Risk Minimisation for Medicinal Products
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The objective of a drug treatment is to deliver specific benefits to the patient. However, no drug is devoid of risk. Effective risk management ensures that expected benefits outweigh any risks of a medicinal product. The concept of risk minimisation is not new but it is evolving rapidly and innovative solutions are expected to emerge in the near future. This document summarises two recent documents published by the Council for International Organizations of Medical Sciences (CIOMS) (1) and the European Medicines Agency (2). They provide guidance on risk minimisation strategies and share the common goal of achieving a positive risk benefit balance.
In May 2014 the Council for International Organizations of Medical Sciences (CIOMS) published “Practical Approaches to Risk Minimisation for Medicinal Product” also known as CIOMS IX. The Council acknowledged that all medicinal products can cause adverse reactions and it is crucial to manage effectively all risks throughout a drug’s lifecycle to ensure a positive risk benefit balance. The fundamental components of risk management include identification, evaluation, prevention, mitigation and communication of risks associated with a medicinal product. Traditionally used routine approaches (e.g. Patient Information Leaflets, Summary of Product Characteristics) are now evolving into more pro-active and individualised management of risks.

The CIOMS group state that risks are traditionally defined by their seriousness and severity, the potential for prevention or early detection, their frequency and outcomes. The International Conference on Harmonisation’s “Pharmacovigilance planning guideline” (ICH E2E) also refers to ‘identified risks,’ ‘potential risks,’ ‘important risks’ and ‘missing information.’ Regardless of the risk definition used, risk management consists of risk prevention and/or risk mitigation (3).

Risk minimisation planning should be present throughout a drug’s lifecycle and it should be appropriately balanced in order to avoid restricted access for those who would benefit from the medicine. Excessive limitations would result in the burden to the patient and to the healthcare system. Logically, risk minimisation plans should start from the least burdensome. It should be carefully considered which risks would require more than routine measures and in order to achieve the safety goals, risk minimisation activities should be tested and evaluated.

There are no universal risk minimisation approaches and they can vary depending on the regions, medical practices and health systems. Many risk management frameworks adopted by regulatory authorities around the world are based on the concepts introduced by ICH E2E with include the Safety Specification and Pharmacovigilance Plan guidelines. Japan, the US and the EU have developed specific legislation for risk minimisation activities.

**Japan**

In Japan, the requirement for a risk management plan is discussed during the pre-registration process and the appropriate plan is then submitted at the time of marketing authorisation application. Additional Postmarketing Phase Vigilance (EPPV) and ‘All-Cases Surveillance’ (‘Zenrei-Chosa’) are examples of activities that are unique to the Japanese market. The EPPV requires the efficient and robust collection of information about a New Molecular Entity (NME) for the period of 6 months. ‘All-Cases Surveillance’ measure can be required for medicines with known serious risks, to assess safety signals of serious risks or where available data suggests a potential for a serious risk. The safety data is actively collected for a limited time and the medicine can be prescribed only by healthcare professionals who agree to actively participate in the scheme (1). Continued over...
United States

The United States approach focuses on the provision of information to healthcare professionals. The documents that have been published since 1999 by the FDA, included routine and non-routine risk minimisation measures (1, 4). In 2007 the FDA was granted powers to request a Risk Evaluation and Mitigation Strategy (REMS) from manufacturers. A REMS is developed to ensure that benefits of a drug outweigh its risks and it can be requested at the time of initial marketing authorisation application but also at any time during the post-marketing stage when new serious safety issues become evident. The proposed measures in a REMS may include:

- A Medication Guide (MG) or a patient package insert (PPI)
- A communication plan
- Elements to assure safe use (ETASU) (certified prescribers to prescribe the drug, certified pharmacists to dispense the drug, drugs dispensed in specific settings only, patient monitoring, patient registry)
- An implementation system
- A timetable for assessment (compulsory for New Drug Applications and Biologics Licence Applications) (minimal timetable for assessment: 18 months, three years and seven years after REMS approval)

The European Union and other countries

In the European Union all Marketing Authorisation Holders (MAHs) are required to have a pharmacovigilance system in place. Since July 2012 every marketing authorisation application is expected to contain a Risk Management Plan (RMP) which would describe the risk management system in detail. Risk minimisation measures proposed in the EU have been described in Module XVI of Good Pharmacovigilance Practice which are summarised further on (2).

Several other countries around the world have adopted frameworks based on European RMPs or the US REMS and introduced specific solutions relevant to their healthcare systems. Those countries are: China, Republic of Korea, Taiwan, Singapore, Hong Kong and Australia (1). Canada, on the other hand, adopted and implemented the ICH E2E guidance and expects Safety Specification, Pharmacovigilance Plan and Risk Minimisation Plan to be provided in Risk Management Plans (1).
Additional Measures

It is recognised that most risks can be effectively managed by routine measures (mainly the information provided to the patients and healthcare professionals) but in some cases the introduction of additional risk minimisation strategies may be necessary to maintain a positive risk benefit ratio. The selection and development of appropriate strategy begins with accurate recognition and characterisation of important risks that need to be prevented and/or mitigated. The risk is characterised by its importance, severity, likelihood of occurrence, public health impact and effect on the risk benefit balance. A potential for prevention and/or mitigation also needs to be studied. Additionally, it needs to be decided whether the strategy will be employed before administration of a medicine (screening test, exclusion criteria) and/or during therapy (monitoring). Following that, a specific and achievable risk minimisation goal needs to be defined as well as a target population (prescribers and/or patients). It should also be considered how a risk minimisation tool will impact the healthcare system and the patient. Too burdensome, excessive or a non-adaptable tool could result in failure of the strategy. Consultation with the target stakeholders could be considered at the planning stages to ensure a seamless implementation. Although the evidence of the effectiveness of risk minimisation measures is still limited, a literature search could help to establish what tools have been applied in a similar situation and what difficulties have been encountered throughout the process (1).

There are a variety of tools that can be applied in a risk minimisation strategy (1). The tool(s) used will depend on the risk characteristics and the goal to be achieved: ‘one tool could address more than one objective and an objective could be addressed by more than one tool’. The following are possible tools:

**Additional information and education**

Communication through routine measures could be deemed insufficient and therefore additional communication tools may be required. They may include:

- Dear Healthcare Provider Letters
- Prescribing/dispensing guides
- Patient brochures and targeted outreach for specific patient populations
- Training programmes

These measures can have a potentially satisfactory outcome, enhance prescriber knowledge and empower patients but they could also be perceived as a marketing tool, so care must be taken to avoid this. Additionally, in order to remain viable they require periodic updates and reassessments. Continued over...
Restricted access

Restricted access tool can be rather burdensome and includes the following measures:

- Patient agreement/consent
- Registration programmes for wholesalers and retailers
- Certification programmes for healthcare providers
- Limited amount/prescriptions
- Product access linked to laboratory tests results
- Prescribing allowed only by specialist physicians
- Prescribing allowed only to patients with right pharmacogenomics profile

These types of programmes allow control of the amounts of drug that reaches the patient and systematises the product use, however the additional burden could be discouraging for both prescribers and patients and divert them to other treatment options.

Controlled regulatory framework

The availability of a medicinal product could also be controlled by regulatory restrictions. These measures ensure that the drug reaches the patients only through approved routes e.g. narcotics and controlled drugs, prescription drugs. The ultimate restriction is market withdrawal.

Manufacturing restrictions

This measure can reduce inadvertent administration or overdose/misuse of a drug. The objective can be achieved by the introduction of low dosage formulations, colour/shape coded dosages or restricted packaging (childproof containers, pack size). In some jurisdictions these tools e.g. pack size may be considered routine risk minimisation.
The implementation of a risk minimisation programme should be supported by an appropriate governance structure within the MAH which ensures approval, advice and oversight of the process. MAHs should also develop a robust tracking system for local implementation.

Following the implementation of a risk minimisation programme, its effectiveness should be evaluated to determine whether it leads to improved patient outcomes. Evaluation begins with the definition of factors that influence a required outcome. It needs to be analysed how the introduced minimisation strategy has affected these factors and subsequently safety outcomes. Evaluation planning should be provided in the form of a study protocol which needs to be included in the REMS and the EU RMP. In the EU, the studies to evaluate the effectiveness risk minimisation measures are defined as Post Authorisation Safety Studies (PASS). The protocol should contain a rationale of the risk minimisation interventions, their specific objectives and an analysis of the performance indicators. A process indicator examines the delivery of the intervention and relevance of content with the objectives. Outcome indicators, on the other hand, focus on the success goals which should be specific, measurable and time-bound. They could include patient health outcomes, morbidity and/or mortality or other safety endpoints. Outcome indicators may be a direct measurement of a hard clinical endpoint or an indirect surrogate e.g. measurement of blood pressure as a surrogate of cardiac risk (1).

In certain cases the evaluation of the change in behaviour affecting patient health can be sufficient e.g. a risk may result from the interaction between two medications and risk minimisation activities would be aimed at avoiding such co-prescription.

The evaluation programme should be ideally simple, practical and user-friendly to minimise burden and to support collaboration. MAHs are encouraged to publish the evaluation results to contribute to the development in the area of risk minimisation.
The CIOMS report also analyses current trends and attempts to predict future directions in risk management. It is expected that this field will develop further and that new minimisation tools will appear. Specific expertise will be needed and this will give rise to a new type of pharmaceutical professional - the risk management specialist. That person will be responsible for the development and implementation of risk minimisation tools and strategies, and the evaluation of their impact.

Some of the emerging tools have been already used but not on a large scale. The importance and application of those approaches may increase as a result of technological advancements and progress in the area of risk minimisation. They include: web-based physician checklists, electronic audit and feedback system, computer simulations, a variety of eHealth tools and web applications.

The role of genetics in risk management is also increasing. A study of pharmacogenetics and pharmacogenomics will eventually predict the likelihood of experiencing benefits or harms from a medicinal product and will help to understand differences in drug responses within a population leading to further avenues for risk minimisation.
Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators

Module XVI was first published on 28 February 2014 and effective from 01 March 2014. This document discusses different risk minimisation measures which can be included in Risk Management Plans. The aim of risk minimisation measures are to “prevent or reduce the occurrence of adverse reactions associated with the exposure to a medicine, or to reduce their severity or impact on the patient should adverse reactions occur” (2).

Each safety concern should be assessed by taking into consideration the seriousness, severity, frequency, impact on public health and preventability of a specific adverse reaction. Additionally, the indication, the route of administration, the target population and healthcare setting should be taken into account. For most medicinal products compliance with routine risk minimisation measures is usually sufficient. These routine procedures including the summary of the product characteristic (SmPC), the package leaflet, the labelling, the pack size, design and the legal (prescription) status are described in Module V. (5)

However, not all safety concerns can be adequately controlled by routine procedures alone and additional risk minimisation measures need to be considered. These might vary greatly depending on their purpose, design, target population and complexity. They might include: patient selection with defined exclusion criteria and contraindications, on-treatment monitoring and appropriate management of the adverse reaction. The delivery of additional risk minimisation strategies might also be supported by educational programmes, controlled access programmes and other measures.
Educational programme

An educational programme supplements the information provided in the SmPC and positively influences healthcare professionals and patients towards the safe and effective use of medicinal products. The educational programme should utilise a variety of tools and media to reduce accessibility barriers (disability, internet access etc) and to appropriately target the specific populations (languages, pictures, graphic support). They all should be tested by users before introduction to the general public. These materials should be deprived of any promotional content and should focus on the management of risk(s) associated with the product (2).

- Educational tools for healthcare professionals should provide specific recommendations on the use and/or contraindications and/or management of adverse reaction(s). Additional information might include recommendations for the selection of patients, treatment management (dose, testing and monitoring), administration and dispensing procedures, and specific advice given to patients. The tool format depends on the scope of communication (e.g. checklist, brochure, posters). A checklist may be suitable where a number of actions are needed before a prescription is issued. A brochure may focus on specific risks, their recognition and management.

- Educational tools for patients and/or carers should be designed to support the right administration of the product and to serve as the reminder about an important activity (diary for posology, required diagnostic procedures). This also includes patient alert cards which ought to be carried by the patients at all times, and which would provide information about the patient’s therapy, and important risks.

Controlled access programme

A controlled access programme limits the availability of medicinal products in addition to restrictions imposed by their legal status. It should only be introduced to minimise important risks of medicines with clearly demonstrated benefits. Examples of controlled access programmes include: testing and/or examination to ensure compliance with specific clinical criteria, documenting the receipt and understanding of information on the serious risks associated with the product, patient follow-up (patient registry) and supply only through registered pharmacies.

Controlled distribution system

A controlled distribution system a medical product is traceable through its distribution chain up to the prescription and/or pharmacy supplying the medicine. This approach could be applicable for misused or abused medicines.

Pregnancy prevention programme

A pregnancy prevention programme (PPP) is introduced for medicinal products with known or potential teratogenic effects in order to reduce pregnancy exposure during treatment. This programme might also include biological fathers if necessary. The PPP can combine a variety of tools: education (guidance and advice for healthcare professionals and patients), controlled access (pregnancy testing at the time of prescribing or supplying the product), limited supply (maximum of 30 days), counselling in case of accidental pregnancy. A pregnancy registry can be used to provide an assessment of effectiveness of the PPP and support further risk characterisation. Continued over...
Direct healthcare professional communication

In direct healthcare professional communication (DHPC) important information is delivered directly to individual healthcare professionals when there is a need to take certain actions or alter their prescribing procedures.

All actions planned as additional risk minimisation measures should be implemented at the appropriate time and frequency with specific consideration given to the target population. Some interventions could be required at the time of launch or only occasionally (e.g. DHPC) whereas some others such as alert cards, controlled access or PPP could be applicable throughout the post-marketing period. The appropriateness and future applications of each measure should be discussed at the time of authorisation and included in the RMP. Special consideration should also be given to the layout and content of educational tools which should be distinctive from any promotional materials. These materials should be submitted for review to the national competent authorities (NCA) separately from promotional materials.
**Evaluation of Risk Minimisation Measures**

The evaluation of individual tools and the overall programme is needed to determine if a risk minimisation action has been effective. Periodic reviews of the interventions should be planned within 12-18 months after initial implementation, then at the time of the renewal of the marketing authorisation and whenever else needed (2).

The evaluation of effectiveness should include a review of the process and outcome indicators (2).

**Process indicators**

Process indicators provide information regarding the extent of the programme implementation and the expected impact on clinical behaviour. This includes the delivery of educational tools to HCP and/or patients and their receipt by the target population. Process indicators also assess the level of clinical knowledge gained through the programme. This could be evaluated by scientifically rigorous survey methods with appropriately defined research objectives, study design, sample size and representativeness. The standard core survey questions could be delivered through telephone, post or electronic communication or in person interviews. Apart from clinical knowledge, the resulting clinical actions also need to be evaluated. This could be done through drug utilisation studies or analysis of prescription records with consideration given to the different national guidelines across the EU.

**Outcome indicators**

Outcome indicators give insight into the level of risk control that has been achieved through the risk minimisation action. The success of a programme is represented by the changes in frequency and/or severity of adverse reactions in a non-interventional study setting. The frequency of the adverse reaction occurrence before and after the intervention should be compared if possible. In special circumstances the effectiveness of risk minimisation measures can be evaluated using spontaneous reporting rates. However, this method could be affected by reporting bias. The evaluation process might reveal that the risk minimisation measures are not sufficient and require amendments. It might also show that they are too complex or unnecessary. In which case the programme should be simplified and at least partly reduced to avoid any undue burden to the stakeholders. Also negative outcomes should be monitored as they might lead to product discontinuation.

The evaluation of the outcomes of specific risk minimisation measures should be included in the PSUR and the RMP. The impact on the safety profile and risk-benefit balance will be the focus of the PSUR and pharmacovigilance planning of the RMP. The evaluation of effectiveness of a risk minimisation measure should include the description and objectives of the tool, analysis of the nature of the adverse reaction, delivery of the risk minimisation measures and outcome indicators.
The authorities in the European regulatory network have different roles and responsibilities in the process of risk minimisation. The European Medicines Agency monitor the outcome of risk minimisation programmes in collaboration with the Member states and the Pharmacovigilance Risk Assessment Committee (PRAC). PRAC and the Committee for Medicinal Products for Human Use (CHMP) make recommendations for the additional risk minimisation measures for centrally authorised products. National Competent Authorities (NCAs) supervise the implementation of additional risk minimisation measures as a condition of the marketing authorisation and facilitate the European harmonisation of those strategies for generics in collaboration with PRAC, CHMP and CMDh. Risk minimisation programmes for generics correspond to those needed for their reference medicinal products whereas the strategy for hybrid medicines might require additional measures.

The ultimate responsibility over the quality and delivery of risk minimisation measures lies with the marketing authorisation holder and its qualified person for pharmacovigilance (QPPV). They are responsible for updating the RMP and ensuring that all risk minimisation tools are up-to-date with the appropriate version control. All relevant documents might be subject to audit and inspection. The marketing authorisation applicant or holder are responsible for the definition of objectives and implementation of additional risk minimisation measures after they have been approved by the NCA. The NCA should also be informed of the progress, changes and issues regarding the implementation of the strategy.

Healthcare professionals and patients are not legally responsible for the implementation of risk minimisation measures but their involvement is crucial for the success of the strategy.
Transparency

Risk minimisation measures should be made available to public in line with a policy of transparency of relevant information. The Agency will publish a summary of the risk management plan and the European Public Assessment Report for centrally authorised products. The Member States will make publicly available: public assessment report, summary of the product characteristics, package leaflet, conditions of the marketing authorisation and summaries of risk management plans.

Global focus on risk management and risk minimisation is increasing to ensure that products can be used in the most effective way. A risk of adverse reactions is inherent to all medicinal products. The objective of risk minimisation tools is to understand the risks and decide on the best measures to prevent or reduce them. The above publications provided an introduction and guidance to risk management activities.
Conclusion

‘Practical Approaches to Risk Minimisation for Medicinal Products by CIOMS Working Group IX outlines different strategies that could be applied globally and provides examples of various solutions adopted by specific countries. The guideline gives a synopsis of the state and current trends in risk minimisation worldwide and predicts future directions in the science of risk management. Module XVI- Risk minimisation measures: selection of tools and effectiveness indicators issued by the European Medicines Agency is prepared specifically for the European market. Good pharmacovigilance practices are compiled to facilitate the performance of pharmacovigilance activities in the European Union. Module XVI describes different tools and approaches to risk minimisation but it does not comment on particular solutions or specified drugs. It is likely that the two publications need to be consulted hand in hand for a robust risk minimisation procedure.

References: