that healthcare professionals and patients are properly informed before making a decision on an individual basis concerning the suitability of a specific treatment. In general, regulators are required to justify their regulatory actions in relation to a product on the basis of an independent assessment.

Following certain high profile product withdrawals in the early 2000s, regulators around the globe have placed greater emphasis on drug safety to ensure confidence in medicines regulation in relation to protection of patient safety and public health. A risk management plan or mitigation strategy essentially requires the following questions to be critically reviewed at each stage of the product life cycle:

- What are the hazards intrinsic to the properties of the product, taking account of the way it is manufactured and controlled?
- Who in the target population is likely to be more susceptible to the highest risks?
- Are the risks identified from independent scientific assessment sufficiently predictable?
- Are there any uncertainties surrounding the assessment?
- How can those risks be effectively mitigated?
- How effective are those risk mitigation activities?

This chapter reviews the current regulatory framework governing risk management in the EU and the US.

EU

Risk management plans are now recognised by European regulators as an appropriate and proportionate means to manage product safety.

Requirement for risk management plans

In the EU, the concept of a risk management plan was formally crystallised in an amendment to Directive 2001/83/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Directive) by Directive 2004/27/EC on the Community code relating to medicinal products for human use (Code for Human Medicines Second Amendment Directive).

EU pharmaceutical law now requires each application for marketing authorisation to be accompanied by a detailed description of pharmacovigilance, and where appropriate of the risk management system which the applicant will introduce. However, the dossier requirements for a risk management plan were introduced in EU pharmaceutical law in 2003 through Directive 2003/63/EC amending Council Directive 2001/83/EC on the Community code relating to medicinal products for human use (Code for Human Medicines First Amendment Directive) in relation to specific areas of long-term patient and environmental safety risk, in particular, the regulatory control of products containing genetically modified organisms (GMO) and advanced therapy medicinal products that use cells, tissues and exogenous genes to produce a medicinal product.

The concept of risk management is not limited to the conduct of pharmacovigilance after a product has been authorised. The requirement for risk management and risk minimisation applies to conduct of clinical trials and assessment of product quality irrespective of the target population and the product types. The requirement for a risk management plan has now been put into practice through implementation of certain EU general or product class specific guidelines that set out the expectations and standards for an assessment of safety, quality and efficacy. The primary objective of these guidelines is to set out the best practice for defining the safe and effective conditions of use of medicinal products and the quality standard for the intended purpose. The adopted guidelines cover the following areas:

- First-in-man clinical trials with investigational medicinal products.
- Clinical development of paediatric medicines.
- Clinical development of similar biological medicinal products (biosimilars).
- Biological and biotechnological products including blood products, vaccines, and advanced therapy products.
- Quality risk management concerning manufacture and control of medicinal products.

The attitude of EU regulators is that every product and process carries an associated risk. While public health protection seeks to safeguard patient safety, it is neither helpful nor productive to over-regulate as this may have a direct impact on timely market access of life-saving medicines to address unmet medical needs. Therefore, the regulatory environment should seek to strike a balance in terms of protecting patient safety from unjustified risks and timely access to innovative medicines.

Consistent with the established principles for better regulations, regulatory authorities are required to apply the rules proportionately so that the objective of public health protection should not hinder the development of pharmaceutical industry and/or trade in medicines within the EU. It is not for regulatory authorities to interfere with how innovative medicines should be developed, provided that certain acceptable regulatory standards are observed. In relation to risk management plans, every enterprise should have a methodology for identifying and evaluating the risks it faces and a process for generating intervention plans to reduce the risks to an acceptable level.

It is generally recognised that at the time of market authorisation, information on a product's safety is relatively limited. This may be attributable to many factors arising from the design and the objectives of conducting clinical trials. Primarily, clinical trials seek to establish the clinical effects of an experimental compound in a well-defined, homogeneous patient population. There is generally a small number of subjects in clinical trials with restricted population in terms of age, gender and ethnicity, restricted co-morbidity, restricted co-medication, restricted conditions of use, and relatively short duration of exposure and follow-up. Because of limited clinical exposure to the experimental compound, pre-approval clinical trial data would not be adequate to characterise or detect rare adverse events that may occur at lower frequency.

Conventionally, many important pharmacovigilance issues have been identified through spontaneous reporting of adverse reactions. However, regulatory agencies across the EU have recognised that there is a need to develop new methodological approaches that seek to augment and strengthen the pharmacovigilance process. It has been suggested that planning of pharmacovigilance activities may be improved if it focuses more closely on information relating to the characteristics of the product and those derived from pre- and post-authorisation data. That is, risk management is a pro-active approach to minimising unjustified risk exposure.

While EU pharmaceutical law has introduced the requirement for risk management plan and system, it does not define it. The agreed working definition by the European Medicines Agency (EMA) is a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products and the assessment of the effectiveness of those interventions.

The established EU practice is that risk management is a continuing process throughout the lifetime of a medicinal product. However, the activities used for risk management may need to be adapted or changed in the light of emerging technical, scientific and legislative developments as well as available information, and these factors should be taken into account when developing risk management plans in the EU.

As suggested by the EMA and the European Commission (Commission) in various guidance documents, the aim of risk management system seeks to ensure that the benefits of a particular medicine outweigh the risks by the greatest achievable margin for the individual patient and for the target population as a whole. This balancing exercise can be done by maximising the benefits or by reducing the risks. Risk management generally focuses on risk reduction. However, in undertaking an exercise of risk management, consideration should be given to maximising benefits through better definition of the characteristics of patients most likely to benefit from treatment.

Risk management plan: components

The standard EU risk management plan consists of two key components:

- A specification for the identified safety parameters.
- An evaluation of the proposed risk minimisation activities.

The specification summarises the safety profile of the medicinal product at the particular time of its life-cycle, and the proposed plan for the conduct of pharmacovigilance. Based on the proposed specification the marketing authorisation holder or applicant should propose appropriate risk minimisation activities that can be effectively implemented. There are two types of risk minimisation activities, namely routine or additional. It is possible that the risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or to the careful use of labelling or packaging, that is, routine risk minimisation activities. However, for some risks, routine risk minimisation activities may not provide sufficient safeguards, and additional safety measures may be necessary.

As adverse reactions arising from medication errors have been considered as a significant factor for hospital admission, the current EU position is that within the evaluation of the need for risk minimisation activities, the potential for medication errors should be addressed, including measures for risk reduction in the design of the pharmaceutical form, product information, packaging and where appropriate the device which is used for delivery of the product.

Given that certain safety concerns may not be fully characterised, greater emphasis is now placed on gathering this information through a post-authorisation safety study (PASS). The current definition for PASS in EU pharmaceutical law is likely to be changed through the Commission's legislative proposal to strengthen and rationalise pharmacovigilance rules and systems in the EU to reflect more closely the process for identifying, characterising or quantifying a safety hazard or confirming the safety profile of the medicinal product through appropriately designed pharmaco-epidemiological studies or clinical trials. However, these studies would ordinarily be considered as falling within the definition for non-interventional studies.

The concept of risk management has also now been adopted in the manufacture and control of medicinal products. Similar to pharmacovigilance, EU pharmaceutical law requires the manufacture and control of an authorised medicinal product to be subject to incremental improvement according to the currently accepted techniques and methods. The EU position on quality risk management is that the principles apply not only to the manufacturing environment but also in connection with pharmaceutical development. The purpose of quality risk management is considered an effective approach to ensure the high quality of the finished product to be delivered to the patient by providing a proactive means to identify and control potential quality issues during development and manufacturing. Use of quality risk management seeks to improve the decision-making should a quality problem arise so that an informed decision can be made. The principles for quality risk management consist of two principal elements:

- The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.

- The level of effort, formality and documentation of the quality risk management process should be proportionate with the level of risk.

Therefore, quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the finished product across the entire product life cycle.

Penalties and enforcement

For centrally authorised products, the Commission has power under Regulation (EC) 658/2007 to levy financial penalties for infringement of certain obligations in connection with centralised marketing authorisations. These obligations include information relating to an assessment of ongoing benefit/risk balance and activities relating to conduct of pharmacovigilance. The Commission may impose a fine not exceeding 5% of the marketing authorisation holder's EU turnover in the previous business year. If the marketing authorisation has not terminated the infringement, the Commission may impose periodic penalty payments on a daily basis not exceeding 2.5% of the holder's average daily EU turnover in the preceding business year.

National regulatory authorities have the power to initiate enforcement actions against companies for breach of regulatory rules governing safe and effective use of medicinal products under the implementing domestic laws. The national enforcement rules and regulatory actions to be taken however must be proportionate, effective and dissuasive. For example, in the UK, offences are created under the Medicines for Human Use (Marketing Authorisations Etc) Regulations 1994 for failure to implement an appropriate pharmacovigilance system as required under EU pharmaceutical law. Any person guilty of an offence arising from conduct of pharmacovigilance is liable to either:

- On summary conviction, to a fine not exceeding the statutory maximum.
- On conviction on indictment, to a fine or to imprisonment for a term not exceeding two years or to both a fine and imprisonment.

Therefore, the possibility for prosecution is there for authorities, and it is merely a matter of discretion as to how the power is to be deployed.

US

In the US, the passage of the FDA Amendments Act of 2007 (FDAAA) constituted the most significant expansion of the drug safety authorities of the Food and Drug Administration (FDA) in decades. Before the passage of FDAAA, FDA had limited authority in relation to requiring the active surveillance and control of risks associated with use of approved drugs and biologics in the practice of medicine. Risk management efforts, ranging from requiring provision of Medication Guides at the pharmacy level to extensive risk minimisation action plans (RiskMAPs), were used for various products. However, the actual authority for more extensive risk management efforts was ambiguous, and largely a function of the inherent power of the agency in approval and labelling change negotiations, or specific authorities associated with certain accelerated approvals.

After a series of high profile crises led Congress to examine drug safety policy and processes, the 2007 legislative reauthorisation of drug user fees included unprecedented statutory authority to address post-market drug safety. This includes, subject to specific standards, authority to mandate Risk Evaluation and Mitigation Strategies (REMS), post-approval studies, trials and labelling changes. A REMS is a strategy to manage a known or potential serious risk associated with a drug or biological product. Such a strategy is required if FDA finds that a REMS is necessary to ensure that the benefits of a drug or biological product outweigh the risks of the product and notifies the sponsor of this determination. A REMS can be imposed at either initial approval or post-approval stage and is a decision that is jointly made by the relevant Review Division and the Office of Surveillance and Epidemiology (OSE).

When is a REMS required?

Factors that are considered in making a pre-approval REMS determination include:

- Estimated size of the treated population.
- Seriousness of the disease or condition that is to be treated with the drug.
- Expected benefit of the drug.
- Expected or actual duration of treatment.
- Seriousness of any known or potential adverse events that may be related to the drug and the background incidence of these events in the population likely to use the drug.
- Whether the drug is a new molecular entity.

If no REMS is in effect, FDA may determine that a REMS is necessary post-approval, if the agency becomes aware of new safety information which can be either:

- A serious risk, which is an adverse drug experience that:
  - results in death;
  - places the patient at immediate risk of death from the adverse drug experience (not including an adverse drug experience that might have caused death had it occurred in a more severe form);
  - results in inpatient hospitalisation or prolongation of existing hospitalisation;
  - results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
  - is a congenital anomaly or birth defect;
  - based on appropriate medical judgment, may jeopardise the patient and may require a medical or surgical intervention to prevent an outcome described above.
- An unexpected serious risk which is a serious adverse drug experience that is not listed in the labelling of the drug or that may be related to an adverse drug experience in the labelling, but differs from such an adverse experience because of greater severity, specificity, or prevalence.

This new safety information can be derived from appropriate:

- Clinical trials.
- Adverse event reports.

- Post-approval studies.
- Peer-reviewed biomedical literature.
- Post-market risk identification and analysis systems.
- New analyses of existing information.
- Other scientific data.

FDAAA also included a process for moving drugs with existing RiskMAPs into the REMS framework, known as deemed REMS. Drugs or biological products approved before the effective date of FDAAA that only had a Medication Guide and no other REMS elements were not deemed to have a REMS.

For approved products, a REMS should be submitted to FDA within 120 days of the sponsor receiving notification that a REMS is required. However, FDA can require shorter timelines in certain scenarios. After submission of a proposed REMS for an approved product, FDA has six months to take action.

REMS components

Depending on the objectives of the programme, a REMS may have several components, including:

- Medication Guide or Patient Package Insert (PPI).
- Communication plan.
- Elements to assure safe use.
- An implementation system to monitor and evaluate whether the elements to assure safe use are meeting the goals of the programme.

Medication Guide. 21 CFR Part 208, implemented before the passage of FDAAA, sets out requirements for the development of Medication Guides when the FDA determines that a prescription drug or biological product poses a serious and significant public health concern requiring distribution of FDA-approved patient labelling. A Medication Guide is required when FDA determines that one or more of the following circumstances exists:

- The drug product is one for which patient labelling could help prevent serious adverse effects.
- The drug product is one that has serious risk(s) (relative to benefits) of which patients should be made aware because information concerning the risk(s) could affect patients' decision to use, or continue to use, the product.
- The drug product is important to health and patient adherence to directions for use is crucial to the drug's effectiveness.

The regulations require that manufacturers ensure that Medication Guides are distributed so that dispensers provide a Medication Guide to each patient receiving a prescription.

Communication plan. A REMS also typically includes a communication plan to ensure that the risks of using a particular product are communicated to prescribers and patients, the ways to minimise those risks, and how to monitor for and report adverse reactions. A plan may include:

- Healthcare professional letters.
- Dissemination of educational information about the elements of a REMS to encourage implementation by healthcare providers.
- Dissemination of information to healthcare providers through professional organisations about any serious risk of the drug and any protocols to assure safe use.

Elements to assure safe use. Elements to assure safe use (ETASU) are required if a drug, which has been shown to be effective but is associated with one or more serious adverse effects, can be approved or marketed only if such elements are part of a strategy to mitigate a specific risk.

Subject to specific standards under FDAAA, ETASU may include:

- A requirement that healthcare providers who prescribe the drug have particular training or experience.
- A requirement that pharmacies, practitioners, or healthcare settings that dispense the drug be specially certified.
- Limiting dispensing of the drug to patients in certain healthcare settings, such as hospitals.
- Limiting dispensing of the drug to patients for whom there is evidence of safe use conditions, such as prior testing, signing an agreement, use of a contraceptive, and so on.
- Subjecting each patient using the drug to certain monitoring.
- Requiring that patients using the drug, or health care practitioners and pharmacists dispensing the drug, to enrol in a registry.

FDAAA stipulates that ETASU should be commensurate with the risk, not unduly burden patient access to the drug to the extent practical, and should minimise the burden on the healthcare system. FDA should also conform these elements with ETASU for other drugs with similar, serious risks and seek to ensure compatibility with established distribution, procurement, and dispensing systems.

Implementation system

An implementation system includes surveillance and monitoring that allow for the ongoing evaluation of the ETASU in a REMS. These systems may include:

- Distribution controls to ensure the drug is shipped only to certified healthcare settings or dispensed from a limited number of pharmacies.
- Maintaining databases for certified prescribers and pharmacists involved in product prescribing, dispensing and use.
- Monitoring systems to ensure to ensure the drug is dispensed only to patients who meet safe use conditions.
- Monitoring of the dispensing of the drug to verify appropriate indications for use.
- Additional monitoring for adverse events of interest.

REMS assessments and modifications

REMS assessments are required to be submitted to FDA to evaluate the extent to which the ETASU are meeting the goals of the REMS, and determine whether the REMS goals or the ETASU should be modified. The timetable for the submission of a REMS assessment is 18 months, three years, and seven years respectively after the REMS is initially approved. More frequent

evaluations can be proposed by the sponsor or specified by FDA, particularly where such assessments are considered necessary to ensure that the benefits of the drug continue to outweigh the risks.

A sponsor is also required to provide a REMS assessment to FDA at the time of filing a supplemental application for a new indication, including the status of any post-approval study or trial required to investigate a safety issue. In addition, an assessment can be ordered by FDA, if the agency determines that there may be grounds for withdrawing approval of the drug. In these cases, the REMS assessment must be submitted to FDA within 15 days of sponsor notification. Assessments can also be eliminated by FDA after three years if FDA determines that the risks of the drug have been adequately identified and assessed and are being adequately managed.

A sponsor may voluntarily propose a modification to the approved REMS at any time, based on a REMS assessment. Such modifications can include the addition, modification, or removal of any REMS component, or changes to assessment requirements. FDA should initiate discussions with the sponsor within 60 days of the sponsor's submission of the revised REMS strategy.

REMS and generic products

FDAAA provides that generic drugs subject to an Abbreviated New Drug Application (ANDA) are subject to only the following elements of the REMS applicable to the reference listed drug:

- The Medication Guide or PPI.
- ETASU.

FDA is required to carry out any communication plan on behalf of generic products. The innovator drug and the generics should generally use a single, shared system for implementing ETASU unless an alternative approach is waived by FDA. Conditions for a waiver include a determination that the burden (on healthcare providers, patients, the generic manufacturer or the innovator company) of creating a single, shared system outweighs the benefit of a single system, or that an aspect of the ETASU is claimed by a patent that has not expired or is entitled to protection as a trade secret. Once an innovator REMS is approved or modified, conforming changes must be made to generic labelling.

These requirements have caused considerable controversy in that some generic manufacturers have accused innovators of using REMS systems to impose undue burdens on generics. However, it is quite clear under FDAAA that without a waiver allowing use of another approach, generics must consider sharing the cost of REMS development and implementation part of the burden of entering the market.

Dispute resolution

A dispute resolution process can be pursued if the sponsor disagrees with a REMS requirement. In addition to more informal processes, a sponsor may request that a dispute about a REMS be reviewed by a Drug Safety Oversight Board (DSOB). FDA can also include review of a dispute on an Advisory Committee agenda, for a REMS for a specific drug, or in relation to a class of drugs.

Penalties

Under FDAAA FDA may also impose civil monetary penalties for violations of the REMS provisions. Under FDAAA, civil penalties may not exceed US$250,000 per violation, or US$1 million for all violations adjudicated in a single proceeding. If a violation continues after the sponsor receives written notice, the penalty is US$250,000 for the first 30-day period (or any portion thereof) that the violation continues, not to exceed US$1 million for any 30-day period and not to exceed US$10 million for all violations adjudicated in a single proceeding. However, FDA may take into consideration whether the sponsor is making efforts to correct the violation when determining the amount of a civil penalty. The agency may also seek injunctive relief if it considers the product misbranded. (As at 1 November 2010, EUR1 was about US$1.4.)

REMS experience to date

As of late 2010, there were 156 products that were the subject of an approved REMS, including former RiskMAP products. Of those, drugs, 153 REMS mandated Medication Guides, 42 had communication plans, and 20 required restrictive ETASU. These include REMS applied to a class of drugs for certain uses, such as use of erythropoiesis-stimulating agents in cancer patients, and long-acting B-agonists for asthma. In addition to the controversies noted above concerning generics and REMS, areas of concern to date in relation to REMS include:

- The increasing burden on industry, the healthcare system and patients caused by the complexity and lack of harmonisation of certain REMS elements and the costs associated with implementation, including unreimbursed costs imposed on healthcare practitioners.
- Approval delays due to the extra time needed to develop REMS, which have now become a factor in the renegotiation of drug user fees and associated agency drug review performance goals.

Critical assessments of REMS are likely to intensify in the coming years. A Tufts Center for the Study of Drug Development survey issued in January found that:

- 75% of respondents thought that the REMS programme needs a major overhaul.
- 68% responded that REMS are a poor substitute for other improvements needed system-wide in drug education, communication, monitoring of use, patient access and delivery of care.
- 86% felt that under current guidelines, risk and benefit information was not well balanced in REMS communications.
- 22% of respondents thought the REMS programme has been an improvement over the existing risk management system.

REMS in the US have clearly benefited patients in relation to certain products, and in some cases REMS have given FDA the confidence to approve or continue to allow marketing of products presenting significant risks. However, it remains to be seen whether FDA has struck the right balance in implementing REMS requirements, and clearly more work is needed to understand the impact of REMS and refine the programme.

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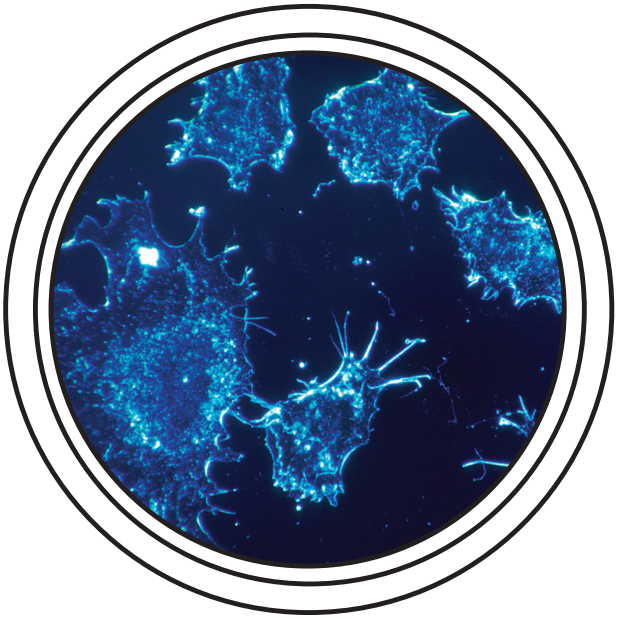

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