Practical Approaches to Risk Minimisation for Medicinal Products

Report of CIOMS Working Group IX

Geneva 2014

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This publication, *Practical approaches to risk minimisation for medicinal products: Report of CIOMS Working Group IX*, is the outcome of a project organised by the Council for International Organizations of Medical Sciences (CIOMS), based in Geneva, Switzerland. At the time the initiative was taken to form this Working Group (WG), a need had been identified for a harmonised risk management toolkit, providing outlines for the content and use of the toolkit, and describing the steps for its development and maintenance as the science of risk management evolves. When this WG began its work in 2010, there was sparse documentation within this exciting area. Gradually, as the topic was developed within the WG, there was also a similar trend in society.

CIOMS is indebted to a large group of scientists from drug regulatory authorities, industry, and academia who contributed their valuable expertise to create this report on *Practical approaches to risk minimisation for medicinal products*. Their contributions are gratefully acknowledged by CIOMS. Each member participated actively in the discussions and in the drafting and redrafting of texts and their review, which enabled the WG to bring the entire project to a successful conclusion. In the course of the process, new members were invited to join the WG, in the light of their particular expertise.

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FOREWORD

Medical science continues to bridge new frontiers with an ever-widening array of medicinal products (also called medicines and drugs in this document) including vaccines and other treatment modalities to improve human health. With newer medicines that are active in the human body in unprecedented ways, the emergence of unknown risks during treatment that were not detected during development becomes a distinct possibility. Furthermore, older marketed medicines are being scrutinised more closely for risks that may not have been recognised during development and their earlier years on the market.

The objective of a drug treatment is to produce desired efficacy without undue harm to patients. Put in a different way, a medicine should have a positive balance of benefits and risks. No medicine is devoid of risk, however, and for that reason, it becomes paramount to appropriately manage all kinds of risks, from the very minor ones to those that are exceedingly serious.

Risk management of medicines is a wide and rapidly evolving concept. The stakeholders involved are diverse and may include patients, physicians, other healthcare providers and, increasingly, communication specialists and behavioural scientists. Risk management encompasses the identification and assessment of risks on an ongoing basis and their minimisation through appropriate interventions, including advice and information to key users. Risk management follows a medicine throughout its lifecycle, from first administration in humans through clinical studies and then marketing in the patient population at large. As part of the continuous monitoring and assessment of risks, 'safety signals' are the first signs of any possible causal relationship between an adverse event and a medicine that can be detected and evaluated. These drug safety signals have been the cornerstone of pharmacovigilance activities for several decades, and have traditionally come from spontaneous individual case reports, but in recent years have been derived from a variety of other sources including electronic medical records, large healthcare databases, and clinical trials.

Evolution of the Council for International Organizations of Medical Sciences (CIOMS)

The CIOMS Working Group Reports have evolved from the initial guidance for international reporting of adverse events with a standardised form (CIOMS I) to guidance on periodic safety update reports (PSUR) by CIOMS II and core data sheets in CIOMS III. These initial CIOMS topics addressed pharmacovigilance issues and focused mostly on the postmarketing phase of medicines development. The need for a harmonised approach to the benefit-risk balance of marketed medicines was addressed in CIOMS Working Group IV, whereas CIOMS Working Groups V, VI and VII focused on pragmatic approaches in pharmacovigilance, management of safety information from clinical trials and on harmonisation of the format and content for periodic safety reporting during clinical trials. CIOMS Working Group VIII provided points to consider to pharmaceutical companies, regulatory authorities, and international, national or institutional monitoring centres wishing to better manage the entire 'lifecycle' of a signal including signal detection, prioritisation and evaluation. The CIOMS/WHO Working Group on Vaccine Pharmacovigilance covered the endorsement of AEFI case definitions and the development of standardised terminology to be used in monitoring safety of vaccines.

The CIOMS IX Working Group on 'Practical approaches to risk minimisation for medicinal products' continues the CIOMS historical attribute of providing practical guidance for all people who are involved with or interested in this aspect of medicinal risk management.

There are existing regulatory requirements for risk management systems at regional and national level (discussed in detail in Chapter II) including risk minimisation plans for the prevention or mitigation of adverse drug effects. Risk management always includes tools for 'routine risk minimisation' such as the patient and physician information (e.g. labelling and package inserts in the United States of America or patient information leaflets and summaries of product characteristics in Europe) as well as legal status such as prescription-only medicine rather than over-the-counter. In some jurisdictions the pack size of the medicine is also considered to be a tool for routine risk minimisation. Routine risk minimisation tools are updated as the benefit-risk profile of a medicine evolves during marketing.

There are certain risks, however, where routine measures for risk minimisation are not sufficient to maintain a positive benefit-risk balance. Therefore, there must be an effort and means to improve the benefit-risk balance for public health and for individual patients if at all possible. These types of risks, once recognised, should be managed with additional risk minimisation tools – the subject of this report. Despite regulatory requirements for risk minimisation planning for specified medicines, there had been no international regulatory guidelines on pharmaceutical product risk minimisation beyond the routine measures on how to achieve this in practice. There have been regional guidelines and laws such as in the US, EU and Japan but no international consensus. With this in mind, this CIOMS IX report aims to provide a practical approach to risk minimisation from a global perspective that could be useful to a range of stakeholders.

As further explained in Chapter II, guidance from CIOMS and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) form a solid foundation for many areas of risk management. These areas of guidance include signal detection and management, risk assessment, and pharmacovigilance planning (see CIOMS VIII and ICH E2E). Until this current CIOMS IX document, specific guidelines have been lacking on how to determine which risks need additional risk minimisation, select the appropriate tools, apply and implement such tools globally and locally, and measure if they are effective and valuable. Potential value should be considered based on evidence, and the tools should not be unduly burdensome to stakeholders, patients and the healthcare system. CIOMS IX has been tasked to address this aspect of risk management. *For the purposes of CIOMS IX, risk minimisation is an overarching concept that covers prevention and mitigation of risk*.

In Working Group IX, CIOMS sought to evolve in approach which meant consulting the most important stakeholders: the patients (covered in Chapter VI). Feedback obtained from stakeholders regarding the role of the patient in this important area of risk minimisation planning is included in Annex IV (Broader Stakeholder Input – Survey). Evolution also means new technology so CIOMS is looking at the feasibility of making CIOMS IX available in an electronic version.

The intended audience for this report is probably the widest of any previous CIOMS report, including those people and organisations that research, provide, and regulate medicines and healthcare as well as patients who take the medicines, their carers and patient groups. The views and recommendations represented in this book are those of the CIOMS IX Working Group as a whole, generally reached through discussion and a consensus process, or in some cases by a majority vote. They do not necessarily represent the views of the individual members or participants' sponsoring organisations.

CHAPTER I:

INTRODUCTION, SCOPE AND BACKGROUND

All medicines have benefits and risks. The process of regulating medicines is designed to assure that, at the population level, the benefits of an approved medicine outweigh its risks. This process has traditionally focused on the routine forms of risk minimisation such as product information (package inserts and summaries of product characteristics) for patients and physicians during and following marketing authorisation; it has not addressed balancing benefits and risks at the level of the individual patient, a step that could further optimise the use of the medicine.

The risk of a particular adverse drug reaction is typically presented as a rate, a practice that may have erroneously suggested that a drug-related risk is simply an unpreventable probabilistic event. This is not always the case. The risks of a medicine are the result of an interaction of the inherent pharmacological properties of the medicine with the way that medicine is used in the 'real world.' Understanding the pharmacological basis of adverse drug reactions can lead to more precise prescribing recommendations; understanding how the medicine is used, or misused, in 'real world' contexts can also lead to improved guidance on prescribing and use of the medicine.

Identifying, assessing, preventing, mitigating and communicating risks are all integral parts of medicinal product risk management. Managing the risks of a medicine is not a new concept; traditional elements have included the medicines regulatory approval process itself, the requirement for prescription status of many medicines, detailed prescribing information for practitioners, and inclusion of understandable information for patients in the product or package insert. In the past two decades or so, there has been increased attention to additional proactive management of certain serious risks in order to optimise the benefit-risk profile at the level of the individual patient. It is important to emphasise at the outset that *if the benefit-risk of a medicine is always negative under all circumstances of use, risk management efforts will not change that balance.*

CIOMS Working Group IX has undertaken the task of describing a set of fundamental principles that should underlie the non-routine efforts at minimising the risks of medicines. Because so much of managing the risks of a medicine involves interactions with the healthcare system, the recommendations and principles put forth in this report are necessarily broad, given the diversity of healthcare systems around the world. A risk management system that may work in one country or region may not likely be feasible, from an operational economic, cultural or other point of view, in other countries or regions. Despite the expected heterogeneity of implementation systems across the world, there is a globally applicable set of principles that can serve as the foundation for selecting the best national or regional approaches to achieving the goals of risk management.

A. Characterisation and dimensions of risks

There are many characterisations and dimensions of the risks of medicines. Risks can be viewed and evaluated according to different regulatory and medical classifications, standards and categories as well as their acceptability (or not) from healthcare professional (HCP), patient and other stakeholder perspectives. The various regulatory and other categorisations of risk, e.g. the European Union's (EU's)

Guideline on good pharmacovigilance practices (GVP), the oncology Common Terminology Criteria for Adverse Events (CTCAE) by the U.S. National Cancer Institute, CIOMS VIII: Practical aspects of signal detection in pharmacovigilance, and the concept of risk level are discussed below. Each of these types of risk classifications and descriptions may be useful in selecting appropriate risk minimisation tools.

The regulatory categorisation of medical safety risks has historically had very fundamental descriptions that characterise individual adverse event reports as 'serious' or 'non-serious,' based on outcomes. A serious adverse event is one that results in death, is life-threatening, requires inpatient hospitalisation or results in prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, or is a medically important event or reaction **(1)**. An adverse event that does not meet one of these criteria is considered a non-serious adverse event. This outcome-based binary classification was developed principally to set guidelines and regulations that govern the pharmaceutical industry's submission of adverse event reports to regulatory authorities.

It is important, in the context of risk management, to go beyond the binary and consider the medical significance and other attributes of a risk. Factors to consider include the *severity* (or intensity) of the risk, the potential for its *prevention or early detection*, its *frequency* and extent of *reversibility*, and the range of *outcomes* that can result from it. Additional considerations include the risk in the indicated population, expected drug usage, the extent of 'off-label use,' and the impact and clinical presentation of the risk in vulnerable populations **(2)**. Off-label usage brings in a new dimension of risk that may occur in a population that was not studied during clinical trial development of a medicine, as patients are exposed to the risks of a medicine for which benefit has not been sufficiently studied with consequent challenges for risk minimisation.

The International Conference on Harmonisation's *Pharmacovigilance planning guideline* – known as ICH E2E **(3)** – introduced the concepts of 'identified risks,' 'potential risks,' and 'important' risks and these definitions have been carried forward into ICH E2C (R2) and ICH E2F **(4)**. ICH E2E introduced the additional concept that missing information could also constitute a form of risk. The EU Committee for Medicinal Products for Human Use's (CHMP) *Guideline on risk management* **(5)** provided the first definition of these terms. The current categorisation of risk utilises the qualifiers 'identified, potential, and important' **(6).** An 'identified risk' is considered to be 'an untoward occurrence for which there is *adequate* evidence of an association with the medicinal product of interest.' A 'potential risk' is considered to be 'an untoward occurrence for which there is *some basis* for suspicion of an association with the medicinal product of interest *but where this association has not been confirmed*.' An 'important' risk is 'one that can impact the *benefit-risk balance* or *impact public health*.' This classification of risks is useful in determining how industry and regulators plan and how medicinal product developers conduct risk management and report postmarketing drug safety issues to regulators.

Deciding what constitutes an 'important risk' is a clinical judgement of its potential impact on public health and is based on the frequency (likelihood of occurrence) of the risk as well as its medical significance.

Despite the parameters outlined above, there is no real consensus on how risk should be defined. CIOMS VIII **(2)** defined risk as 'the probability of developing an outcome' and emphasised that 'the concept of risk does not involve severity of an outcome.' CIOMS VIII further describes characterisation of risk by including the variables 'frequency 'and 'severity.' The concept of 'safety/medical risk level = probability x severity' can provide a concrete basis for risk characterisation and categorisation. This equation is derived from 'risk = probability (of an event) x consequences' **(7)**. Within the risk management plan (RMP) template safety specification section currently applicable in the EU, guidance is provided in a tabular format as to what variables should be evaluated and presented regarding characterisation of an important risk or risks, including preventability **(8)**.

From a medical standpoint, there is no universally accepted categorisation of manifestations of safety risks. One commonly used categorisation scheme is described in the Common Terminology Criteria for Adverse Events (CTCAE) **(9)**, which is often used to describe adverse events noted during clinical trials of oncologic agents, though its use goes beyond oncology. In this system shown in Table 1.1, severity with some degree of measurable parameters is utilised as the variable for assigning a numerical value (grade):

Table 1.1: Common Terminology Criteria for Adverse Events (CTCAE) grading parameters

Grade 1: Mild
► Asymptomatic or mild symptoms; ► Clinical or diagnostic observations only; ► Intervention not indicated.
Grade 2: Moderate
► Minimal, local or non-invasive intervention indicated; ► Limiting age-appropriate instrumental ADL.*
Grade 3: Severe or medically significant
► Not immediately life-threatening; ► Hospitalization or prolongation of hospitalization indicated; ► Disabling; ► Limiting self-care ADL.*
Grade 4: Life-threatening consequences
► Urgent intervention indicated.
Grade 5: Death related to adverse effect (AE)

**ADL = activities of daily living.*

It is of note that the CTCAE includes an additional parameter regarding the impact on activities of daily living (ADL), which is not routinely considered within the characteristics of a medical safety risk. This aspect of ADL does not encompass social or economic restrictions that can result from an adverse event.

In some cases, organ-specific grading systems may exist to classify certain adverse events. For example, the Drug-Induced Liver Injury Network (DILIN) has developed a severity grading system in drug-induced liver injury **(10)**. This system is based on a combination of laboratory measures and clinical features. Because the severity of drug-induced liver injury can vary widely, the goal of the DILIN severity grading system is to categorise severity in an objective manner.

The goals of risk minimisation should be directed towards better patient outcomes. Regardless of the risk being minimised and the specific approach to minimising that risk, the goals of the effort should focus on improving patient outcomes. While optimising the benefit-risk profile of a medicine can focus on the benefit side, the risk side, or both, many risk minimisation programmes are directed towards lowering the frequency, the severity, or both the frequency and severity of an adverse drug reaction. While nomenclature varies across regions and countries, the CIOMS Working Group IX, for operational purposes, distinguishes between *risk prevention (reducing the frequency of occurrence of an adverse drug reaction)* and *risk mitigation (reducing the severity of an adverse drug reaction when it occurs).* CIOMS Working Group IX uses the umbrella term ***risk minimisation*** to describe collectively ***risk prevention*** and ***risk mitigation***. For example, a risk minimisation programme that seeks to avoid co-prescribing of two medications that when given together result in a serious or life-threatening adverse drug reaction is a risk prevention effort, since it aims to avoid the development of the adverse drug reaction in some patients. It is important to understand that risk prevention does not necessarily imply risk elimination. Risk elimination is achieved only when the risk no longer occurs in any patient who takes the medicine. While the aspirational goal of a risk prevention plan may be to eliminate all risk, the complexities of factors leading to adverse drug reactions necessitate that risk prevention plans strive to reduce the frequency of risk as much as possible. On the other hand, a risk management plan that monitors for the earliest signs of a potential adverse drug reaction and recommends stopping the medicine before the adverse drug reaction becomes more severe is an example of risk mitigation.

• Risk and population being treated

The frequency and severity of a particular risk can vary in different populations and in different healthcare settings. Vulnerable populations, including pregnant women, children, the elderly, and other populations not normally or extensively studied during the development of a product, may be at greater risk for the development of certain adverse events.

It is important to understand the range of populations in which the medicine may be used, on- and off-label, for several reasons. Firstly, risk tolerance may vary based on the population being treated, the indication being treated, or both. For example, there is very low tolerance for exposure of pregnant women to a teratogenic drug if treatment with that medicine is not essential. Secondly, variations in the frequency and severity of a risk across populations and across indications can mean that risk minimisation may be needed in some settings but not in others. At the time of medicinal product approval, the determination of the need for a given risk minimisation plan is based partly on data from the clinical trial population studied and on the anticipated use of the product in actual practice. Once the product is marketed, studies of its use in actual practice, along with prospective data collected from further interventional or observational studies with safety objectives, further inform the determination of the need for risk minimisation.

• Preventable and unpreventable risks

Risk elimination, the absolute or complete prevention of risk, can usually only be accomplished by not administering a medication to a patient. In the context of risk minimisation planning, this approach is generally feasible when there are known factors that put a particular patient at high risk for an adverse outcome, and absence of these risk factors puts the patient at little or no risk of the adverse outcome. This approach requires that there be a method, such as a screening test, to identify patients with the risk factor. This approach, however, also effectively eliminates any benefit that a patient may have derived from the medicine, and as such one should consider the overall benefit-risk balance and the availability and acceptability of alternative treatments. Medical need is clearly a key consideration in this setting.

In the above framework, one example of a 'risk factor' can be the use of a concomitant medication that results in a serious adverse event from drug-drug interaction. In this case, a risk minimisation strategy could be the avoidance of concomitant treatment. Another example would be the development of congenital malformation in children whose mothers had been exposed to a certain medicine during pregnancy. In this case, the 'risk factor' is pregnancy, and the risk minimisation approach would aim to prevent exposure to the medicine during pregnancy.

At the other end of the spectrum there are unpreventable risks, such as idiopathic reactions without any known risk factors, which would not be amenable to any form of risk prevention. In these cases, it is not possible to identify patients who will be at high risk of the adverse event. After an adverse drug reaction occurs, a case becomes an exercise in risk mitigation and the approach to risk minimisation focuses on ensuring that only those patients for whom the benefit-risk balance is favourable continue receiving the medicine.

In some cases, effective monitoring of the patient may also have an impact on severity or allow harm reduction if the monitoring is used to identify the early appearance of a particular biomarker that would represent the potential onset of an adverse drug reaction. If this results in an intervention, such as stopping treatment with the medicine, which would then halt further clinical manifestations, one can infer that the mitigation measure was effective. Since the appearance of a biomarker after drug exposure implies the onset of an adverse drug reaction, regardless of overt clinical signs and symptoms, the outcome in these situations is that potential harm was reduced in severity.

It should be noted that an adverse drug effect that is unpreventable today, could become preventable at some point in the future, given further advances in medical sciences – especially in pharmacology, genomics, and technology. Therefore, in such cases, there could be a transition from a risk mitigation to a risk prevention strategy.

The development of an effective risk minimisation strategy requires that the relationship of drug exposure to the adverse outcome be well understood. In some cases, the adverse event occurs with increasing doses of the medicine, and, if reversible, can be effectively managed by dose reduction. In other cases, the adverse event may be related to cumulative dose and may not be reversible; in this situation, it is important to monitor cumulative dose and, in some cases, markers of toxicity throughout and possibly after treatment. The potential for early recognition of possible signs and symptoms that enable the patient to alert the healthcare professional (HCP) or to take actions and avoid progression to irreversible harm is an important characteristic of a risk. This is because it offers an opportunity for early detection and harm reduction.

B. General principles of risk management

Risk management (including risk minimisation) is the responsibility of the entire medication use system. Medication use systems have multiple stakeholders and are quite complex. Stakeholders include first and foremost the patient, patients' caretakers (or carers), physicians and other practitioners who prescribe medicines, pharmacists, pharmacies, hospitals and other healthcare facilities and organisations, distributors and wholesalers, insurance companies and other payers, pharmaceutical companies, regulatory authorities and other parties. Understanding the dynamic interactions amongst these stakeholders is essential to implementing the most effective risk minimisation programme possible.

Risk minimisation and risk minimisation planning, should occur throughout a product's lifecycle. While the pre-approval clinical research process is governed by laws and regulations to protect research subjects, and clinical trial protocols include systematic collection of adverse event data, the minimisation of specific serious risks of a medicine need to be considered from the earliest stages of development. Consideration during the pre-approval phase needs to focus both on minimisation of the specific serious risks during development and also on planning for the minimisation of these and other emerging risks once the product is marketed. In this respect, CIOMS Working Group VI established the principles for a systematic approach to pre-approval risk management and introduced the concept of a Development Risk Management Plan (DRMP) as a means of minimising risks to clinical trial subjects and as a basis for submission and postmarketing plans. During the marketing phase, as more fully outlined below and explained in more detail in this book, the risk minimisation plan is implemented, its performance is monitored, and changes are made accordingly.

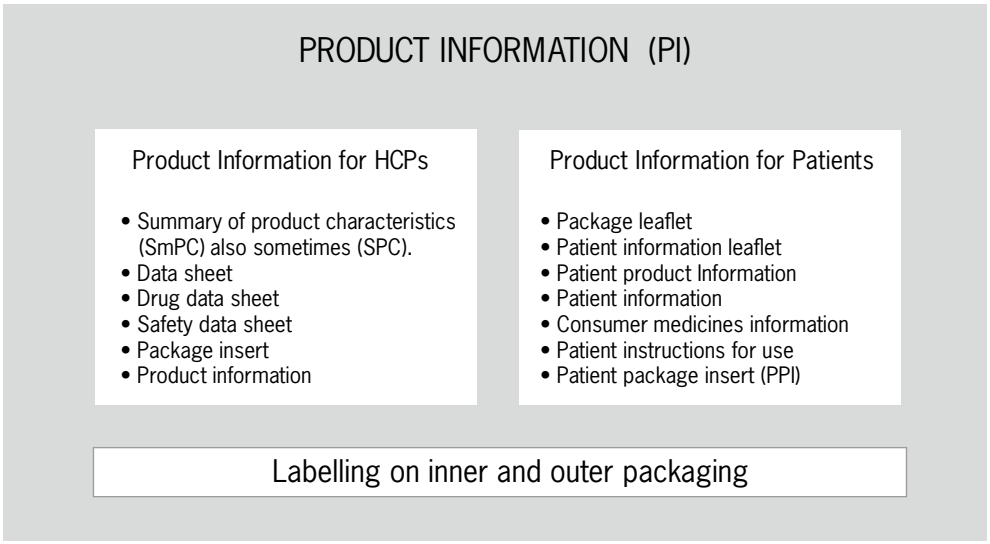
Risk minimisation should balance optimisation of benefits and risks, prevention and mitigation of risks, and preserving access to needed medicines. While strong measures to prevent or mitigate risks might be successful in achieving those goals, they may be so burdensome that they inappropriately limit access to the medicine. In some cases, persons for whom the benefits outweigh the risks would not receive the medicine because of these access limits, a result that would have a negative public health impact. To achieve the proper balance, risk minimisation planning should thus consider the 'burden' of a plan. *The **burden** of risk minimisation plans includes the burden to the **patient** and the burden to the **healthcare system**.* Methods to identify and quantify these burdens are not fully elaborated at present, and will require further development. Despite this limitation, it is important that sources of burden be identified both during planning and as part of assessment of the risk minimisation plan.

The burden of the risk minimisation plans should be justified by the benefits of the medicine (compared to the next best alternative treatments), and the effectiveness of the plan. Risk minimisation plans can vary from minimally burdensome to extremely burdensome. The burden may be on practitioners, on patients, on other parts of the healthcare system, or on several parts of the system. In any case, burdens on any part of the system, regardless of magnitude, should only be accepted when considered necessary to ensure that the goals of the plan are met. Burdens that do not contribute to attaining the goals of the plan are not justified. Evaluations of risk minimisation plans also impose burdens on the healthcare system. *The burden of the risk minimisation plan and its evaluation should be proportionate to the level of risk.* Another important consideration is that the burden may vary according to the country and the healthcare system. For example, a requirement to have an annual MRI scan might not be too onerous in a healthcare setting

where most big towns have a hospital with an MRI scanner but could be a major deterrent to treatment in a setting where MRI scanners are scarce and patients have to travel considerable distances to reach one.

Risk minimisation plans should carefully select risks that require more than routine risk minimisation measures. In determining the need for a plan that includes additional to routine risk minimisation measures, it is necessary to determine if there are one or more risks associated with the medicine that cannot be minimised using the traditional tools of product information for prescribers (and for patients depending on jurisdiction, see Fig. 1.1). Some product information may be considered a non-routine, additional risk minimisation tool, e.g. medication guides. In the U.S. medication guides are required in addition to routine measures, when the FDA determines that for better patient health and adherence purposes, a certain product needs to have additional risk minimisation information distributed to the patient when the medication is dispensed. (See Chapter III.)

Fig. 1.1: Examples of nomenclature for components of product information



The basic consideration here is whether or not product information is sufficient to ensure that the medicine will be used in a way that ensures that its benefits outweigh its risks. This determination is not always straightforward, and requires knowledge of: the specific risks of the medicine; the indication; the population being treated; the overall benefit-risk profile; how the medicine will be used in actual practice; the settings of care; and how the medicine might be misused. Because the decision to institute certain risk minimisation measures involves an interplay of these factors, it may be possible that certain risk minimisation measures could be necessary for one indication, population, or healthcare setting, but not for others.

Risk minimisation plans follow a stepwise approach, and start with the least burdensome measures needed in order to accomplish their goals. In developing a risk minimisation plan that includes non-routine measures, it is first necessary to define clearly the goals of the plan. Only after these goals are set can the details of the plan be developed (discussed in Chapter III). *Development of a risk minimisation plan should consider the setting(s) in which the medicine is used.* For example, inpatient and outpatient settings present different challenges for the implementation of a risk minimisation plan. Similarly, there are practical differences between risk minimisation plans for widely used medicines and for those used more narrowly. These and other factors should be carefully considered in the development of a risk minimisation plan.

Just as the clinical setting should be considered, so too should the broader healthcare system in which the plan will be implemented. *The logistics of a risk minimisation plan should be workable within, and ideally integrated into, the healthcare system in which it is being used.* Individual healthcare systems, and the medication use systems within them, have established workflow practices in clinics, pharmacies, and

other settings. The logistics of a risk minimisation plan, to the extent practicable, should be consistent with these workflow practices. As risk minimisation plans evolve, some may include critical elements that are not consistent with current workflow practices or existing systems. As risk minimisation efforts become more widely used, some changes in the medication use system may need to occur to accommodate risk minimisation efforts.

While the practical elements of risk minimisation plans vary according to the healthcare system in which they are implemented, some general principles apply. *Some risk minimisation plans restrict access to only those patients with a favourable benefit-risk profile, but cannot further predict or prevent individual risk.* For example, a drug may be known to cause aplastic anaemia and may be the only treatment for a particular serious, life-threatening disease. In this case, it is important to determine that the risk of aplastic anaemia justifies the benefits of the drug for a particular patient, even if no additional measures can further prevent the occurrence of this adverse drug reaction. In this case, proper patient selection would aim to ensure that persons for whom the benefits of the drug do not outweigh the risks do not get the medicine. Other risk minimisation plans can more accurately identify patients for whom the benefit-risk is more favourable. For example, if a pharmacogenomic test can identify patients at high risk for a serious adverse event, such a test could be used to screen patients prior to receiving the medicine. For patients found to be at high risk, alternative treatment can be considered. In each of these cases, the risk minimisation plan includes appropriate patient selection.

To the extent possible, additional risk minimisation activities should use tested approaches. Using approaches that are known to be effective in previous situations can help to ensure effectiveness in a new situation. However, there is not yet a substantial body of literature on the effectiveness of risk minimisation plans for medicines. Testing of a proposed risk minimisation plan in the premarket setting may shed some light on the future effectiveness of the plan in the marketed setting. However, Phase III clinical trials cannot shed light on the degree to which healthcare professionals will accept and adopt the risk minimisation intervention under 'real world' circumstances. In addition, the controlled environment of premarketing clinical trials would limit the generalisability of assessments of risk minimisation plans to the post-marketing setting.

To be successful, risk minimisation interventions require careful dissemination planning. Dissemination of risk minimisation interventions is an active process whereby the target audience(s) is made aware of, receives, accepts, and implements the information and intervention. Effective dissemination of risk minimisation interventions requires a proactive, systematic and controlled approach and strong organisational commitment. Understanding the manner in which the risk minimisation intervention is to be delivered is essential if the dissemination process is to be successful.

Evaluation of the effectiveness of risk minimisation programmes is essential and should be planned prospectively, on a case by case basis, and in line with applicable legal requirements. This evaluation may include measurement of programme implementation and patient outcomes. It should include not only effectiveness of the programmes, but also measurement of the programme's negative consequences, such as undue burden and unnecessary limitations on access.

Risk minimisation is an iterative process. The initial planning and implementation of a risk minimisation plan that includes additional risk minimisation activities, is followed by an evaluation of its effectiveness. The results of this evaluation may point to needed changes in the risk minimisation plan. In addition, postmarketing safety surveillance (pharmacovigilance) activities may identify previously unknown risks, or may better characterise known risks. The results of such safety surveillance may require reassessment of the benefit-risk profile of the medicine, which may in turn lead to changes in the risk minimisation plan.

Risk minimisation planning involves multiple disciplines and areas of expertise. Risk minimisation planning needs to consider not only the specific risks of a medicine, but also the settings, healthcare systems, and medication use systems in which the medicine is used. For this reason, planning of additional risk minimisation activities requires a team whose members' expertise spans a wide range of areas, some of which may need to be contracted in from external organisations. Additionally, engagement of external stakeholders early in planning is recommended.

In the selection of risks for additional risk minimisation interventions, there is a pressing need to improve the process because our current process is flawed and not comprehensive. Our current approach focuses on adverse drug reactions as represented in the Warnings and Precautions section of the product information. However, the overarching objective of risk minimisation is to ensure safe and appropriate use and improve the benefit-risk balance of the medicine. We therefore need to combine risks identified through the clinical development programme for the medicine with the risks that are identified through a systematic analysis of how the medicine is expected to be used in the actual healthcare system, with real patients, in the real world.

This book focuses on important considerations in the design, implementation, and evaluation of risk minimisation plans which utilise additional risk minimisation activities. Chapter II summarizes the adoption and implementation of risk minimisation systems by international, national and regional regulatory bodies around the world. Chapter III addresses the selection of individual risk minimisation tools and includes the use of a decision tree approach that can be used to compile a risk minimisation plan. Chapter IV covers governance issues in risk minimisation planning and implementation primarily from a pharmaceutical company perspective. Chapter V discusses the evaluation of effectiveness of risk minimisation strategies both at the level of individual risk minimisation tools and implementation of an entire risk minimisation programme. Chapter VI focuses on matters facing the many stakeholders involved in, and affected by, a risk minimisation plan with an emphasis on patient involvement. Chapter VII describes current trends at the time of publication and offers ideas for future directions in this rapidly evolving field. The Working Group's conclusions and recommendations, as appropriate, are summarised at the end of each chapter. Annex I provides a Glossary. The Annexes also contain points to consider for the design of a study to assess effectiveness of risk minimisation, patient feedback obtained by CIOMS, many real-life examples of actual risk minimisation plans as well as points to consider regarding vaccine risk minimisation.

C. References

1. International Conference on Harmonisation (ICH) E2D Guideline. Post-approval safety data management: Definitions and standards for expedited reporting. Brussels, Belgium: ICH. 2003.
2. Practical aspects of signal detection in pharmacovigilance: Report of the CIOMS Working Group VIII. Geneva, Switzerland: CIOMS. 2010.
3. ICH E2E Guideline: Pharmacovigilance planning. Current Step 4 version, 18 November 2004.
4. ICH E2C (R2) Guideline: Periodic benefit-risk evaluation report, 2012 and ICH E2F: Development safety update report, 2010. http://www.ich.org/products/.
5. Guideline on risk management for medicinal products for human use. Committee for Medicinal Products for Human Use (CHMP). London, UK: European Medicines Agency. 2005 (doc. ref. EMEA/CHMP/96268/2005).
6. Guidance on format of the risk management plan (RMP) in the EU – in integrated format. London, UK: European Medicines Agency. 2012 (doc. ref. EMA/718034/2012).
7. Risk assessment in regulation. United States Nuclear Regulatory Commission. (http://www.nrc.gov/about-nrc/regulatory/risk-informed.html, accessed 18 January 2014).
8. Guideline on good pharmacovigilance practices: Module V – Risk management systems. London: European Medicines Agency. 2012.
9. Common Terminology Criteria for Adverse Events v4.0 (CTCAE). U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 2009. (evs.nci.nih.gov/ftp1/CTCAE/, accessed 18 January 2014).
10. Severity grading in drug induced liver injury. Drug-Induced Liver Injury Network (DILIN), U.S. Department of Health and Human Services, National Institutes of Health. (http://www.livertox.nih.gov/Severity.html), accessed 26 January 2014).

CHAPTER II:

INTERNATIONAL REGULATORY CONTEXT AND BACKGROUND

A. Introduction

Risk minimisation activities have traditionally included some form of standardised information directed at healthcare professionals (HCPs) and/or patients. The terminology for each differs globally (see Chapter I, Fig. 1.1, and Annex I Glossary). For the purpose of this document, the term Product Information (PI) will be used to cover all forms of information directed specifically at healthcare professionals or patients which constitutes 'routine risk minimisation.' It should be noted that the terminology may differ across countries and even within a particular jurisdiction.

This PI documentation, included in the medicinal product packaging or provided as supplementary information, has been the main mechanism by which risk has been communicated to healthcare professionals and patients in an endeavour to reduce adverse events associated with medicines. Historically, risk minimisation has largely been reactive, with particular activities put in place in response to identified risks. However, a number of well-publicised drug withdrawals led to the realisation that there needed to be a more proactive approach to pharmacovigilance in general, and risk minimisation in particular.

In 2001 the International Conference on Harmonisation (ICH) started to develop its E2E pharmacovigilance planning guideline. ICH is a tripartite forum with representatives of regulatory authorities and the pharmaceutical industry associations in the European Union (EU), Japan and the United States of America (US). ICH E2E introduced the concept of a Safety Specification, which discussed what was known and not known about the medicine at the time of authorisation. The Safety Specification ends with a list of safety issues which were defined as important identified risks, important potential risks and important missing information.

The second part of ICH E2E is the Pharmacovigilance Plan. This describes how the sponsor intends to identify and characterise further the safety issues from the Safety Specification. While forming the basis on which the assessment of the need for risk minimisation activities can occur, ICH E2E *deliberately did not venture into the area of planning risk minimisation activities*. In view of the inherent difficulties in developing risk minimisation activities for regions with widely different cultures, medical practices and healthcare systems, this was felt to be an area where harmonisation would be especially challenging. Although the risks for a medicinal product will be very similar, due to variations in different populations and indications, the risk minimisation approaches may need to vary considerably between different regions and countries.

ICH E2E reached step 4 in November 2004. It was adopted by the EU in December 2004, published in the U.S. *Federal Register* in April 2005, and adopted by Japan in September 2005. Since that time, regulatory authorities around the world have increasingly established frameworks for managing risks using the concepts introduced in ICH E2E to identify the safety issues or concerns, plan how to further investigate them, and most importantly, plan how to minimise their effects at the patient and public health level. For the majority of medicines, routine risk minimisation activities are deemed sufficient to manage risks by providing good quality product information.

Risk minimisation activities that go beyond the routine product information are usually reserved for some medicines with particular risk profiles and may include new chemical entities or biologicals, new situations

such as an extension of the use of the medicine into new populations, or new formulations and routes of administration. The marketing authorisation holder (MAH) or sponsor (usually the pharmaceutical company) outlines what activities they consider necessary for the safe use of the product and the regulatory authority either agrees with the proposals or may request additional activities based on their own assessment of the known and potential risks associated with the use of the product. Ultimately the risk minimisation activities undertaken are the responsibility of the sponsor and agreed to by the authorities. The regulator's decision to accept a particular risk minimisation activity is based on their knowledge and experience that the proposed approach is implementable in the relevant jurisdiction.

This chapter outlines the different approaches used by regulatory authorities in adopting the ICH guidelines and the methods for risk minimisation planning in their region.

B. Context

While there is a range of risk minimisation tools currently available, the implementation of certain procedures in some countries may be less straightforward. For example, when the need for additional risk minimisation activities has been identified, and an overall risk minimisation strategy is needed (e.g. dissemination of additional healthcare professional (HCP) education beyond what can be conveyed in the product information), the task of identifying specific risk minimisation tools to execute that strategy within different regions and countries can be complex. This is due to the various factors already articulated in relation to ICH E2E, including local variations in the practice of healthcare, different regulatory frameworks, and even cultural differences.

Many risk minimisation activities are physician-based, such as educational activities for prescribing physicians or the monitoring of blood parameters such as liver enzyme levels when prescribing certain medicines. While regulatory authorities can mandate the inclusion of these activities in a risk minimisation plan, their ability to influence the uptake of these activities may be limited depending on the structure of the healthcare system and on clinical judgment by the medical practitioners.

In some countries there is no specific legislative basis for the government to require a pharmaceutical company to provide or undertake a risk management plan or risk minimisation activities. Instead, the health authorities take action based on broader, less specific authority within existing regulations.

Other countries have adopted a 'legislative approach' with the passage of laws requiring a risk management plan, with appropriate risk minimisation activities, to be implemented for certain medicines. The plans have usually been required for new chemical entities or where there is an extension to the indication of the product, particularly into paediatric populations or new indications. In these cases there usually also exist legislative powers allowing the regulatory authority to require a pharmaceutical company to develop a risk management plan should a safety issue be identified postmarketing. Australia is an example of this approach.

This chapter describes several different approaches to adoption of Risk Management Plans (RMPs) across the globe. Not all countries where an RMP is required are discussed. In general, those countries where there is a requirement for an RMP for some medicinal products tend to be those with the most well-established regulatory schemes and healthcare systems. This is due to the need to have systems where controls on supply or provision of information can easily be put in place and support the risk minimisation activities.

C. Case studies of country approaches to risk minimisation activities

Case examples of the various approaches that have been undertaken by regulatory authorities where risk minimisation activities have been required as part of the marketing authorisation of a medicine, are provided below. They include those countries where specific requirements have been introduced (EU, Japan

and the US); where a country has adopted requirements from another jurisdiction as part of a legislative requirement (Australia); or countries using broader and less specific authority within existing legislation (Canada). These examples provide models for countries that have not yet developed formal risk management or risk minimisation activities. As the requirements by a jurisdiction are subject to change, it should be noted that the examples quoted in this book are current at the time of the writing of the CIOMS IX report.

• Countries or economic/political bodies with legislated requirements

Japan, the US, and the EU are three jurisdictions, amongst others, that have developed formal and legislative requirements for risk minimisation activities as part of risk management planning. The approaches adopted by these jurisdictions are outlined in this section.

i. Japan

In Japan, risk management and risk minimisation plans can be required throughout the lifecycle of a registered drug, as mandated by Japanese legislation. The requirement for a risk management plan (RMP) is determined during the consultation process with the Japanese Ministry of Health, Labour and Welfare (MHLW) that occurs at the pre-marketing stage. It is not obligatory for the pharmaceutical industry to undertake this consultation process but use of this mechanism means companies can discuss development strategies with the authorities and thus streamline approvals if they so choose. During the consultation process, the regulatory authority and the sponsor discuss identified/potential risks to plan safety measures proactively. If the authority identifies that the risk associated with a particular medicine is considered high, then they require that a strict (robust) RMP be developed by industry and submitted at the time of application for registration.

An RMP and plan of postmarketing studies are components of New Drug Applications (NDA) in Japan. This requirement was implemented in early 2013. After submission as a part of the NDA, the regulatory review team discuss the appropriateness of the plans with the applicant during the review period. Approval for the RMP is obtained from the Japanese Pharmaceuticals and Medical Devices Agency (PMDA). The executive summary of the RMP is subsequently published on the PMDA website in order to share it with relevant stakeholders.

Additional risk minimisation activities undertaken in Japan include Medication Guides for patients and Guidelines on adverse drug reaction reporting for patients and healthcare professionals (HCPs).

The following are examples of two unique activities undertaken in Japan which involve risk assessment, risk minimisation, and evaluation of the effectiveness of risk minimisation:

1. Early Postmarketing Phase Vigilance (EPPV)

This is a requirement for most products that are classified as a New Molecular Entity (NME) as a condition for approval, but may not be required for all NMEs, for instance, when the safety profile is similar to a currently approved medicine. The aim of EPPV is to collect information about a medicine, including safety information, and to ensure that the information is collected efficiently, and that it is robust and accurate. In addition, the EPPV provides an opportunity for rapid dissemination of information to early prescribers concerning any new safety signals detected during this period. For this reason, EPPV can be considered to contribute to risk minimisation.

The EPPV involves a concentrated period of vigilance during the first six months of marketing of the NME. Under EPPV, the marketing authorisation holder (MAH) is required in principle to contact all HCPs who would be in a position to prescribe the new medication before marketing (delivery) of the product and subsequently every two weeks for the first two months and then every month for the following four months. The purpose of these contacts is to inform the HCPs that the product is new and that especially any new, unknown serious adverse reactions to the medication should be reported. The contacts are made through

the company's Medical Representatives or in some cases via wholesalers or distributors and through electronic means. It should be noted that in Japan most ADRs are collected by medical representatives of the MAH visiting the prescribers. After six months, the MAH has to submit a summary report to the PMDA. The report includes cumulative adverse drug reactions and the result of an assessment of these by the MAH. After submission and review of the report by the PMDA, the MAH may be required to update safety information in the product label.

It should be noted that because of the system of frequent contacts, any new safety issues can be rapidly communicated to prescribers as a form of risk minimisation for an evolving safety issue. Note that EPPV is not a study and the adverse event reports received during EPPV are considered spontaneous rather than solicited.

The Japanese guidance on the RMP classifies the EPPV both as an additional activity for the pharmacovigilance plan (since it contributes to better collection of information) and as an additional activity for risk minimisation (because of earlier provision of new safety information during the EPPV). There are at least a few documented cases in Japan where a new signal detected during EPPV has resulted in immediate information distribution and a decline in the adverse event of interest.

2. 'All-Cases Surveillance', called 'Zenrei-Chosa' in Japanese.

All-Cases Surveillance (ACS) is required for situations in which a known serious risk exists or the authorities wish to assess signals of serious risk or to identify an unexpected serious risk when available data indicates this potential. There are two main purposes of ACS: one is to collect benefit-risk data efficiently, and the other is to collect information on the number of exposed patients and therefore to be able to determine the overall risks associated with the medicine. Examples of products for which an ACS would be required include orphan drugs and anti-cancer drugs with a new mechanism of action and molecular targeted drugs. Of 26 new molecular entities that the PMDA approved in 2009, seven carried conditions for approval; of those, six were required to follow the Zenrei-Chosa system.

The ACS is limited in time and does not result in an ongoing database of patients once it is completed. It is based on contracts with the medical institutions that have access to prescribing the drug. Upon completion there is no remaining 'registry' and no additional follow-up. It is also enforced more completely than EU/US registries which are in most cases voluntary; ACS is a requirement involving HCPs and patients. This is very different from how registries outside Japan are run and so ACS should not be confused with a registry. The HCPs must participate because they cannot prescribe the drug outside the ACS. Only institutions that have contracted to participate in the ACS are given access to the drug through the distribution system. However, in addition there is a per-subject payment (although in most cases it goes to the institution rather than directly to the HCP).

After collection of the required data from the targeted number of patients, the MAH is required to submit a report to the regulatory authority. Following a review of this information the authority may request further changes to the label or undertake other regulatory action.

ii. United States

The cornerstone of the US approach has been the provision of information to healthcare professionals including information through product labelling. The FDA's postmarketing safety monitoring also allows ongoing assessment of the product's benefit-risk profile.

Prior to the passage of the 2007 legislation, early efforts at risk minimisation that went beyond labelling for prescribers and routine activities included, for a small number of drugs, additional measures, such as restricted access, patient labelling, or both. (See Annex I Glossary for what constitutes US labelling.)

In 1999, the FDA had published '*Managing the risks of medical product use: Creating a risk management framework*' **(1)**. This publication was followed in 2005 by publication of '*Guidance for industry: Development and use of risk minimisation action plans*' **(2)**, which provided recommendations for processes or systems to minimise known safety risks, including the following:

- Targeted education and outreach to communicate risks and appropriate safety behaviours to healthcare practitioners or patients;
- Reminder systems, processes, or forms to foster reduced-risk prescribing and use;
- Performance-linked access systems that guide prescribing, dispensing, and use of the product to target the population and conditions of use most likely to confer benefits and to minimise particular risks.

Risk management efforts in the U.S. based on the above framework were instituted between 2005 and 2008.

In September 2007, the U.S. Congress passed the Food and Drug Administration Amendments Act of 2007, known as the FDAAA (U.S. Public Law 110–85). Title IX, Sections 901–921 of this Act modified the Food, Drug, and Cosmetic Act by granting FDA, amongst other authorities, the authority to require manufacturers, under certain circumstances, to develop and implement a Risk Evaluation and Mitigation Strategy (REMS).

A REMS is a required risk management plan that utilises tools beyond routine labelling to ensure that benefits of a drug outweigh its risks. These provisions, which became effective on March 25, 2008, authorise the FDA to require application holders to develop and comply with REMS if specific statutory criteria are met. The new regulations and requirements apply to prescription products approved under New Drug Applications (NDAs) and Abbreviated New Drug Applications (ANDAs), as well as products approved under Biologics License Applications (BLAs).

Prior to initial approval of an application, FDA offices responsible for review of the drug or biologic and for post-approval safety review determine whether a REMS is needed to ensure that benefits of the drug outweigh its risks. FDAAA requires FDA to consider certain factors in making the determination:

- Estimated size of the population likely to use the drug;
- Seriousness of the disease or condition that is to be treated;
- Expected benefit of the drug;
- Expected or actual duration of treatment;
- Seriousness of any known or potential adverse events and background rates of disease incidence;
- Whether the drug is a new molecular (chemical) entity.

After a drug is approved, FDA may become aware of new safety information about a serious risk associated with the use of the drug and determine that a REMS is necessary to ensure that the benefits of the drug outweigh its risks. New safety information may be derived from a clinical trial or study, spontaneous adverse event reports, the published literature, or other scientific data. It may also be based on a new analysis of existing data or an assessment of the effectiveness of an approved REMS.

All REMS for NDAs and BLAs must include a timetable for assessment of the REMS. The FDA also determines which of the following additional elements will be included in a REMS, if criteria specified in the law are met:

- A Medication Guide (MG) or a patient package insert (PPI);
- A communication plan;
- Elements to assure safe use (ETASU);
- An implementation system.

An MG is a form of patient labelling whose format, content, and distribution requirements are set forth in regulations. An MG may be required as part of REMS to inform patients about serious risks associated with the product and may also be used to provide patients with information necessary for the safe use of the product. REMS with communication plans are designed to ensure that healthcare providers are made aware of important information for safe use of the drug and can include a Dear Health Care Professional letters as well as letters to professional societies. An ETASU is required if necessary to mitigate a specific

serious risk listed in the labelling of a product, thus enabling access for patients to drugs that would otherwise not be approved.

An ETASU includes:

- Prescribers have relevant training or are certified to prescribe the drug;
- Pharmacies or healthcare settings are certified to dispense the drug;
- Drugs are dispensed in specific settings;
- Drugs can be dispensed to patients with evidence of compliance to specific requirements such as laboratory tests;
- Each person prescribed the drug is appropriately monitored; and
- Each person using the drug is enrolled in a registry.

The FDA may also require an implementation system for REMS with certain elements to assure safe use. An implementation system requires the application holder to take reasonable steps to monitor, evaluate, and improve implementation of the elements to assure safe use by healthcare providers and other participants.

The minimal timetable for assessment of a REMS includes assessment by 18 months, three years, and in the seventh year post-REMS approval. The FDA may require more frequent assessments specified in the REMS. The assessments can be removed after three years if FDA determines that serious drug-related risks have been adequately identified, assessed, and are being adequately managed.

iii. European Union

The EU provides a unique example of the challenges of risk management as it is made up of member countries that may have their own national laws regarding medicines regulation in addition to those introduced by European Directives and Regulations.

The European Medicines Agency (EMA) co-ordinates pharmacovigilance within the 28 member states of the EU (as of 2014) and three states within the European Economic Area (EEA), namely Iceland, Liechtenstein and Norway. These thirty-one countries have a wide range of healthcare systems, varying medical practices and a diversity of cultures. This creates challenges for implementing a standard approach to risk management.

An additional important consideration is that in the EU, medicines can be authorised by four different routes:

- Centralised
- Mutual Recognition
- Decentralised
- Single National

The centralised authorisation procedure is a single, pan-European licence with one set of product information – albeit translated into 24 national languages. The other three routes all lead to separate national licences, but in the case of the mutual recognition and decentralised procedures, there is again one single set of product information. The medicines authorised by the centralised procedure have a marketing authorisation (MA) covering all of the EU whereas medicines authorised by mutual recognition or decentralised procedures will have MAs only in the countries that the sponsor included in the application which in theory could range from 2–28 national MAs. Should an MAH only intend to market a product in one EU country, they can apply for a single national MA but marketing of a new product in more than one country requires one of the other authorisation routes.

The European Medicines Agency is responsible for the centralised procedure for human and veterinary medicines. The centralised procedure is compulsory for:

- human medicines for the treatment of HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions, and viral diseases;
- medicines derived from biotechnology processes, such as genetic engineering;
- advanced-therapy medicines, such as gene-therapy, somatic cell-therapy or tissue-engineered medicines; and
- officially designated 'orphan medicines' (medicines used for rare human diseases).

For medicines that do not fall within the above mandatory scope, companies have the option of submitting an application for a centralised MA to the EMA under the 'optional scope', if the medicine is of significant therapeutic, scientific or technical innovation, or if its centralised authorisation would be in the interest of public health.

Applications for authorisation via the centralised procedure are submitted directly to the EMA and evaluations are undertaken by the EMA's scientific committees. These committees are made up of experts nominated by the Member States augmented by experts appointed by the European Commission. Some committees also include members representing patients and healthcare practitioners. For each medicine, a Rapporteur and Co-Rapporteur are appointed from two Member States (MSs) to lead the evaluation which is usually carried out by national experts from the same MSs. The rapporteurs' assessment reports are discussed by the EMA's scientific committees which in the case of human medicines is the Committee for Medicinal Products for Human Use (CHMP). The CHMP adopts an Opinion on whether the product should be authorised and if so, the conditions necessary for its safe use in the EU. This includes adoption of the Summary of Product Characteristics (SmPC) and Package Leaflet. For Advanced Therapy Medicinal Products (ATMPs) as defined in Regulation (EC) No. 1394/2007, the Committee for Advanced Therapies (CAT) is responsible for preparing a draft Opinion for final adoption by the CHMP with the assessment reports written by CAT rapporteurs. The Opinion is then sent to the European Commission, which has the ultimate authority for granting the single marketing authorisation for the EU.

The provision of advice on the RMP is the responsibility of the Pharmacovigilance Risk Assessment Committee (PRAC), which issues formal advice on the RMP to the CHMP or the CAT. The CHMP (or CAT) will consider the PRAC advice which forms part of the final Opinion of the CHMP as to whether the product should be authorised.

The PRAC can also give advice on risk management for products being authorised via non-centralised procedures. In these circumstances, their advice goes to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) and/or to the Member State(s) who made the request.

Risk management in the EU

Risk minimisation, in the form of the Summary of Product Characteristics (SmPC), the Package Leaflet and the labelling on the inner and outer packaging, has been in place in the EU for many years. Following several well-publicised safety issues in early 2000/2001, the European Commission undertook a review of the EU pharmacovigilance system. The outcome was Directive 2004/27/EC which amended Directive 2001/83/EU, and Regulation 726/2004 which introduced the concept of a risk management system. The specifics were not defined in the legislation and at the same time, the legislation also introduced the concept of the pharmacovigilance system which all Marketing Authorisation Holders (MAH) were required to have. The requirement to have descriptions of these two systems entered into force in November 2005.

The EMA produced a Guideline on Risk Management Systems for medicinal products for human use which, following public consultation and revision, was published in October 2005. This guideline, along with one on the pharmacovigilance system was incorporated subsequently into 'Volume 9A of *The Rules governing medicinal products in the European Union*.'

The guidance identified those products and circumstances where an RMP would be required since, at that time, not all products were required to have them. The guideline also introduced the concept of 'routine' and 'additional' risk minimisation activities. Routine risk minimisation activities, or measures, were those which every product was required to have by EU law and included: the SmPC, Package Leaflet, Labelling,

Legal Status and Pack size. Any risk minimisation activities outside these were termed 'additional' and were made a condition of the marketing authorisation; the MAH was legally obliged to follow them.

Pharmacovigilance in the EU was strengthened further by new legislation that came into force in July 2012. Regulation (EU) No 1235/2010 **(3)**, amending Regulation 726/2004 and Directive 2010/84/EU, amending Directive 2001/83/EC, brought in the requirement for every marketing authorisation application to contain a risk management plan. The new legislation also introduced the possibility of mandatory post-authorisation efficacy studies (PAES) and emphasised the importance of measuring the effectiveness of risk minimisation measures. A Risk Management System and Risk Management Plan were defined in the Directive as follows:

- Risk management system: 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 activities and interventions [DIR Art 1(28b)].
- Risk management plan: A detailed description of the risk management system [DIR Art 1(28c)].

A number of countries had started accepting the EU RMP format as discussed below under 'Countries that have adopted guidelines from other regions.' However, many required certain elements to be 'customised' to fit local legislation or practice. To facilitate submissions of a similar RMP to different countries, the EMA took the opportunity of new guidelines to change the format of the RMP to a modular one comprising seven parts. Parts II and III are the safety specification and pharmacovigilance plan from ICH E2E whilst the other parts include a description of the product(s) (Part I), plans for efficacy studies (Part IV), risk minimisation measures (Part V), a summary of the RMP (Part VI) and the annexes (Part VII). Within Part V, the applicant is expected to discuss how they will measure the effectiveness of risk minimisation activities and any formal studies to do this will be included in Part III: the Pharmacovigilance Plan. The safety specification is itself divided into modules, which, whilst arranged slightly differently, have similar content to ICH E2E and the previous version of the EU RMP. The use of parts and modules means that sections can easily be removed or added to customise RMPs for use in different regulatory settings.

Operational aspects of risk management for products in the EU centralised procedure

By their nature, the medicines most likely to need additional risk minimisation activities are those authorised via the centralised procedure. The legislation mandates the CHMP to provide details of the conditions and restrictions necessary for the safe and effective use of a centrally authorised medicinal product. This provision may apply to any such medicine which has risks requiring additional risk minimisation activities. For medicines needing these conditions, the issue was how to ensure that effective risk minimisation took place in Member States that had different healthcare systems, medical practices and cultures when there was a single EU-wide authorisation. The solution was in the form of what became known as the 'key elements' for safe and effective use. The CHMP would recommend, and if appropriate the European Commission would adopt into the Commission Decision, what needed to be done to ensure the safe and effective use. These key elements specify the principles of what needs to happen. The individual Member States have a legal obligation to implement these measures locally in their territory. How they are implemented is up to the Member State. For example, a typical condition of the marketing authorisation might say:

Prior to launch in each Member State the marketing authorisation holder (MAH) shall agree an educational programme with the National Competent Authority.

The MAH shall ensure that, following discussion and agreement with the National Competent Authorities in each Member State where Product X is marketed, at launch and after launch, all healthcare professionals who are expected to prescribe Product X are provided with the following items:

- *Summary of Product Characteristics (SmPC)*
- *Educational material for healthcare professionals*

The educational material for healthcare professionals should provide information on the following safety concerns:

- *Adverse reaction X*

- *Contraindication for use in patients with…*
- *Drug-drug interactions including involvement of CYP… substrates and inhibitors*

The MAH would discuss with the national regulatory authority (known in the EU as the national competent authority) exactly what format the educational material should take, a mock-up of what they intended to say, and the plan for dissemination. The national competent authority would check the material to ensure that it complied with the key elements, was not promotional and the communication plan would ensure that the relevant healthcare professionals received it.

Another example where the freedom for local implementation is key can be seen in the instance when either controlled distribution or controlled access is required (also known by the umbrella term 'restricted access'). Due to different healthcare systems it would be impossible to specify the exact form this should take since there is no common model in the EU. Instead, by merely mandating that restricted access should happen, the MAH can choose the most appropriate method for a particular country and agree it with the national competent authority. However, even if the degree of control implied by controlled distribution or controlled access is not required, MAHs should ensure that any educational material is distributed to the appropriate healthcare practitioners before they can prescribe, dispense or use the product to which it refers and this again will be healthcare system-dependent.

By specifying the tools and the key elements, a harmonised risk minimisation strategy can be put in place that can be implemented successfully in all EU countries. The European Commission has been quite clear that this method should not lead to the 'lowest common denominator' being specified. If the CHMP believes that certain measures are essential but local legislation in a particular Member State does not permit them, then the CHMP has the duty to recommend what is required. The particular Member State would then have to choose between not having the product used in its country and changing national legislation. However, so far this has not happened and, with some ingenuity, all required additional risk minimisation measures have been able to be implemented.

Occasionally some Member States have included additional risk minimisation measures because local experience suggests that they are needed in that country. This is allowed under the system since the conditions in the marketing authorisation are what the CHMP, and the European Commission, believe are essential, i.e. the minimum needed, for the safe and effective use. It is therefore permissible to have more measures than the essential ones, but not fewer.

The risk management plan in the EU may also contain risk minimisation activities to prevent or reduce risks to people who are not the patient or to the environment. Examples of this could be information on the safe disposal of a used product including in the most severe cases a requirement for unused or spent product to be returned to a pharmacy. This could be important for example with an opioid patch which will still contain residual product when it is disposed of, or products which would harm aquatic life if disposed of in landfill sites draining into streams or rivers.

In the legislation that came into force since July 2012, the EU requires the publication of a summary of the RMP, thereby increasing the transparency of which risk minimisation activities are required for a particular medicinal product.

• Authorities that have adopted guidelines from other regions

With the growing use of formal risk management and minimisation plans in the ICH countries of US, Japan and Europe, countries outside of these jurisdictions have started to request or require submission of either a local risk management plan or for copies of REMS or RMP that pharmaceutical manufacturers have submitted to the FDA or European regulatory authorities at the time of application. In most cases, where these (non-ICH) regulators have accepted EU RMPs or the US REMS they have also required modifications that address local or country specific health system issues. In some cases, regulatory authorities have limited the requirements to specific classes of high-risk medicines.

i. China

The China Food and Drug Administration (CFDA), previously known as the State Food and Drug Administration, published the Special Examination and Approval Procedures in New Drug Registration in January 2009. The purpose of the new procedures is to encourage the development of innovative new drugs in China while also increasing risk controls. It involves a priority review system with shorter timelines for approval of clinical trial applications for new drugs that have significant therapeutic promise. They involve products aimed at the treatment of diseases such as AIDS or malignant tumours or rare diseases or new biological products without prior approval intended for marketing in China or overseas. Article 18 of the regulation requires that a 'Risk Control Plan' be submitted at the time of application for clinical trials for new drugs that fall under the priority system. The outline of the Risk Control Plan essentially follows the categories of an ICH E2E Pharmacovigilance Plan with a summary of confirmed and potential risks as well as important missing information. Interestingly, the Chinese Risk Control Plan starts at the initiation of clinical trials in China at a point in time when relatively little will be known about the safety profile of an innovative new chemical entity.

ii. Republic of Korea

The Korean Food and Drug Administration (KFDA) published a draft Guidance on Pharmacovigilance Planning in August 2011. The Guidance describes a risk management document that is essentially identical to ICH E2E with Safety Specification, Pharmacovigilance Plan and Action Plan for Safety Issues but interestingly is generally referred to as the 'Risk Evaluation and Mitigation Strategy' (REMS) system in that country. Under the Korean REMS system, risks are to be assessed prior to the approval of a new medicine and then post-approval, and the REMS is to be part of a systematic drug safety information system for prescribers and patients.

iii. Taiwan

In Taiwan a draft 'Guideline on Risk Management Plan and Suggested Format and Contents' was announced in January 2011. The Guideline calls for a 'Risk Management Plan' which follows the same format and content as the U.S. FDA's REMS. The plans would be fully implemented at the time of approval with review by the Department of Health after the second and fifth years of implementation unless a different review schedule was announced. According to the draft guidance the documents are to be submitted in Chinese and will be made available for public view on the Department of Health website. The requirement for a REMS or RMP submission in Taiwan is also linked to the system of using a Certificate of Pharmaceutical Particulars (CPP) from an advanced country as part of the approval process for a new drug in Taiwan and in such cases either a US REMS or EU RMP may be part of the submission if the CPP is from the US or an EU member state.

iv. Singapore

The Singapore Health Sciences Authority (HSA) at the time of review of a new molecular entity currently request that the US REMS and/or EU RMP for the compound be submitted if either of these plans are in place for that product at the time of marketing authorisation application in Singapore. This is in addition to the HSA request for submission of the approved US Product Insert or EU SmPC for a newly submitted marketing authorisation application in Singapore. The more recent practice of requiring submission of the existing REMS/RMP appears to provide additional information to assist the HSA's review in the same way as having the approved product information from these regions.

v. Hong Kong

Similar to the practice in Singapore, the Hong Kong Department of Health will request submission of any active US REMS or EU RMP at the time the marketing authorisation application is submitted for a new chemical entity.

Just as risk minimisation practices in the US and Europe are constantly evolving, the requirements in the Asian countries mentioned above are expected to continue to change and may develop additional local requirements, but at this time it should be noted that these developed and rapidly developing Asian countries are drawing from the experience and guidelines developed from the ICH process as individually implemented in the US and Europe to augment their own risk management and minimisation practices.

vi. Australia

Australia is an example of a country whose regulatory authority, Australia's Therapeutic Goods Administration (TGA), has adopted guidelines from another international regulator, the European Medicines Agency. *The Therapeutic Goods Act, 1989* (the 'Act') provides the current legislative framework for therapeutic medicines and devices in Australia. Various amendments have occurred over time to update the Act in order to reflect international trends in therapeutic goods regulation and the legislative framework, as in most countries, is evolving.

In 1991 the Minister for Aged, Family and Health Services commissioned a report into the future of drug regulation in Australia **(4)**. The report undertaken by Peter Baume looked at whether Australia should adopt a 'go-it-alone' approach or seek international harmonisation. The report considered that the benefits of harmonisation such as a reduction to the costs of regulation, both to sponsors and to the regulator, the reduction in time involved in assessment and access to overseas expertise and ideas outweighed potential difficulties including the unique Australian environment and context. There were 24 recommendations, which included adopting the European application format; thus applications assembled according to the 'Notice to applicants for marketing authorisations for medicinal products for human use in the Member States of the European Community' would be acceptable in Australia and the previous format (NDF4) would be phased out. The TGA would also review and adopt where appropriate (as well as provide comment) on what was then the Committee for Proprietary Medical Products (CPMP) guidelines. The report also recommended consultation with the pharmaceutical industry and also to consult further should uniquely Australian standards be subsequently required. The TGA, rather than developing its own guidelines on therapeutic goods regulation, sought to minimise the impact of regulation on registration of therapeutic goods by adopting existing international guidelines. The recommendations were subsequently implemented and the TGA has continued to adopt European Union guidelines including those developed by the European Medicines Agency (EMA).

With the introduction of risk management plans by the EMA, the TGA began to request these in relation to some applications. In 2008, following an internal review of the current postmarketing functions within the agency which recommended a more transparent separation of pre- and postmarketing decisions, the requirement for risk management plans (RMPs) for high-risk medicines as part of the management of medicines safety in the postmarketing period was formalised.

In late 2008 the TGA notified industry that they would be adopting the current EMA guidelines on RMPs on 1 April 2009. While not mentioned specifically in legislation, s28 of the *Therapeutic Goods Act, 1989* provides the TGA with the power to impose conditions on registration of medicines and provides the mechanism by which the requirement for an RMP can be mandated through legislation.

The TGA undertook an extensive communication strategy to inform industry of the requirement through its website, communication with Medicines Australia, the peak pharmaceutical industry body in Australia, and presentations at a range of fora such as conferences.

As the format of the RMP required in Australia is essentially in the European format, some modification of the RMP to reflect Australian health system requirements and context has occurred. While pharmaceutical companies have undertaken various approaches, the industry has increasingly moved towards providing

an annex that reflects the Australian context and that outlines the differences and reasons for differences between the proposed EU and Australian RMP (for example differences between the summaries of product characteristics or provision of alert card to patients). This is recorded in the RMP as the Australian Specific Annex (ASA). Thus the core RMP reflects the EU requirements with the addition of an ASA in most cases.

Australia has not as yet adopted all the new EU RMP requirements introduced in July 2012 relating to efficacy and continues to accept both versions of the EU RMP. Sponsors have been requested to provide a short synopsis of any effectiveness studies being undertaken where this has been required in the EU.

Upon registration of a medicine, the TGA publishes an Australian Public Assessment Report that is similar to the European Public Assessment Report published by the EMA. This document outlines the assessment and findings on data submitted by the sponsor, including the RMP submitted for that particular medicine.

The TGA assesses all educational materials provided as part of a risk minimisation strategy to ensure that it focuses on the safety issues identified in the RMP. As part of its assessment of effectiveness of these risk minimisation activities, the TGA requires the accreditation of educational materials provided to HCPs by professional colleges for continuing professional development. This ensures that the educational materials provided will be effective in producing an educational outcome.

In Australia, both consumers and healthcare professionals regard the National Prescribing Service (NPS) as an important source of information on medicines. The TGA works with the NPS to ensure consistent messages to HCPs and consumers on important safety information for new and older medicinal products. The NPS regularly publishes information on newly registered medicines; this ensures that health professionals have multiple sources of information about risks and benefits associated with the use of a new medicine, including information on contraindications and precautions.

• Countries that use other legislative authority

i. Canada

Health Canada is an official observer at, and active participant in, the International Conference on Harmonisation (ICH). As such, Health Canada is committed to the adoption and implementation of ICH guidance.

In February 2009, Health Canada adopted and implemented the ICH E2E Guideline by publishing the *Notice Regarding Implementation of Risk Management Planning including the adoption of ICH Guidance Pharmacovigilance Planning – ICH Topic E2E*. In the Notice, Health Canada further advised that the EU format represents an acceptable approach to fulfilling requests by Health Canada for an RMP unless there are special considerations related to medical practice or populations in Canada.

Health Canada expects the following information to be provided in Risk Management Plans (RMPs):

1. Safety Specification, which is a summary of the known important safety information about the health product and is a means to identify gaps in knowledge;
2. Pharmacovigilance Plan, which is based on the Safety Specification and identifies and characterises known or potential safety concerns; and
3. Risk Minimisation Plan (RMinP), which provides approaches to minimise any identified or potential safety risk, as required.

Health Canada accepts Risk Management Plans in other recognised formats, as long as they cover the elements described in the EU guidance. An appendix to the notice highlights additional Canadian specific sections to the EMA Guideline on Risk Management Systems in order to provide a Canadian context to submitted RMPs. Health Canada may request RMPs when they are considered relevant to decisions regarding the benefit-risk profile of a drug.

Criteria which could be used by Health Canada to request an RMP include, but are not limited to:

1. new drug pharmaceutical submissions involving a new active substance;
2. all biologicals (including subsequent entry biologics);
3. any drug that is coming back to the market that was previously removed from the market due to a serious safety issue; or
4. a previously reviewed RMP that has undergone significant changes.

RMPs can also be requested as part of an ongoing review or other situations in order to make informed decisions about the health product.

Requests for such documents currently involve pharmaceuticals, biologics and biotechnology-derived products for human use, within the scope of ICH. Natural Health Products, Medical Devices and Veterinary Products are outside the scope of this interim implementation plan. Part of the intent of the interim implementation is to determine whether Health Canada should implement RMPs across all health product lines. RMPs may be requested in Canada as part of a New Drug Submission or during the post-approval period.

In Canada, risk management planning does not reduce the scientific standards for market authorisation of therapeutic products, nor does it replace the precautionary approach that is taken to managing risks associated with those products. On the contrary, implementation of RMPs further strengthens the rigour of post-market surveillance, allowing for earlier identification of risks associated with therapeutic products and earlier interventions to minimise those risks.

While drug manufacturers assume ultimate responsibility for monitoring their products post-authorisation to ensure that a drug's benefits continue to outweigh its risks, Health Canada has a regulatory mandate to intervene and protect the public from exposure to harm when scientific evidence suggests that such harm exists. RMPs provide for a more proactive means of managing risks associated with products, reflecting the fact that the responsibility of the manufacturer continues after a product is marketed.

The implementation of RMPs is intended to fit into a broader product vigilance framework that is being established at Health Canada. The intent of this initiative is to provide a standardised and systematic integrated risk management approach, including the use of regulatory tools to support and enhance health product vigilance review activities for pre- and post-authorisation of health products. One purpose of the RMP implementation is to investigate how risk management planning will integrate with ongoing and future pharmacovigilance activities.

Currently, Health Canada requests submission of RMPs on a voluntary basis. There is an international trend to formally incorporate such plans through legislation and regulations. Future plans for modernisation of Canadian legislation and regulations to adopt a product lifecycle approach to pharmaceuticals will likely include discussions around the ability to require RMPs for certain products.

D. Discussion

The ability of a sponsor to propose and a regulator to agree to a specific type of risk minimisation activity is dependent on the health system of the jurisdiction and the control mechanisms available to a regulatory authority to mandate the activity.

For countries with legislated requirements for risk management plans and large markets, such as the EU, US and Japan, the requirement to include specific risk minimisation activities, such as restricted prescribing, is often easier. Even in these cases, the complexity of such activities may be a significant barrier to their use where the regulator has no direct capacity to mandate the activity without the agreement of other bodies or agencies.

While there are a number of examples where effective risk minimisation activities have been put in place across different countries, such as with isotretinoin, thalidomide and clozapine, these have usually been

well-established medicines with evidence of benefit in certain populations or where specific manageable safety issues have been identified. Consequently, there has been a willingness for other bodies or agencies to put in place requirements that maintain the availability of the medicines when safety issues requiring risk minimisation activities have been identified. The ability to institute risk minimisation activities, such as prescriber restrictions, registries and pathology test requirements for new medicines prior to marketing authorisation appear harder to establish due to a lack of experience or knowledge of the medicine and its effectiveness in a population.

This problem may be compounded for countries that have no legislated requirement for an RMP and also no ability to mandate the risk minimisation activity.

In both cases (legislated and non-legislated RMP requirement) any negotiations with relevant agencies are usually hampered by confidentiality arrangements with sponsors at the time of marketing authorisation. As a result of this, any negotiation with other agencies around control mechanisms to achieve the activity are not possible.

Risk minimisation activities used by regulators are therefore often restricted to labelling (considered routine risk minimisation), the requirement of sponsors to provide education to prescribers on identified and potential safety issues or prescribing to specific populations and the creation of registries that may include the requirement to undertake specific testing prior to dispensing of the medication. For regulators there will often be a constant tension between requiring a sponsor to undertake a specific risk minimisation activity as part of registration and ensuring a medicine is available to the population that may benefit from it.

In many circumstances the ability of a regulator to require risk minimisation activities by a sponsor for a new medicinal product being evaluated for registration, especially in small markets, will require the identification of the most efficient risk minimisation tool – that is one that minimises the risk without imposing such a burden on the sponsor and other stakeholders that may cause the sponsor to withdraw the product from the market. Nevertheless the regulatory authority will need to consider whether the benefits of a product outweigh the risks associated with the use of a product; and where there are considerable risks, whether these can be managed in that jurisdiction.

To ensure that risk minimisation activities are efficient, consideration also needs to be given to the cost of evaluation of the effectiveness of the risk minimisation activity to the sponsor and the healthcare system (health professionals, consumers and regulators) to achieve the desired outcome. Where there is a significant risk but with significant benefit, then higher costs of both implementing and measuring effectiveness may be acceptable.

Product information is recognised as one of the primary risk minimisation tools for appropriate prescribing and conveying safety information to prescribers (and patients according to jurisdiction). Mechanisms to encourage, or require prescribers, to read this information prior to prescribing may be the most cost efficient way for regulators and sponsors to minimise risks associated with new medicines and new extensions of indications of older medicines; and ensure they are prescribed to the appropriate patients and that appropriate monitoring is undertaken when required.

Educational activities for prescribers associated with new medicines may also be a cost-effective tool for risk minimisation of new medicines for regulators. The requirements around education of prescribers by sponsors should consider whether the evaluation of effectiveness of the educational activity requires that a process or behavioural change measure be undertaken. The requirement for education of prescribers could be that prescribers have: 1) attended the educational programme (process, no outcome), 2) understood the messages related to the education (pre- and post-evaluation of education provided – education outcome), or 3) incorporated activity into their prescribing procedures (e.g. completed the required patient test and acted on results – behavioural outcome). While the latter would be difficult (behaviour change), the use of a third party, such as a professional college and existing continuing development programme requirements, would provide an effective and independent assessment of the educational activity.

Summary

This chapter has outlined the various approaches taken by regulatory agencies in regards to risk management and minimisation. The approaches adopted include country-specific requirements that have been adopted through legislation (USA and Japan), regional requirements that allow individual country modifications (EU), adoption of another region's requirements enshrined in legislation (Australia), and the adoption of guidelines from another region without specific RMP-related national regulations (Canada).

It is evident that there is a range of approaches to the formal adoption of risk minimisation requirements of a sponsor that can be developed by a regulatory agency. The approach adopted is influenced by the agencies to align with established international practice.

E. Recommendations

1. Regulators should consider harmonised approaches to risk minimisation such as consistent definitions, terminology and evaluation strategies.
2. Regulators should consider broader health system mechanisms to support risk minimisation such as healthcare professional training, continuing education and patient/consumer information.
3. Sponsors should consider developing overarching risk minimisation goals (or objectives) and then tailoring the implementation of those goals to the healthcare system and regulatory framework of the relevant jurisdiction and inclusion in the RMP.

F. References

1. Managing the risks from medical product use: Creating a risk management framework. Report to the U.S. FDA Commissioner from the Task Force on Risk Management, U.S. Department of Health and Human Services, Food and Drug Administration, May 1999.
2. Guidance for industry: Development and use of risk minimization action plans. U.S. Department of Health and Human Services, U.S. Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), March 2005.
3. Implementing regulation on the performance of pharmacovigilance activities. European Union Regulation No. 1235/2010 of the European Parliament and of the Council, Official Journal of the European Union, L348/1,31.12.2010, http://eur-lex.europa.eu/.
4. Baume P. A question of balance - Report on the future of drug evaluation in Australia, Department of Aged, Family and Health Services, 1991.

CHAPTER III:

PRINCIPLES OF IDENTIFICATION AND APPLICATION OF ADDITIONAL RISK MINIMISATION TOOLS

A. Introduction

This chapter presents key principles and guidance that should be considered when selecting, developing and applying additional risk minimisation tools needed to manage *important identified* and *potential* risks associated with medicinal products. In most cases, routine risk minimisation (that is, the routine information provided to the patient and healthcare professional (HCP), the product label, package insert, summary of product characteristics, and sometimes medication guide, depending on the jurisdiction) is considered to be sufficient to maintain a positive benefit-risk balance. However, when routine measures are not deemed to be sufficient, additional risk minimisation strategies become necessary and these are implemented through one or more risk minimisation tools. The tools are described in a plan and implemented in a risk minimisation programme.

The key principles for selecting and developing risk minimisation tools are affected by several factors including the regulatory environment, public health considerations, stakeholder benefit-risk acceptance, healthcare systems, demographics, disease status, and socio-economic background of the indicated patient/population, as well as prior knowledge and experience of stakeholders with a similar or even the same risk.

These key principles include:

1. **Risk identification**: Accurate *recognition* and *characterisation* of important risks that need to be prevented and/or mitigated is the basic starting point for a risk minimisation strategy.
2. **Goal setting:** Risk minimisation requires overall *goals,* specific *objectives* and *targets*. There should be a high-level, pre-defined goal, e.g. global strategy for risk minimisation, followed by determination of objectives, involving more specific outcomes, and finally specific targets for risk minimisation interventions. In order to define the goal, a risk should be evaluated for the possibility of its reduction (incidence or frequency, severity) and/or its elimination. Once that has been determined, a practical goal can be more easily defined. Each goal should have one or more stated objectives expressed in terms of SMART criteria (i.e. specific, measurable, achievable, relevant, time-bound). See Fig. 3.1.
3. **Healthcare system integration:** Risk minimisation tools should be *designed* to fit within an existing applicable regulatory and legal framework, patient care environment, and healthcare system. A risk minimisation plan should be flexible enough so that adaptations into effective local (country/regional) programmes will be able to meet expectations of its outlined goals and objectives. See Figs 3.1 and 3.2.
4. **Burden considerations:** The impact of risk minimisation *burden* that may be imposed on users and the healthcare system should be in proportion to the expected reduction of the frequency and/or severity of the targeted risk. Whenever possible and practical, risk minimisation plans should seek to adequately limit any undue burden on stakeholders and the healthcare system as a whole. Risk minimisation burden may not only impact effectiveness of a risk minimisation programme but

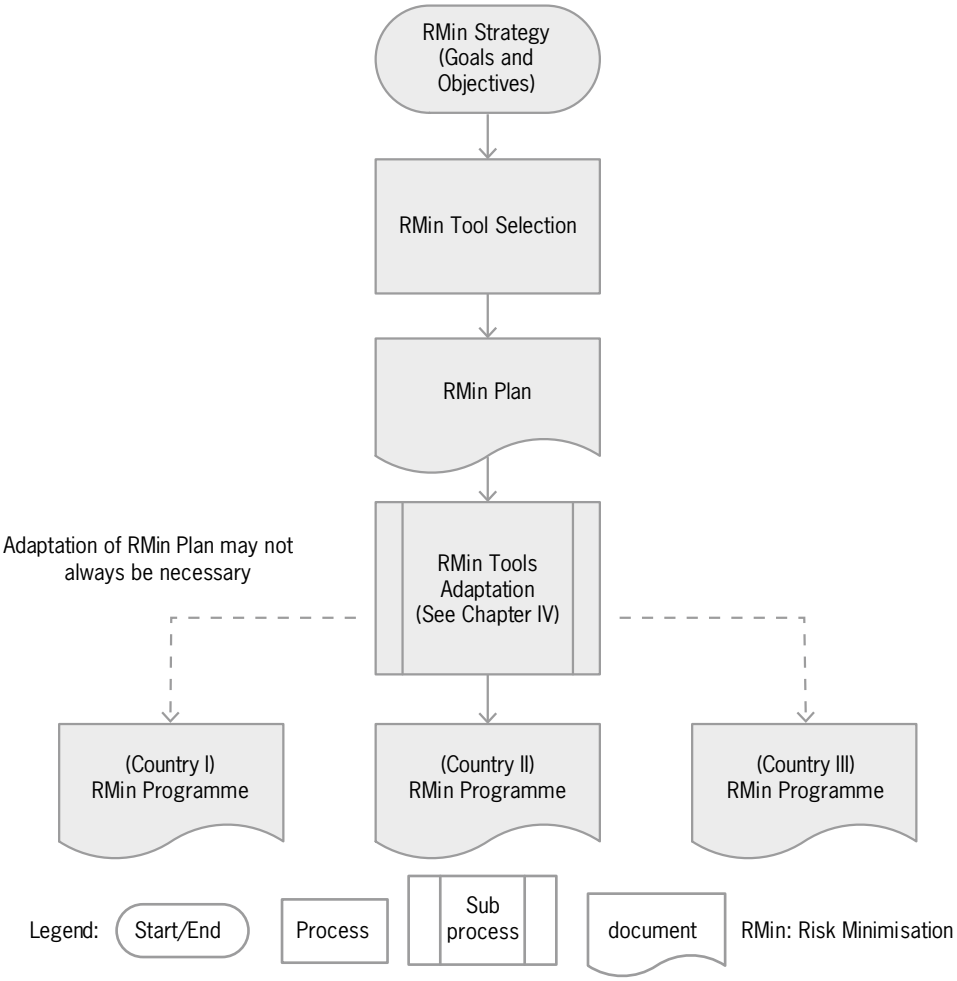
may also prevent or reduce access by a patient to a needed medicine. This principle indicates that effective risk reduction should proceed from an understanding of the end users **(1)**. See Fig. 3.2 on the *minimisation-burden balance*.

5. **Evidence-based risk minimisation:** Whenever possible, risk minimisation tool selection should be evidence-based, for instance through review of the scientific literature and competent authority websites, as regards tool effectiveness in achieving goals and desired objectives.

6. **Proportionality:** Risk minimisation tool(s) should reflect the *level of risk*, and should be aimed at the risk minimisation goals, objectives and targets. In addition, public health impact and benefit-risk balance acceptability are key considerations. See Fig. 3.1.

It is important to address missing information for any of the above points in order to achieve an accurate and complete analysis. In these circumstances, additional data gathering activities may be required to further characterise a given risk. As a result, the additional risk minimisation activities may be needed until missing information has been provided, which could support reverting to routine risk minimisation, continuing existing activities, or taking additional action.

Fig. 3.1: Overview of risk minimisation activities



B. Considerations in risk minimisation tool selection

• General guidance for tool selection

Risk analysis should include a determination of the circumstances under which risks might become manifested in the patient population, including all those covered by the therapeutic indication, or a selected subgroup, prior to specific risk minimisation tool selection. This systematic risk analysis can be facilitated via the use of certain methodologies such as Failure Mode and Effect Analysis [FMEA] and other techniques **(2, 3)**. (Please refer to Annex VII for an illustration of the application of FMEA techniques to a medicinal product).

Regardless of methodology, additional analysis should:

- Map the patient *journey* through the healthcare system , i.e. identify the steps involved in the healthcare delivery process for the patient from point of diagnosis, drug prescription to termination of therapy, including monitoring practices;
- Identify and characterise the points in the healthcare delivery system where processes may need introduction and utilisation of additional risk minimisation;
- Identify those stakeholders in the healthcare process who will eventually become the 'targets' for a risk minimisation intervention.

Any *clinically relevant* missing information, for any of the above must be addressed in order to achieve an accurate and complete analysis. Additional activities, such as pharmacovigilance, can further characterise a given risk, and as such, decisions regarding additional risk minimisation may be modified when missing information gaps have been addressed with relevant data.

• More specific considerations in risk minimisation tool selection

Risk minimisation goal

Once a risk and its level have been established, a goal must be set and linked to this important identified or potential risk with focus on its prevention and/or mitigation. For example, the risk minimisation goal for a teratogenic drug X could be 'to prevent exposure to drug X during pregnancy.' Goals should reflect a global strategy for risk minimisation.

Risk minimisation objectives

Generally, objectives will be set for *how a goal is achieved*, and can be focused on various activities including changing or modifying behaviour of patients, HCPs, or both, or educating users of a medicine to recognise early signs and symptoms of a particular adverse event so that earlier diagnosis and appropriate intervention can improve clinical outcome at the patient level. In relation to the above example of the teratogenic medicine, an objective could be to educate prescribers and patients on the key pregnancy prevention interventions that are needed for that particular medicine (e.g. contraception, pregnancy testing).

If the risk minimisation plan involves restricted access to a medicine, consideration should be given to how its objectives will be achieved and how it could impact access to the medicine by stakeholders.

Risk minimisation 'targets'

A risk minimisation 'target' is defined as the stakeholder or site for the risk minimisation intervention. For example, targeted populations are those who could receive an educational intervention geared to specific prescribers and/or patients regarding required monitoring in a scenario where a risk minimisation programme will utilise a new test that they are not familiar with. In this case, if the HCP is not familiar with how to perform a particular test, or how its results should be interpreted, some form of 'education' will be needed. Patients, on the other hand, may need to be informed that they will be monitored with a new test

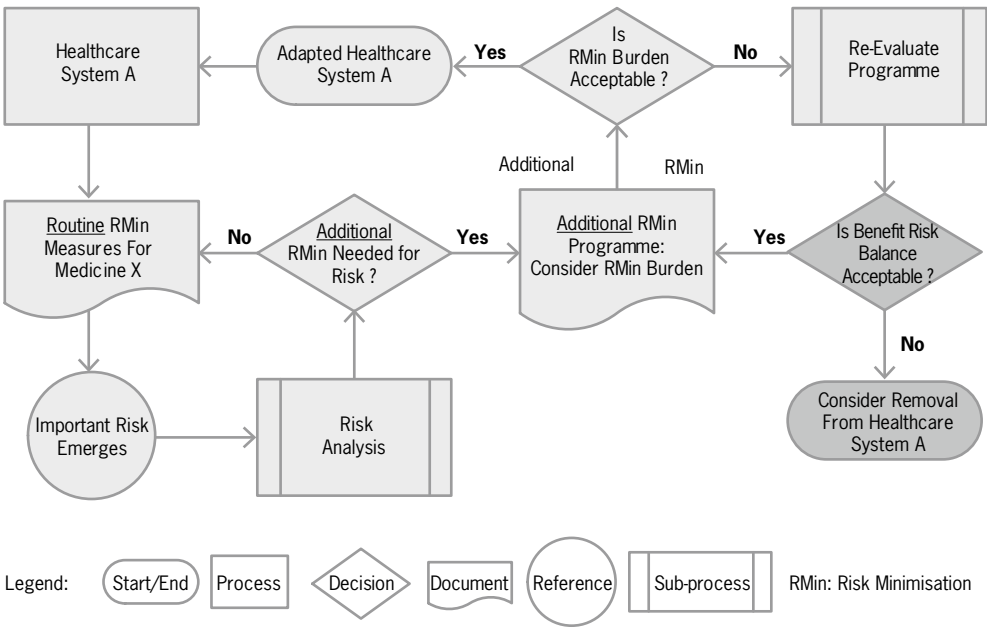
that is not yet 'standard of care' for the healthcare system they are using. This would be an example of an 'informed consent' tool for patients in the postmarketing setting outside of a clinical trial.

Failure mode and effect analysis (FMEA) or other methods can be used to determine appropriate targets for risk minimisation. Awareness of the process chain and regional cultural and medical practices of the relevant healthcare system may be needed to accurately select impactful tool targets. Regional variation is a very important component of appropriate tool selection since certain diagnostic monitoring tools may not be available in given regions/countries, or are prohibitively expensive, or are not considered 'standard of care'.

• Risk minimisation induced burden

An important caveat in risk minimisation tool selection is whether the tool places an impractical, unrealistic or undue burden on the patients, HCPs and/or the healthcare system. It is important to note that there is already a burden to a healthcare system due to risks that will regardless get absorbed and managed through 'usual' healthcare delivery in a given system ('routine' risk minimisation). When the 'usual' healthcare system cannot manage a particular important risk appropriately, additional risk minimisation should be considered. However, there may be a new burden induced by imposition of additional risk minimisation that can also impact the healthcare system in such way that it may not adapt to, and be able to deliver the intervention, which could ultimately defeat the goal of the additional risk minimisation. This scenario can be viewed conceptually as a *minimisation-burden balance*, which is dependent on the type and category of risk. See Fig. 3.2.

Fig. 3.2: Burden considerations and integration of RMin in healthcare systems



Risk minimisation imposed burden could include disruption of the normal, or usual, workflow of a healthcare system that may already be overtaxed in certain regions. For example, a risk minimisation tool such as a frequent blood test that is not readily available at a patient's usual healthcare centre, and as such will require an ill patient to travel long distances, might be overly burdensome. If there is an absolute requirement for a frequent specified blood test in this scenario, then home visits to the bedridden patient from mobile healthcare personnel could be a viable alternative. However, if the healthcare system is not equipped to deliver this service, for example, due to time, disruption of 'routine' care, staffing costs, etc., a risk minimisation programme will likely not be effective. Therefore, a risk minimisation programme needs to

consider these 'burden factors', and aim for a favourable minimisation-burden balance, in order to achieve effective risk minimisation without incurring undue burden on patients or the healthcare system.

Patient and HCP perspectives of a potential risk minimisation burden impact should be considered in the early phase of risk minimisation planning. This can be achieved using approaches such as the Delphi process **(4)**, where an iterative survey among a group of HCPs or group of patients afflicted with the same disease enables a consensus opinion on a scientific issue or topic to be reached. Selecting a risk minimisation tool with higher burden requirements should be reserved for those medicinal products that have the greatest potential for a favourable benefit-risk balance, as well as achievable objectives. The notion of proportionality between the measures proposed and the frequency and severity of the risk being minimised has to be considered in the development of a risk minimisation plan. Consultation of target stakeholder focus groups could be considered as part of the validation of a proposed approach.

Potential burden factors may include:

- *Individual vs. population* burden of tool application on relevant stakeholders (physicians, pharmacists, patients, industry, healthcare centres, regulators, and others).
- *Burden tolerance* will vary depending on a particular medicinal product's benefit, other available therapeutic alternatives, and the level of risk involved. A larger burden may be acceptable for a potentially lifesaving medication for an unmet medical need. Even in non-life-threatening indications such as acne, the benefit-risk balance may only be positive if a potentially burdensome risk minimisation tool is applied to manage a severe teratogenic risk of a medicine (e.g. female patients undergoing monthly pregnancy tests to establish they are not pregnant).
- *Prior stakeholder experience* with specific tools and combinations of tools will impact their fidelity to a given risk minimisation programme. It should be kept in mind that if a risk minimisation plan results in overly burdensome risk minimisation programmes, it is likely that prescribers will avoid the drug in question, or avoid the risk minimisation programme, and prescribe potentially therapeutically less effective alternatives.

C. Risk recognition, characterisation, and categorisation

Developing a risk minimisation plan involves multiple steps, and should take into consideration the healthcare system as well as regulatory, legal, and medical governance requirements which will have to be incorporated into a resulting risk minimisation programme.

For healthcare systems in particular, the level of 'standard of care' is an important variable that should be considered when designing a risk minimisation programme. This is especially regarding the feasibility of introducing risk minimisation tools which are normally not available, or not used routinely, in a particular healthcare system.

Healthcare systems usually include hospitals, clinics, chronic care facilities, and other healthcare delivery institutions for populations residing within a particular region. They may be specialised for particular patient populations or may be general healthcare delivery institutions. These systems may have been directly designed and organised by governments, private institutions or combinations thereof, or they may have developed randomly, often in order to meet the needs of a rapidly growing population, or due to budgetary reasons. As a result, notions and concepts of what is 'state of the art' and what is the 'standard of care' may vary, and even fluctuate regionally. Risk minimisation tool selection should be based on a logical sequence of decision points (see Fig. 3.3) that is driven by facts, data, and analysis, whilst taking regional or national variations into account.

Risk recognition

No medicinal product is without risk **(5)**, and it is clearly a matter of having a process in place that enables the recognition of an emerging (or previously undetected) risk, especially in the postmarketing setting where greater numbers and more diverse people are exposed to the medicinal product than in clinical trials. It is the responsibility of industry, competent authorities, and healthcare systems to contribute to and maintain ongoing pharmacovigilance activity, e.g. 'signal detection' and any other means of risk recognition. An initial part of this process often includes triage within the signal detection process (see Fig. 3.3).

Risk characterisation and categorisation

Risks may be inherently part of the patient's biological/clinical profile, where there can be predisposition to be afflicted with a given adverse drug reaction (ADR) due to any number of circumstances. For example, a patient may have an underlying cardiovascular disease with QTc interval prolongation and be at risk of developing a cardiac arrhythmia when exposed to a particular drug. In a different scenario, a patient may not have any biological risk for developing an ADR, but due to a problem with healthcare system dynamics, may be exposed to unsafe or ineffective use of a medicine, for instance through a medication error.

Any risk associated with a medicine needs to be thoroughly characterised and subsequently categorised according to the level of supporting scientific evidence. Designation of risk level will include the dimensions of **severity** and **likelihood of occurrence**, both of which drive **public health impact** and effect on the **benefit-risk balance**. Risk characterisation is a prerequisite to appropriate categorisation. Categories used in current EU guidance documents, for example, address these concepts by distinguishing between identified risks, potential risks and missing information *(level of evidence)* and importance *(level of risk)*. (See Chapter I).

The CIOMS VI Working Group recommended the concept of safety management teams (SMTs) for risk management **(6)**. Such a responsible team should collect all available facts, identify missing information, and provide an impact analysis. Risk characterisation and categorisation actions rely on availability and reliability of relevant data. For older marketed products, this may be challenging since relevant data may be less robust than required as they may have been produced and evaluated based on different scales, regulatory approaches and healthcare settings that have evolved over time. For newer products, the challenges are different due to the shorter timeframe for any data collection and uncertainties from real world experience that still need to be assessed.

D. Basic assessment of risk prevention and mitigation

Apart from routine and additional pharmacovigilance data needed for filling knowledge gaps and missing information, there should be an initial assessment of a risk's potential for prevention and mitigation. If it is determined that a risk cannot be prevented in some or even all exposed patients, an analysis of potential mitigatory actions will be needed. Risk impact analysis will lead to an initial consideration of how to manage the risk. As mentioned previously, techniques such as FMEA can be utilised to analyse the patient care process to determine 'failure modes,' which will help determine where risk minimisation actions may be most important. This should include identification of the key stakeholders involved, some of whom may become the risk minimisation 'targets' for risk prevention and mitigation actions.

Risk prevention

Risks can sometimes be prevented in individual patients if testing is available (e.g. a specific biomarker screen) to identify those who will be more likely to have a particular adverse drug reaction (ADR). For these patients, one can consider this to be absolute risk prevention, which implies that the population at risk will not be exposed to the medicine because they were excluded. In the clinical trial setting, exclusion criteria may be applied in this manner.

In the postmarketing setting, removing access to a medicine would achieve a risk prevention goal. However, this also effectively eliminates any potential benefit that an affected patient may have derived from the medicine, and as such the patient would have to seek another therapeutic alternative, if available. This brings in the context of benefit-risk balance into play since the therapeutic alternative may be less efficacious than the medicine with the risk of ADR and therefore, *the risk of inferior benefit or treatment* becomes a concern. Clearly, the medical need and importance of a required therapy must be weighed against the risk of ADR in this setting.

Examples of risks amenable to risk prevention include medication errors where measures are taken to ensure appropriate use of the medication. Other preventable risks can be those where a co-medication is given that will prevent a reaction that would otherwise possibly arise when the medicine is taken. This is the case, for instance, when leucovorin (folinic acid) is administered to patients taking methotrexate to prevent anaemia and other adverse effects caused by methotrexate, which is a structural analogue of folic acid. Of interest, leucovorin is also used to treat (mitigate) methotrexate overdose and, as such, acts as an antidote.

In contrast, the concept of an *unpreventable* risk should be distinguished. Unpreventable risk has been defined as a *'complication that cannot be prevented given the current state of medical knowledge'* **(5)**. An example of this could be idiopathic reactions without any known risk factors, which would not be amenable to any form of risk prevention. Another example of an *unpreventable* risk could be mechanism-related adverse reactions that are not preventable at the doses needed for efficacy. For those risks that can be prevented, risk minimisation would be to decrease frequency of the risk *per se* or decrease the exposed population at risk through awareness of and/or compliance with conditions for appropriate use.

As previously mentioned, there are risks that cannot be entirely prevented, such as aplastic anaemia that can develop with exposure to chloramphenicol. Once it has occurred, risk mitigation becomes more difficult since it is an idiosyncratic reaction that occurs irrespective of dose **(7)**. Also of note are medicines with a *cumulative* effect (and thereby representing potential *cumulative risk*) such as chloroquine, which can be monitored for cumulative total dose to prevent reactions such as cardiomyopathy. This is important especially since chloroquine-induced cardiomyopathy may be reversible if detected early **(8)**. Another example of a medicine with *cumulative risk* potential involves methotrexate and hepatotoxicity **(9)**.

Risk mitigation

Effective risk mitigation depends on appropriate monitoring *during therapy*, and occasionally *after* the medicine has been stopped – for those medicines with long-lasting effects. The potential for early recognition of possible signs and symptoms that enable the patient to alert the HCP or to take actions and avoid progression to irreversible harm is an important characteristic of a risk because it offers an opportunity for early detection and harm reduction. For example, petechiae in immune thrombocytopenia, or a tingling sensation in peripheral neuropathy, could possibly enable the application of measures to further mitigate risk. This could include information about early recognition, so that risk mitigation measures can be provided to patients, for instance via patient alert cards, web-based materials, or visualised information on electronic data carriers. In addition, information could be provided to HCPs to make them aware of the importance of early detection of signs and symptoms, such as monitoring liver enzymes through designated lab testing intervals, thereby allowing for dose reduction or discontinuation of the medicine (temporary or permanent) should the liver enzymes become elevated according to parameters set for the medicine in question.

Other methods of risk mitigation can be demonstrated with medicines that can be administered with incremental dose increases in order to monitor effect and possibly reduce development of a severe ADR.

The ability to detect early manifestation(s) of a risk is more problematic in certain vulnerable populations who may lack sufficient language capacity, e.g. non-native speakers, very young children**,** people with developmental disabilities or comatose patients **(10)**. In addition, HCPs and others involved with patient care may differ in their interpretation and terminology of adverse events, which may produce further obstacles in risk communication **(11)**. Reversing signs and symptoms that have resulted from an ADR ('risk reversibility') refers to the possibility of mitigating the ADR by taking specific actions. One of the first steps in mitigating an ADR is dose reduction or drug discontinuation in an attempt to halt progression and/or

reverse the ADR entirely. At times, depending on the indication (benefit), it may be necessary to discontinue a drug or possibly treat the ADR until it has abated and then attempt a re-challenge to continue treatment.

Risks that cannot be prevented or mitigated

Most risks cannot be entirely eliminated; however they may still be reduced in severity and possibly frequency with an appropriate risk minimisation plan. If an important risk is neither preventable nor mitigable, it should then be assessed from a benefit-risk perspective taking acceptability into account for those stakeholders involved, usually the patients and HCPs.

In the situation where the benefit-risk balance is acceptable for a risk that cannot be minimised or prevented, an active approach for risk communication beyond standard product information should be considered to heighten risk awareness and allow for proper individual benefit-risk discussion. An example could be a severe idiopathic risk that requires additional communication measures such as educational activities, or patient informed consent (outside of the clinical trial setting as described previously).

Adverse drug reactions that cannot be mitigated or reversed require the tool selection goals and risk minimisation 'targets' to be aimed at ensuring awareness of the risk (seriousness, probability, and consequences), and to provide appropriate information, including the availability and benefits of other therapies, for the benefit-risk decision-making process. Patient stakeholders should be fully informed and have an opportunity to discuss benefit-risk within this context with their HCPs. Individual patient preferences in regard to accepting or tolerating certain risks in exchange for specific benefits should play a key role in determining whether a patient receives the medication.

Circumstances may lead to the ultimate decision of removing a drug from the market if the above actions cannot be applied or are proven ineffective to maintain a positive benefit-risk balance.

E. Selection of risk minimisation tools and tool types

General steps

The tools selected for a risk minimisation programme should be in line with the goals, objectives and risk minimisation 'targets' of a given risk minimisation strategy, that will reflect the optimal possibility of achieving a decrease in risk severity and/or frequency. Again, there should be an evaluation of which key stakeholders are involved, as well as the context of how the risk occurs within the healthcare system(s) and populations that may be exposed, taking any relevant regional and country considerations into account.

Initial steps in tool selection can include the following considerations:

- **Evidence:** Conducting a comprehensive published literature and competent authority website search, to determine what types of tools and risk minimisation programmes, if any, have been used for similar risks is a key consideration. At the time of publication of this book, there is a paucity of data evaluating risk minimisation plan effectiveness, especially regarding outcome indicators (please see Chapter V on measuring effectiveness). Regional variation to potential risk minimisation programmes should also be considered since tool availability and effectiveness may differ between countries and regions.
- **Stakeholders:** Engaging key stakeholders (e.g. via in-person interviews or focus groups) to generate concepts in regard to which risk minimisation tool types to use, is an important consideration, especially regarding the level of potential burden that would be imposed, and subsequent level of acceptability. Here again, using methodology such as the Delphi process can help achieve this step **(4)**.
- **Healthcare system(s):** There should be an analysis of the targeted healthcare systems to determine where risk minimisation tools could be incorporated most easily and effectively. Here, the potential for adaptation must be considered as there are many variations to healthcare systems from country to country and possibly within the same given jurisdiction. For example, the possibility of restricting prescriptions to hospitals and particular medical specialists varies between different healthcare systems.

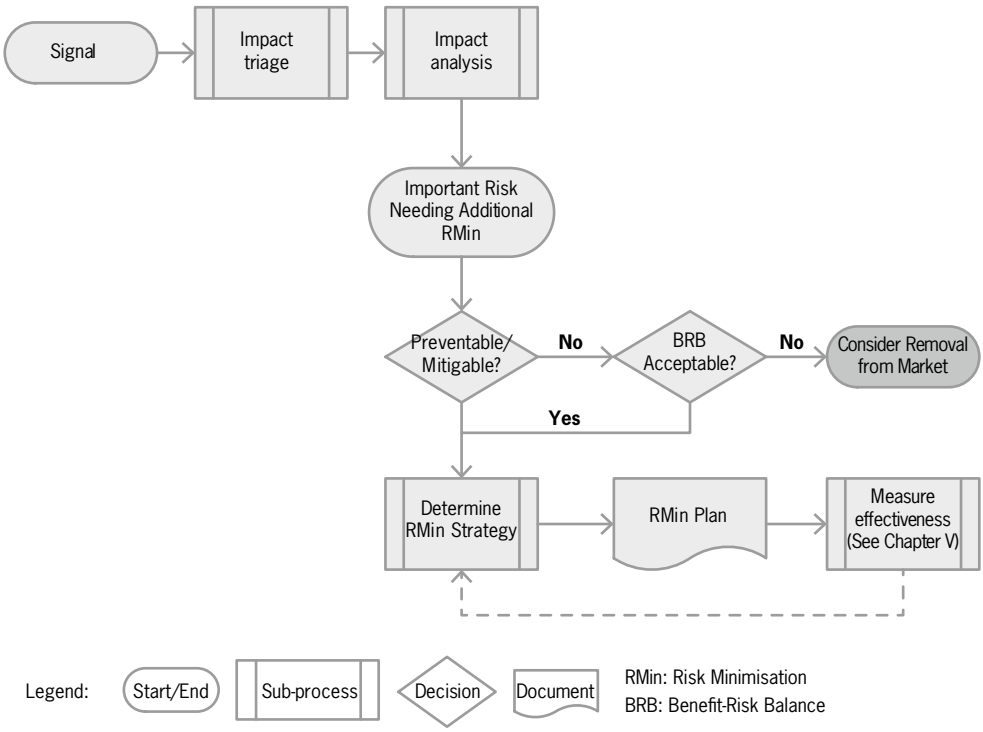
Specific tool selection

Practically speaking, one of the first questions that must be addressed is whether a risk minimisation programme will incorporate an activity/tool that will be utilised: 1) before administration of a medicine, for instance, a screening test or exclusion criterion, or 2) during therapy, such as monitoring specific laboratory values or detection of early signs or symptoms to avert potentially more serious drug-induced injuries. There may be situations where risk minimisation will be needed both before and during therapy. This will be dependent on the medicine, the nature of the risk, and approach necessary to apply risk minimisation.

Once the decision has been made as to when the risk minimisation activity will take place, consideration should be given to geographical regions or national areas, standards of care and healthcare systems. For example, if a biomarker test is selected for a given risk minimisation programme, there needs to be verification of how the test is used in the various locations by the HCP targets.

A high-level schema of applying a risk minimisation strategy from detecting an important risk to measuring effectiveness of additional risk minimisation measures, is presented in Fig. 3.3 in the format of a decision tree or algorithm.

Fig. 3.3: Risk minimisation decision algorithm



Tool types

Once it is determined by a drug manufacturer or after consultation with a regulatory agency that an important risk requires additional risk minimisation, a number of factors will need to be considered to guide risk minimisation tool selection:

- level of risk
- objectives of risk minimisation
- 'target(s)' for risk minimisation intervention
- characteristics of prescribers (e.g. specialists vs. generalists)
- characteristics of potential patients (e.g. vulnerable population, possible limited access to proposed interventions)
- regions involved (especially regarding 'standard of care')

Consideration should be given to what will potentially be the most effective tool to achieve the objective(s). There are numerous types of risk minimisation tools, and appropriate matching of certain tools to a given risk is essential for optimising effectiveness in relation to the set goal, which can help optimise time and resources. *One tool could address more than one objective and an objective could be addressed by more than one tool.*

A comprehensive risk minimisation approach may often require a combination of risk minimisation tools, depending on severity of risk and whether the risk can be minimised and/or mitigated. Generally, as the level of risk associated with a medicine increases, the tools needed to ensure safe use of the medicine are likely to be more prescriptive and/or restrictive. *Selection of tool types should be commensurate with risk and the possibility to prevent (or reduce) its frequency and/or severity.*

Tool types will fall into specific risk minimisation strategies that include communication, restricted access, controlled regulatory framework, and manufacturing restrictions. Registries, which are not risk minimisation tools, play a role as a strategy where specific risk minimisation tools *per se*, can be incorporated and implemented.

• Communication – Additional information and education (including training)

Communication is a useful additional risk minimisation strategy to consider whenever routine product information is deemed insufficient. It should be used for an important risk where heightened awareness of circumstances for use beyond routine product labelling may minimise or mitigate a risk. There are different levels of intensity, outreach and compliance measures that can be applied within a communication plan. In the U.S., Medication Guides are a type of product information required in addition to routine measures, when the FDA determines that for better patient health and adherence purposes, a certain product needs to have additional risk minimisation information distributed to the patient when the medication is dispensed. A communication plan can include additional informational material tools such as a Direct Healthcare Professional Communication (DHPC), also known in the U.S. as Dear Health Care Provider (DHCP) Letter, Dear Health Professional Society Letter, or educational programmes, including voluntary training programmes, training programmes with voluntary certification, mandatory certification, or a reminder system. See Table 3.1.

Table 3.1: Communication tools

	Advantages	Disadvantages
Dear Healthcare Provider Letters: Information	• Fast information dissemination. • Broad outreach.	• Effect fades if no labelling changes. • Variable impact on prescribing. • Patient input usually not sought.
Prescribing/ dispensing guides and targeted outreach to HCPs: Education	• Enhances prescriber knowledge. • May be clinically useful. • Can be integrated into CME* activities. • Can be kept/used as reminder. **CME = Continuing medical education.*	• Requires periodic reassessment and updating. • Can be burdensome to prescribers. • Requires consistency with labelling. • May not be suitable for all countries. • May be perceived as marketing tool.
Patient brochures and targeted outreach for specific patient populations: Information or Education	• Patient empowerment with proper directions. • May enable early recognition of AE* with resulting earlier treatment. **AE = Adverse effect.*	• Requires periodic reassessment/updating. • May not be suitable for all countries. • Impact yet to be established. • Health literacy dependent. • Can be burdensome for dispensers. • May be perceived as marketing tool.

Situations in which educational components of targeted communication could be considered:

- When risk minimisation is possible through the more appropriate use of the product and better handling of complicated administrative procedures requiring additional demonstration and understanding;
- When risk mitigation is possible through better recognition of potential signs and symptoms with resulting prompt management of any idiosyncratic reactions.

• Restricted access – Reminder systems

Restricted access tools such as requirements for physician certification or frequent patient testing before dispensing, carry significant burden, and should be used for circumstances of serious risk where significant benefit can be derived (see Tables 3.2 and 3.3).

Table 3.2: Restricted access – Reminder systems

	Advantages	Disadvantages
Patient agreement / consent	• Informed patient consent. • Standardisation of the info received at treatment initiation. • Can allow documentation of informed consent.	• Burdensome for prescribers or dispensers. • May discourage some patients. • Limits availability and accessibility. • Unintended consequence of diversion to other options.
Registration programmes for wholesalers and retailers, e.g. restricted pharmacies distribution	• Standardisation of information to a limited number of distributors. • Increases likelihood of "authorised" information dissemination to healthcare professionals. • Fosters prescribing/dispensing compliance.	• Burdensome for wholesalers/retailers. • May overly restrict drug use for patients by prescribers/dispensers.
Certification programmes for HCP (physicians, pharmacists)	• Standardisation/ systematisation of product use.	• Burdensome for prescribers. • May discourage product use.
Limited amount/prescription or number of prescriptions or limited amount/pack	• Decreases availability, so may decrease consequences of accidental and/or intentional overdose. • Promotes regular follow-up of patients at risk of ADR.	• Decreases availability. • Less convenient for patients who require multiple doses. • Increased cost.

Restricted access should be limited to particularly important risks in those rare scenarios where:

- heightened awareness of circumstances of use is not sufficient, but where compliance measures are required. In these cases the choice may be between ensuring knowledge of the circumstances for use (physician certification), or actual compliance measures in enforcing circumstances for use (e.g. 'no blood, no drug' approach for clozapine);
- risks are expected to be minimised by these interventions; or
- a clear therapeutic need for the product and significant benefit can be derived (e.g. treats a serious/ life-threatening disease without alternative therapies, and has a documented advantage over existing therapies or documented efficacy where alternative therapies have failed).

• Restricted access – Performance-linked access systems

Table 3.3: Restricted access – performance-linked access systems

	Advantages	Disadvantages
Product access linked to laboratory tests results (e.g. biomarker or drug blood level)	• Prevents unintended exposure. • Addresses benefit-risk balance. • Effective when other risk management systems have been shown to be ineffective.	• Burden on the health care system. • Restriction of health care professional autonomy. • Economic and benefit-risk impacts often not assessed. • May result in reduced prescription levels and patients discontinuing.
Prescribing allowed only by (board-certified) specialist physicians	• Use optimised by requiring prescribers with specialised knowledge. • Should help limit misuse.	• Access to specialist may be limited in certain area (e.g. rural). • Access limited in certain healthcare systems (e.g. delays, need for referral).
Prescribing/reimbursement allowed only when drug prescribed within the indication (no off-label use)	• Very limited and specific indication can help optimise product use. • May help reduce off-label use.	• Very limited and specific indication may prevent use in some patients.
Prescribing allowed only to patients with right pharmacogenomic profile	• Patient selection to optimise benefit and/or minimise risks. • Personalised treatment. • Enables exclusions of nonresponders for which the benefit-risk is always negative. • Enables products for which the toxicity is identifiable to still be available on the market.	• Absence of data on use in certain genotypes (orphan genotypes). • Relies on genetic testing availability (cost effectiveness, approval). • Data on test sensitivity/specificity not always available. • Increased costs. • Benefit-risk assessment of testing is often not available.

• Controlled regulatory framework

Restriction of a drug through a regulatory framework can also be applied when there is clearly a significant public health impact, and distribution of the drug requires control in order to help ensure that only those patients who need the medication receive it. Availability of this regulatory option will vary by jurisdiction. In the worst case scenario, a drug can be removed from the market with this form of risk minimisation. See Table 3.4.

Table 3.4: Controlled regulatory framework

	Advantages	Disadvantages
Drug restriction through regulatory scheduling e.g. narcotic and controlled drugs, prescription drugs	• Helps control distribution. • Introduces one or more safety checks. • Fosters benefit-risk discussions between patient and healthcare providers.	• Burdensome for prescribers and/or dispensers and patients. • More difficult for outpatient settings.
Ordering product to be withdrawn from market	• Eliminates exposure to risk. • Attracts public attention to risk through media attention.	• May damage manufacturer and regulatory authority reputation. • Perception of failure to properly manage risk. • Product unavailable to all patients. • Increased costs of product recall and production line shutdown. • Unintended consequence of diversion to less appropriate prescribing options.

• Manufacturing restrictions

Manufacturing restrictions allow for the use of risk minimisation tools that can be applied by modifying the physical appearance of the drug, its packaging or its dosing. This type of risk minimisation action has been used with some opioids and can also be applied to non-prescription medications and may be incorporated prior to introduction to the market. See Table 3.5. In some jurisdictions aspects of this risk minimisation tool such as pack size are considered as routine risk minimisation.

Table 3.5: Manufacturing restrictions

	Advantages	Disadvantages
Low dosage formulations	• Reduces unintentional or intentional overdoses. • May reduce misuse of product due to lower concentrations.	• Requires more frequent prescription filling. • May increase costs to manufacture through changing production methods or adding production lines. • May increase packaging costs.
Colour/shape coded dosages	• Improves product recognition by patients. • Reduces unintentional ingestion.	• May increase manufacturing costs through changing production. methods or adding production lines.
Restricted packaging	• Reduces unintentional ingestion by children.	• May increase manufacturing costs. • Could be problematic for elderly or physically impaired patients.

Special strategy settings: Registry

A drug or patient registry can have a broad range of compliance measures applied to it based on the level of risk to be minimised. Registries tend to be used primarily for risk assessment, but occasionally

a registry can be part of a risk minimisation programme, if the intent is to apply risk minimisation tools that intervene with routine clinical practice, rather than just collect clinical data. This could be the scenario when a patient must register before receiving a particular drug.

Registries, therefore, are not a risk minimisation strategy *per se*, but allow a controlled setting for inclusion of risk minimisation activities and may or may not be mandatory. For example, if training of prescribers is mandatory (i.e. a registry of certified prescribers), then the risk minimisation tool connected with this registry is considered to be a restricted access programme, and if it is optional then it can be considered to be an educational programme.

A registry can be patient-based, disease-based, or product- based and can involve data collection. It may also be put in place to ensure compliance with risk minimisation interventions, in which case, as with all risk minimisation programmes, increasing levels of risk minimising tool intensity and restrictiveness may be introduced if measures of success are not met.

• New tool development

Risk minimisation tools that have been used effectively before may be adapted and re-applied to a different medicine with a similar risk. However, if a tool type has been selected that is novel or untried for a new risk, a prototype should be developed and tested iteratively with individuals from the target user group. If the tool has an informational or an educational component for patients, consideration to the design and formatting of information, with attention to literacy and numeracy issues is critical. Tool prototypes should undergo both formative and summative (validation) testing. A variety of qualitative and quantitative methods are appropriate for use at this stage. Following the development of a final draft version of the tool, pilot testing should be undertaken in as close to 'real world' circumstances as possible. Based on the pilot results, the tool can be revised and/or modified as needed to optimise usability. Best practice should also be applied in human factors usability.

Ideally, marketing authorisation holders (MAHs) should allocate sufficient time for this process, which could take many months to execute and roll out, depending on the proposed tool. The safety management teams (SMTs), as recommended in CIOMS VI **(6)** and further elaborated in this book (see Chapter IV on Governance and Implementation), may be involved in the risk minimisation tool development process.

In order to promote successful regional/local implementation, it is very important to involve, as far as practical, regional representatives and medical key opinion leaders of the countries where a particular risk minimisation tool will be used, to have an early and better understanding of feasibility. For example, if a given screening test in a risk minimisation programme is 'standard of care' in certain countries, but not in others, the dividing line between what is 'informational' material vs. 'educational' material about the test for a patient and HCP will be availability and familiarity with the screening test. If a particular healthcare system does not utilise the designated screening test, then material with an educational focus is more appropriate.

F. Examples of risk minimisation tool selection

Risk prevention example

The use of a biomarker (HLA-A*3101 in Europeans and HLA-B*1502 in Asians) to identify patients at greatest risk for the development of Stevens-Johnson Syndrome (SJS) and its more severe variant, toxic epidermal necrolysis (TEN), associated with carbamazepine exposure has been described in the literature **(12, 13)**. There is a strong association between the presence of these alleles in the respective racial groups and the potential risk of SJS–TEN in patients who receive carbamazepine. Patients who tested negative for the alleles did not develop SJS–TEN. The application of the biomarker screening as a risk minimisation tool has been implemented in most hospitals in Taiwan, where one of the studies took place. The epidemiological expectation will be a greatly reduced incidence of SJS–TEN due to carbamazepine

at these hospitals. However, screening for specific alleles may not be applicable for other drugs based on current scientific knowledge.

Risk mitigation example

An example of risk mitigation involves the monoclonal antibody natalizumab (Tysabri©), which was developed to treat multiple sclerosis. Natalizumab use is associated with the development of progressive multifocal leucoencephalopathy (PML), a rare but potentially life-threatening infection affecting the central nervous system. In order to facilitate early detection of PML, the MAH has additional risk minimisation tools in place, which include educational materials aimed at HCPs and patients. These materials address signs and symptoms that are suggestive of development of PML, as well as recommendations for diagnostic workup when clinically indicated. The objective of these risk minimisation tools is to help provide early diagnosis of PML. If PML is detected early, natalizumab therapy can be stopped and the drug removed from the body by a technique called plasma exchange. This is important since natalizumab has a very long-lasting effect within the body. In addition to these risk mitigation tools, the MAH has developed a risk stratification algorithm that comprises duration of treatment (>two years), prior immunosuppression, and a positive biomarker (positive serology for the John Cunningham or JC virus). The risk of developing PML whilst on natalizumab appears to be much higher when all these three risk factors are present, thus allowing HCPs and patients to have an informed discussion on benefits and risks of continuing natalizumab treatment. For more details of the natalizumab risk minimisation programme, please refer to Annex III Real-Life Examples.

Finally, another example of risk mitigation is clinical 'desensitisation' after resolution of an adverse drug reaction (ADR) with incremental doses of the suspect drug, which has been carried out with medicines such as trimethoprim/sulfamethoxazole **(14)**. This is an especially important form of risk minimisation when the medicine, in this case, an antimicrobial combination, has a clear and substantial benefit; trimethoprim/sulfamethoxazole is critical in preventing certain opportunistic infections, including those occurring in human immunodeficiency virus (HIV)-infected patients. This clinical risk minimisation method is dependent on the drug and indication/severity of disease in question **(15)**. If this methodology is applied to another drug where there may be no experience or familiarity, educational material for the HCP should be considered and incorporated into the risk minimisation plan.

G. Conclusions

Risk minimisation, in the context of managing important risks that require additions to routine activities, is fast becoming an area that will require resources, time, and further development in order to have a significant impact on patient safety and public health. There will likely be more scientific developments that can be applied to risk minimisation, such as recognition of relevant genomic types and other biomarkers. Furthermore, ongoing risk minimisation programmes may themselves evolve and demonstrate how to best manage risks based on a feedback loop that evaluates effectiveness.

Points to consider:

- CIOMS IX has put together general principles that should be followed when developing a risk minimisation programme. In selecting and developing risk minimisation tools, the MAH should consider several factors including the regulatory environment, public health considerations, benefit-risk acceptance by stakeholders, healthcare systems, and prior knowledge and experience with similar or even the same risks.
- These principles will lay down a foundation for a global strategy that will include the goals, objectives and 'targets' for a given risk minimisation programme.
- Important risks need to be understood from a perspective of what will be needed to minimise them, and what tools to use so as to have the greatest impact on such risks, to ultimately promote the safe and effective use of a medicine.

- Risk minimisation tool selection can be challenging, and requires an understanding of the tool or tools that will be applied, including their advantages and disadvantages.
- A global strategy on risk minimisation including global goals and objectives should provide the framework for local applicability and implementation of a risk minimisation programme.

Recommendations

- Risk minimisation tool selection should be based on an organised process.
- Risks should be assessed for their impact or potential impact on benefit-risk as well as the ability of a risk minimisation strategy to prevent or reduce the severity of one or more specific adverse drug reactions.
- The risk minimisation tool(s) and strategy proposed should be proportionate to the level of risk.
- Tools should be selected based on the expectation that they will have an appropriate as well as an expected effect and meet objectives whilst avoiding undue burden on key stakeholders and the healthcare system.
- As far as practicable, risk minimisation tools should be designed to fit within an existing applicable regulatory structure, patient care environment, and healthcare system.
- Initiation of tool application should be based on whether the tool (intervention) is part of the 'standard of care' in the healthcare system, progressing to higher levels of risk minimisation if the tool is not standard of care or lower level interventions are assessed to be ineffective.
- Regional and national variations of risk minimisation programmes can impact their adaptation and implementation, so it is important to bring in these aspects early in the discussion.
- Burden factors on patients and the healthcare system need to be considered for all additional risk minimisation programmes as they can potentially impact programme effectiveness as well as access to medicines.

H. References

1. ICH Q9 harmonised tripartite guideline: Quality risk management. EMA/INS/GMP/79766/2011. London, UK: European Medicines Agency, 31 January 2011.
2. Wood DF. ABC of learning and teaching in medicine: Problem based learning. BMJ. 2003, 326 (7384): 328–330.
3. Rodriguez E, Heaton S. Bayer HealthCare's experience in drafting development risk management plans during the drug development process. Originally published in e-journal Drug Development. 2008, 54–55 (available from http://webprofile.info/erodriguez/Heaton.pdf, accessed 30 April 2014).
4. Hsu CC. The Delphi technique: Making sense of consensus. Practical assessment research and evaluation (a peer-reviewed electronic journal). 2007, August, Vol. 12, No. 10, (http://pareonline.net/pdf/v12n10.pdf).
5. Moore N. Assessing drug safety. BMJ. 2005, 330:539.3.
6. Management of safety information from clinical trials. Report of CIOMS Working Group VI. Geneva, Switzerland: CIOMS. 2005.
7. West BC, DeVault GA, Clement JC, Williams DM. Aplastic anemia associated with parenteral chloramphenicol: Review of 10 cases, including the second case of possible increased risk with cimetidine. Reviews of Infectious Diseases. 1988, Vol. 10, No. 5: 1048–1051.
8. Costedoat-Chaumeau N. Cardiomyopathy related to antimalarial therapy with illustrative case report. Cardiology. 2007, 107: 73–80.
9. Kevat S, Ahern M, Hall P. Hepatotoxicity of methotrexate in rheumatic diseases. Med Toxicol Adverse Drug Exp. 1988, May-June 3(3): 197–208.
10. Chandrika D. Language proficiency and adverse events in US hospitals: A pilot study. International Journal for Quality in Health Care. 2007, Vol.19, No. 2: 60–67.
11. Reporting adverse drug reactions: Definitions of terms and criteria for their use. Report from a series of international working groups convened by CIOMS. Geneva: CIOMS. 1999.
12. Chen P, Lin JJ, Lu CS, Ong CT, Hsieh PF, Yang CC et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. N Engl J Med. 2011, 364: 1126–1133.
13. McCormack M, Alfirevic A, Bourgeois S, Farrell JJ, Kasperavičiūtė D, Carrington M et al. HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. N Engl J Med. 2011, 364: 1134–1143.
14. Yoshizawa S, Yasuoka A, Kikuchi Y, Honda M et al. A 5-day course of oral desensitization to trimethoprim/sulfamethoxazole (T/S) in patients with human immunodeficiency virus type-1 infection who were previously intolerant to T/S. Ann Allergy Asthma Immunol. 2000, September 85(3): 241–244.
15. Solensky R. Drug desensitization. Immunol Allergy Clin North Am. 2004, August 24(3): 425–443.

CHAPTER IV:

GOVERNANCE AND IMPLEMENTATION

A fundamental requirement for any marketing authorisation holder (MAH) –usually a pharmaceutical company– is to have in place appropriate internal governance and operational infrastructure at the central and affiliate offices to support effective execution of risk minimisation activities throughout the organisation. In this respect, governance relates to the cohesive policies, guidance, processes and oversight needed in order to assure consistent standards at a global, regional and national level. Although the risk minimisation strategy is generally set centrally, implementation will occur at a regional and national level by affiliates/ local operating companies, where the activities are carried out in 'real world' conditions by healthcare professionals and programme administrators charged with this responsibility. Proactive communication, development of guidelines for affiliates, and including a clear delineation of respective roles and responsibilities and monitoring of the implementation process, are therefore very important.

The primary focus of this chapter is to give practical advice on these various aspects, with a focus on pharmaceutical companies whose responsibility as MAHs is to set up adequate controls and oversee consistent implementation of their risk minimisation programmes. However, this chapter could also be informative to other readers including the regulatory authorities who have an interest in the effective implementation of risk minimisation programmes on a global, regional and national basis.

A. General considerations

Unlike pharmacovigilance activities which have a circumscribed scope, the task of developing and implementing risk minimisation activities will typically involve a more diverse group of professionals, many of whom reside outside the traditional medical or regulatory functions. This requires strong cross-functional collaboration, communication and coordination, a model increasingly used, especially taking into account recent developments in periodic reporting such as the Development Safety Update Report (DSUR - CIOMS VII and ICH E2F) and the Periodic Benefit-Risk Evaluation Report (PBRER – ICH E2C (R2)).

A further challenge in multinational organisations is the implementation of a global ("core") risk minimisation strategy/plan for a particular product. In such instances, even in the face of an agreed global or regional risk minimisation plan, multiple affiliate and marketing functions (for whom the regulatory requirements agreed with the authorities will not always be known or understood) are likely to be responsible for actual implementation. The situation is further complicated by the fact that implementation is largely undertaken at a national level where differences in healthcare systems, regulatory and cultural differences, will impact on what is and what is not considered appropriate in a given country (e.g. use of registries to restrict access to an approved product.) Some degree of variation in how local risk minimisation activities are implemented, therefore, is to be expected and must be managed as part of the overall planning process. Flexibility in the system is necessary provided that the core goals of the plan and appropriate conditions of safe use can be met. This will be particularly relevant for a region like the EU. Part of the process will involve seeking review and input from the local regulatory authority; from a compliance perspective, any agreements with individual regulatory authorities should be documented, irrespective of local regulations. As a result of these factors, it is important to establish clear and effective processes for coordinating activities at the central office and across affiliates and local operating companies.

B. Governance considerations

Risk minimisation procedure

In the same way that the CIOMS VI report **(1)** recommended a systematic approach to managing safety during clinical development, the CIOMS IX Working Group advocates a similar approach to risk management planning overall and risk minimisation implementation in particular **(2-7)**.

Pivotal to this approach is the creation of a procedure or set of procedures that will:

- Describe the process for designing the overall risk minimisation strategy (core risk minimisation plan) and the regional/national risk minimisation plans that detail actions to be taken in order to implement such a strategy at the local level;
- Allow for early input from affiliates to assess the practicalities of the proposed risk minimisation tools within their particular country;
- Describe the process for implementing and executing local risk minimisation programmes;
- Describe the process for monitoring the effectiveness and execution of the risk minimisation activities;
- Clearly define roles, responsibilities and management controls throughout the process, including documentation of decisions taken and agreements made locally (e.g. with the regulatory authorities);
- Assure consistent implementation of the core risk minimisation plan globally. The paramount need for clear standards to support consistent implementation wherever the drug is marketed is critical. For example, if core risk minimisation measures cannot be accommodated within the healthcare system of a particular country, the company should seriously consider not launching in that market if conditions of safe use cannot be assured (even if marketing authorisation has been obtained); and
- Enable timely and effective decision-making in order to address findings.

The procedure(s) could include the following sections, although nomenclature, number of committees and internal functions may vary from company to company:

1. Risk minimisation process overview
    - 1.1. Regulatory requirements
    - 1.2. Design and risk minimisation tool selection
    - 1.3. Implementation
    - 1.4. Assessment reporting
2. Roles and responsibilities (as applicable)
    - 2.1. Head of global safety
    - 2.2. Risk management and pharmacoepidemiology function
    - 2.3. Safety management team (SMT)
    - 2.4. Risk minimisation design team
    - 2.5. Risk minimisation implementation team
    - 2.6. Affiliates (including the General Manager, Medical Director, local SMTs if applicable)
    - 2.7. Other (e.G. Licensing partners)
3. Management controls and governance (as applicable) (See below.)
    - 3.1. Risk minimisation advisory committee (provides technical advice)
    - 3.2. Risk minimisation approval and oversight committee

3.3. Local governance (e.g. Ensure resources and budget availability, address local issues in implementation)

4. Design and risk minimisation tool selection (as applicable) (See Ch. III)
   4.1. Evaluation of the need for additional risk minimisation activities
   4.2. Development of core risk minimisation strategy and plan
   4.3. Creation of regional/local risk minimisation plans
   4.4. Re-evaluation of the core risk minimisation strategy and plan
   4.5. Discontinuation of risk minimisation programmes
5. Effectiveness evaluation (See Ch. V)
   5.1. Documentation and tracking including metrics
   5.2. Evaluation and reporting
6. Implementation (See below.)
   6.1. Assembly of the risk minimisation implementation team
   6.2. Communication of the risk minimisation strategy
   6.3. Monitoring of local affiliate risk minimisation implementation
   6.4. Detailed guidance for implementation
   6.5. Local affiliate implementation including monitoring

• Management controls and governance

Central governance and oversight are necessary in any pharmaceutical company to assure consistency and adherence to standards, as well as to monitor implementation in each country, including oversight to ensure that educational activities and communication of benefit-risk information are appropriate, and balanced in content. In particular, given that risk minimisation activities, including education and other forms of communications to patients and healthcare providers, are not intended for commercial purposes, it is important to ensure that the integrity of the risk minimisation activities can be preserved and that regulatory authorities can be assured that these activities are not conducted as a promotional exercise.

The structure and constituency of the governance committee(s) and frequency with which metrics are generated and reviewed will depend on the size of the company and its product portfolio, company structure and culture, availability of internal expertise, and nature and scope of the risk minimisation programme, as well as how long it has been in effect. In smaller companies, there may be a single group handling all aspects of governance and technical advice. Therefore, the CIOMS IX Working Group decided that it would be inappropriate to be prescriptive on how individual companies should organise their governance structures.

Whatever the size and organisation of the company, however, they should consider putting in place management controls that:

- Are designed to ensure that the core risk minimisation strategies and plans are comprehensive, medically sound, practical and capable of achieving their stated goals (approval of the Core Risk Minimisation Plan);
- Provide oversight and an advisory role across all risk minimisation programmes;
- Ensure consistent standards and 'shared learning' across products and regions, including the regulatory environment and external expectations;

- Ensure that regional/local risk minimisation programmes are consistent with the core strategy/plan and regulatory requirements;
- Assure oversight for implementation, execution and effectiveness assessment of the tools planned, including ensuring adequate resources for implementation;
- Provide appropriate metrics and tracking tools (preferably web-based) which can be provided both internally and externally to ensure that commitments are being met;
- Include appropriate corrective and preventive actions (CAPAs) where shortfalls are identified; and
- Can address issues in implementation, when escalated.

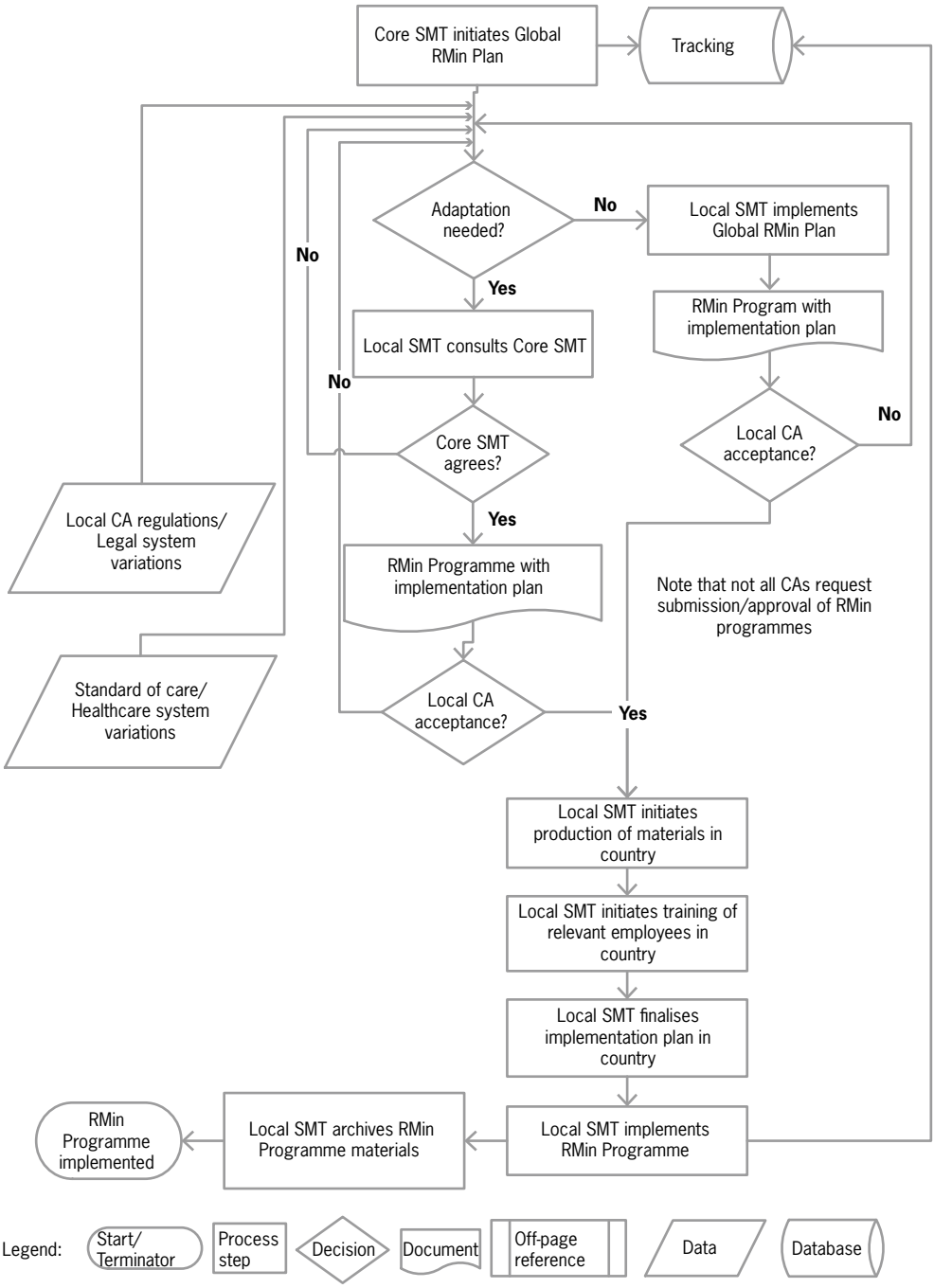
• Implementation tracking and metrics

The evaluation of the implementation of a risk minimisation programme needs to be addressed from the start and should be supported by a tracking process. Tracking risk minimisation activities begins with the distribution of the tools and continues until a defined endpoint that has been agreed upon with the regulatory authorities. Effectiveness of risk minimisation programmes should ideally be measured via process and outcome indicators; the methods used for such measurement and their reliability should also be assessed periodically (see Chapter V). An overview of start and end dates of local risk minimisation programme implementation within countries, as well as any local adaptations and versioning, requires a reliable tracking system, preferably one that utilises a dedicated database. This may not be feasible or necessary in all companies as long as an appropriate tracking system is in place by other means. Tracking provides all stakeholders with reliable access to information and data regarding the progress of local risk minimisation programmes, and can provide important data needed for measuring effectiveness. (See Fig. 4.1, Overview of risk minimisation implementation.)

The content, timing and communication process of implementation by the affiliates should be clearly understood in order to facilitate the development of appropriate and timely metrics. If implementation issues arise, such as milestones agreed with the regulatory authorities at a local or regional level, that are not met, then the reasons for the shortfall should be documented and appropriate corrective and preventive actions (CAPA) put in place. Whatever the frequency of review of metrics and CAPA, it would be advisable to coordinate the timing with important regulatory milestones and commitments such as EU-RMP/REMS updates and PSUR/PBRER submission to the authorities whenever possible.

The example below describes how important it is to build metrics into the system to be able to assess what does and does not work in terms of implementation. The reader will find detailed suggestions in Chapter V for further reference on how to include an effectiveness evaluation of implementation of risk minimisation interventions.

Fig. 4.1: Overview of risk minimisation implementation



RMin: Risk Minimisation / CA: Competent Authority / SMT: Safety Management Team

Box 4.1: Illustration of need to build in metrics

An (anonymised) real-life example illustrating these concepts involves a pharmaceutical company, 'PharmaCo,' which has developed a risk minimisation strategy for its new product ('Drug X') involving physician screening to determine patient eligibility prior to prescribing. To aid physicians in conducting this screening in a standardised and comprehensive way, PharmaCo developed a physician screening checklist. This checklist had been developed and found to be effective in a small, well-designed and executed pilot study.

Eighteen months after the risk minimisation intervention had been implemented, reports indicated that a substantial proportion of new patients on Drug X were not appropriate candidates for the product. On the surface, such results would suggest that the physician screening checklist was not an effective risk minimisation tool for Drug X. On closer scrutiny, however, PharmaCo found evidence that a significant percentage of prescribers had never received the screening checklist. Moreover, of those who had, the vast majority either did not use it or used only selective parts of it. There were many reasons for this lack of uptake aside from availability. These included: lack of understanding on the part of prescribers as to the importance of rigorous patient screening, inadequate time within the appointment with the doctor to complete the checklist, and resistance on the part of the clinical staff to ensuring that there was a blank copy of the screening checklist in the chart of each patient who was potentially eligible for Drug X.

In this instance, without knowledge of the intervention's implementation process, an erroneous conclusion could have been drawn as to the effectiveness of the risk minimisation effort.

C. Implementation considerations

• Communications

The task of developing and implementing risk minimisation plans involves cooperation across a diverse group of professionals and multiple functional areas within a company. New patterns of operating and new processes to support successful collaboration need to be established.

The process of educating internal stakeholders should start early and senior management support and understanding are crucial. Internal stakeholders should be educated as to what risk management and risk minimisation activities involve, why they need to be conducted and what is the value of such activities to the organisation as a whole. In delivering this information, it is important to consider the following:

- Build on previous successful organisational change management experiences.
- The targeted audience should be diverse, ranging from corporate/local marketing, business partners in licensing agreements, medical, senior management, legal, compliance officers, quality, and local regulatory, medical and safety personnel.
- Communication should be tailored to the particular audience; what may work with medical and regulatory personnel may not be effective with commercial colleagues.
- The appropriate channel for communication may vary. In some cases a written communication will suffice but sometimes face-to-face communication will be preferable.
- Financial considerations should be communicated early; budget holders accountable for implementation of costly risk management programmes will need to be informed as far as possible in advance so that appropriate resources and finances can be planned within the long timeframes of the budget cycle.

Additional risk minimisation activities over and above labelling are generally not required for the majority of products in most countries. As a result, developing and implementing a risk minimisation strategy and plan will not necessarily be an everyday or common occurrence. In these circumstances, and taking into account staff turnover, it is likely that repeated internal communication and retraining will be needed at a central and affiliate level whenever a new risk minimisation programme has to be implemented.

• Internal infrastructure and skills

It is important to ensure that the right skill sets are either available internally or accessible through external experts or contractual arrangements to develop a risk minimisation plan which goes beyond routine practice, namely prescribing information and patient package inserts (see Fig. 1.1 in Chapter I). The CIOMS Working Group IX considered that the multidisciplinary Safety Management Team (SMT) concept proposed by CIOMS VI should continue into the postmarketing period and form the core group to propose and develop the global risk management strategy and plan. However, in making this recommendation, the WG also acknowledges that the skill sets required to develop a complex risk minimisation strategy (e.g. requiring multiple additional risk minimisation activities) are likely to extend beyond those traditionally found in the safety, regulatory or medical departments. This takes into account the scope of risk minimisation planning, design and implementation activities which go beyond the usual SMT activities and will include:

- Assessing the need for risk minimisation strategies;
- Designing and developing appropriate educational, communication and other risk minimisation tools;
- Piloting or pre-testing tools, where appropriate and possible;
- Applying the methodologies needed to assess the effectiveness of the risk minimisation strategies; and
- Designing appropriate metrics and tracking tools.

For example, in developing effective risk communication tools for the purposes of risk minimisation, the SMT could utilise the expertise of other functions in developing and delivering educational initiatives to patients and healthcare professionals (e.g. medical affairs and commercial/marketing). However, as alluded to before in this chapter, it is important to ensure that development of the risk minimisation materials remains fully under company governance oversight in order to ensure that risk minimisation educational materials do not become promotional in nature.

As a result of all these considerations, the WG concluded that further expertise would likely be needed and foresees the emergence of a 'risk minimisation specialist' role to support and enhance core SMT capabilities (see also Chapter VII). Regardless of whether or not such a dedicated role(s) exists in a pharmaceutical company, the team responsible for developing and implementing the risk minimisation strategy and associated plan are, nevertheless, likely to need to have or have access to either knowledge of or associated skills which incorporate the multiple disciplines and methodologies described further in Chapter VII, including communication expertise, behavioural science, FMEA and other research methods.

Another possible but more extreme model could be to establish a separate functional area devoted to the science of risk minimisation. Ideally, this function should have its own budget, staffing and reporting structure that is independent from the commercial side of the organisation. This approach would be advantageous from the perspective of facilitating high standards and consistency across programmes, as well as helping to address any external perceptions that product promotion is carried out under the guise of 'risk minimisation.' It should be recognised, however, that this model is unlikely to be practical or feasible in most companies. Overall, the way in which a pharmaceutical company chooses to organise its risk minimisation expertise will depend on many factors such as size of the organisation and its portfolio, as well as the number of active risk minimisation programmes it has in place.

• Local implementation

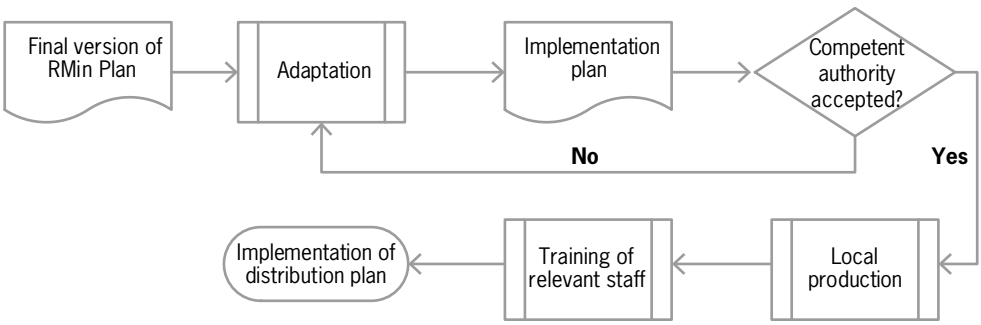
Local implementation of a core risk minimisation plan even in countries with no formal requirement for one or within a region such as Europe, often presents with practical challenges. For example, the EU-RMP for a centrally-authorised product will have been agreed at an EU level following PRAC and CHMP consideration. However, whilst some aspects of the plan may not be feasible at a national level due to local considerations including healthcare systems, there is provision in the EU guidelines to deal with this situation but this does have implications for national negotiation, agreement on how it will be implemented, what changes are needed and how this is documented.

In implementing a core risk minimisation plan, particularly in countries where there are no local regulatory requirements for any such plans, the global SMT will need to rely on local knowledge at the affiliate company and therefore should have close communication and early input from local SMTs (or equivalent) regarding the implications of a given risk minimisation programme. This is particularly important in terms of implementation, potential differences in acceptability of the benefit-risk balance, feasibility of utilising a particular tool or set of tools within a certain country or region, and measuring the effectiveness of the programme at the local level.

Ideally, this should involve development of local versions of the core risk minimisation plan (including appropriate risk minimisation tools) to fit local circumstances. At a minimum, local modifications of the core plan should be documented. This latter step is essential in order to develop programmes that are effective at the local level, so close communication and interaction with local affiliates regarding the development and implementation of a local plan will be important in these circumstances.

The second phase of implementation is the operational component regarding how local responsible teams implement the risk minimisation programme. As such, they will require a final version of a risk minimisation tool set (e.g. educational pack) prior to distribution so that needed adaptations, distribution and /or implementation plan (where appropriate), and local regulatory authority approval (where required) can be obtained in a timely manner. The impact of differing timelines in a region like Europe should not be underestimated given the necessity of interaction with multiple national competent authorities and differing timelines for approval of the risk minimisation materials. Once these steps are achieved, local production of materials and training of relevant company representatives, including medical staff, and implementation of a distribution plan, can commence (see Fig. 4.2). Training should also cover the provision of tracking information and other metrics as discussed earlier in this chapter.

Fig. 4.2: Implementation steps at the regional level



When a pharmaceutical company considers that a local implementation plan is necessary, the following points should be considered for inclusion:

1. Goal(s) – what is the activity seeking to achieve? (e.g. providing detailed guidance to HCPs to ensure regular liver enzyme monitoring.)
2. Objectives – what is sought to be achieved? (e.g. HCP undertakes regular liver enzyme monitoring and takes action where appropriate to reduce the occurrence of liver failure.)

3. Outputs – what are the short term outputs? (e.g. education of healthcare professionals on the importance of liver enzyme function monitoring.)
4. Activities – what needs to be done? How will dissemination to HCPs occur? (e.g. developing educational materials for HCPs.)
5. Inputs – what are the resources and skills needed to achieve the project? (e.g. skills in writing, educational methodologies, stakeholder engagement.)

D. Conclusions and recommendations

- MAHs should create an appropriate governance structure that provides or ensures:
  - Approval, advice and oversight of the process;
  - Approval of the core risk minimisation strategy and plan;
  - Consistency of local programmes with the core strategy, core risk minimisation plan and regulatory requirements;
  - A robust tracking system for local implementation;
  - Appropriate metrics and corrective and preventive actions (CAPA) and their regular review.
- Adequate resources for implementation and evaluation should be allocated for:
  - Local and global levels;
  - Issues resolution (at a global level).
- Whatever the frequency of review of metrics and CAPA, it would be advisable to coordinate the timing with important regulatory milestones and commitments such as EU-RMP/REMS updates and PSUR/PBRER submission to the authorities whenever possible;
- Pharmaceutical companies need to foster cross-functional collaboration of their respective experts and acquire (or have access to) new skill sets currently not necessarily available in traditional settings;
- In implementing its risk minimisation strategies, MAHs should ensure:
  - Adequate internal communication and infrastructure, including the education of key internal stakeholders and the availability of appropriate skill sets;
  - Support of local implementation efforts including development of a core risk minimisation plan and tools, provision of educational materials for affiliates on their use, and institution of tracking procedures that provide a way to measure implementation of risk minimisation activities at the local level.

E. References

1. Management of safety information from clinical trials. Report of CIOMS Working Group VI. Geneva, Switzerland: CIOMS. 2005.
2. Dusenbury L, Brannigan R, Falco M, Hansen W. A review of research on fidelity of implementation: Implications for drug abuse prevention in school settings. Health Educ Res. 2003, 18: 237–256.
3. Dana A, Schneider B. Program integrity in primary and early secondary prevention: Are implementation effects out of control? Clin Psychol Rev. 1998, 18: 23–45.
4. Elliott D, Mihalic S. Issues in disseminating and replicating effective prevention programs. Prev Sci. 2004, 5(1): 47–53.
5. Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implementation Science. 2007, 2:40 (http://www.implementationscience.com/content/2/1/40, accessed on 19 Apr 2012).
6. Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for integrating research findings into practice. The Joint Commission Journal on Quality and Patient Safety. 2008, 34(4): 228–243.
7. Forgatch M, Patterson G, DeGarmo D. Evaluating fidelity: Predictive validity of a measure of competent adherence to the Oregon model of parent management training. Behav Ther. 2005, 36(1): 3–13.

CHAPTER V:

EVALUATING EFFECTIVENESS OF RISK MINIMISATION

A. Introduction

Risk minimisation programmes are public health initiatives which attempt to **positively influence** patients' or healthcare professionals' **behaviours** and, through these changes, lead to improved patient **outcomes**. Evaluating the effectiveness of risk minimisation strategies, the subject of this chapter, has been advocated by regulatory authorities for over a decade **(1–3)**. To date, however, limited guidance has been provided on how this could or should be undertaken as suggested by the methodological gaps identified in a recent review on risk minimisation interventions **(4)**.

The purpose of this chapter is to delineate a planning process for evaluating the effectiveness of risk minimisation tools, interventions and programmes. This planning process is designed to lead participants through a step-by-step approach for examining health and behaviour at multiple levels. At the outset it is important to emphasise that although there always needs to be a statement by the marketing authorisation holder (MAH) in a Risk Management Plan (RMP) on how the effectiveness of any additional risk minimisation activity will be measured, one should also take into account the additional burden of the evaluation process if it involves healthcare professionals (HCPs) or patients.

A variety of structured conceptual approaches **(5–12)** has emerged since the preliminary planning systems developed in the second part of the 20th century **(13–15)**. All these systems involve (1) identifying factors that influence a desired outcome, and (2) explaining how interventions in the 'real-world' setting may affect these factors and outcomes. These two components form the basic principles of the methodology proposed in the remainder of this chapter. However, because the risk management field is evolving and the methodological framework is complex, all stakeholders involved in establishing, implementing and approving studies to evaluate the effectiveness of risk minimisation programmes should remain pragmatic and evaluations should be kept as simple and as robust as possible.

B. Study protocol considerations

At the point where a study of effectiveness of additional risk minimisation is planned, the level of change/achievement of outcome indicators constituting success should have already been considered. The next step in evaluating the effectiveness of a risk minimisation intervention (containing one or more tools) or programme (containing one or more interventions) is to develop a study protocol (hereafter called 'protocol'). One key consideration in the protocol development process is to specify the metrics and thresholds by which programme success will be measured **(1, 16, 17)** and audited. Ideally, the protocol should be written **prior** to the implementation of the programme at the regional or national level. The basic elements of the protocol are to be provided in the REMS and REMS Supporting Document **(16)** or in Part III.2 ('Pharmacovigilance Plan') of the EU Risk Management Plan (RMP), while the full protocol is appended in Annex 6 of the EU RMP **(17)**. In the EU, studies undertaken to evaluate the effectiveness of

risk minimisation activities (i.e. one or several activities organised in a risk minimisation programme) are legally defined as Post Authorisation Safety Studies (PASS) to which additional requirements apply **(18)**.

Ideally, the protocol should cover the areas summarised in Table 5.1. Its purpose is to provide a rationale for the proposed risk minimisation programme which includes:

1. **The nature and structure of the programme and the individual interventions in the programme:** The risk minimisation strategy chosen by the applicant, including the national or regional variations whenever appropriate, and
2. **How the overall success of the intervention(s) and the programme will be evaluated:** This includes the proposed methods of evaluation (design including comparison, if any) **(4);** a rationale for the chosen indicators (type of data that will be collected); the plans to evaluate unintended and/or unfavourable consequences; the time points for the analyses and the planned duration of the study.

Table 5.1: Areas to consider when writing a protocol

AREA	DESCRIPTION
Structure	▶ Description and rationale of the risk minimisation interventions (and tools) that are included in the programme with their specific objectives.
Design	▶ Key aspects of the study design, including comparison (if any) and planned duration of the study.
Process indicators	▶ Indicators selected to address adequacy of content with the objective(s) of an intervention. ▶ Indicators selected to address coverage, utilisation or maintenance (i.e. frequency and duration).
Outcome indicators	▶ Outcome indicators can include knowledge/awareness, attitudes, behavioural intent, and actual behavioural performance (e.g. provision of patient counselling). They depend on the nature of the risk minimisation *interventions*. ▶ Outcome indicators relevant to the success of the risk minimisation *programme* can include, for example, patient health outcomes, rate of contra-indicated co-prescriptions, morbidity, and/or mortality.
Analyses	▶ Measure of performance (i.e. measured against the threshold for success). ▶ Time points at which data will be collected. ▶ Analyses that will be performed. ▶ Region or country of interest for the analyses. ▶ Any other relevant parameter to be included in the analyses.

As such, the protocol should describe (a) the overall **goal** of the programme and a description of the selected endpoint(s), (b) the various **interventions** that compose a programme (see Chapter III for further details), (c) the specific **objective(s)** and the 'risk minimisation target' of each intervention (recipient or audience of the intervention e.g. patients, nurses, pharmacists and/or physicians), and (d) the **tools** (e.g. a checklist, a website, survey, other media) used.

In addition to the above, an analysis plan in the protocol should refer to the parameters which are collectively referred to as 'performance indicators'. These performance indicators fall into one of two categories **(19)**:

- '**process**' indicators that monitor the fidelity in the implementation and the delivery of an intervention by healthcare providers and other parties responsible in the healthcare system. Monitoring of process indicators would aim to provide an estimate of how successfully the steps of an intervention have

been implemented in the field and whether this intervention has been carried out as intended. They also serve as a basis for the corrective actions, which may be required to improve the implementation and delivery of the risk minimisation intervention, by the relevant stakeholders.

- '**outcome**' indicators that are specific, measurable, time-bound safety endpoints used to measure the overall success of the risk minimisation programme.

More specifically, the indicators selected to evaluate the performance of the individual interventions and the overall programme should be relevant, well-defined, sensitive, reliable, evidence-based, objective and tailored to the programme **(1)**. The analysis plan of the protocol should also refer to the *effectiveness threshold(s)* (see Glossary, Annex I) that will be considered for determining success, the *time-points* at which the analyses of the 'performance indicators' will be undertaken and the countries *or regions* of interest for the analyses.

The rest of the chapter will now elaborate on the study output using Russell Glasgow's RE-AIM framework planning model as overall guide **(8–9)**.

C. Evaluating the study output and results

Broadly speaking, a comprehensive evaluation of the overall effectiveness of a risk minimisation programme involves measuring performance in several different aspects (also called 'domains' or 'dimensions' in the literature on effectiveness measurement) of the programme. In the following discussion, we describe the key dimensions of the RE-AIM framework, the name of which is an acronym for Reach, Efficacy/Effectiveness, Adoption, Implementation, Maintenance. (Table 5.2) **(8–9)**. RE-AIM is one of multiple different frameworks that can be used to guide an evaluation design. Most of these employ many of the same or similar concepts **(20)**: (1) programme coverage, or '*reach'* is the extent to which the programme reached the intended target population; (2) *'efficacy/effectiveness'* is the effect on the primary outcome measures (i.e. a change in behaviour affecting patient health status) and the burden on the healthcare system (see more on 'burden' in Chapter III); (3) *adoption* is the extent to which targeted settings/sites agree to participate in implementing the programme; (4) *implementation* is the degree to which the programme was implemented as originally designed , and the cost of implementation; and (5) *maintenance,* also called *'adherence',* is the degree to which an intervention continued to be delivered over time with a reasonable level of fidelity. In the RE-AIM model, 'efficacy' interacts with implementation to determine effectiveness **(8)**.

Table 5.2: Five dimensions of the RE-AIM model for evaluating public health interventions

(From Glasgow **(8–9)**)

DIMENSIONS	DEFINITION
REACH	The number, proportion and representativeness of participants (e.g. patients, healthcare professionals) in the risk minimisation programme. Also known as 'coverage' or 'distribution.'
EFFICACY/ EFFECTIVENESS	Changes in primary study outcomes, quality of life, and potential negative effects.
ADOPTION	The number, proportion and representativeness of settings that agree to participate in and implement the risk minimisation programme to the targeted recipients.
IMPLEMENTATION	The degree to which an intervention was delivered as intended to the targeted recipients and the cost of implementation.
MAINTENANCE	The extent to which an intervention was delivered over time as designed.

Although cost and cost-effectiveness of the risk minimisation programme is important from an implementation and replication standpoint **(8–9)**, a detailed discussion of these issues is beyond the scope of this chapter. The reader is referred to general textbooks on this topic for further details **(21)**. The CIOMS Working Group IX considered that this is an area where more experience is required **(8)**.

D. Evaluating implementation fidelity of risk minimisation interventions

A risk minimisation programme is a coherent and systematic collection of interventions that may take place at the community, state, national, regional or international level. *Implementation fidelity refers to the degree to which a proposed risk minimisation programme is actually carried out in 'real world' conditions as intended.*

The degree of fidelity with which a risk minimisation programme, as with any public health intervention, is implemented, is critical to its success **(13–14, 22–24)**. Without evaluating implementation fidelity, it is not possible to determine whether a risk minimisation intervention's ineffectiveness is attributable to poor implementation or to design inadequacies intrinsic to the intervention itself. Conversely, in the face of a positive impact, it is not possible to know if these outcomes could have been improved further **(25)**. Therefore, an accurate understanding of the effectiveness of a given risk minimisation effort requires a clear understanding of the implementation process itself.

Evaluating the implementation process involves addressing as a minimum the four key areas of implementation fidelity described in Table 5.3 **(13, 25).** These are **'exposure'** (i.e. amount delivered; or 'dosage' according to Knutson **(13)** and Carroll **(25)**), **content, frequency and duration** (the latter two are also collectively called **utilisation**). Additional variables may be required to describe the target setting (e.g. urban or rural care, primary or hospital care; primary, secondary or tertiary hospital care), the practice (e.g. general practitioners or specialists, physicians, pharmacists or nurses) and the knowledge (e.g. understanding of the clinical problem itself) and special skills that would be required.

As with any public health intervention, the degree of fidelity with which a risk minimisation programme is implemented determines the quality of delivery and level of commitment and adequacy of resources of those implementing the risk minimisation programme. Collecting data on a range of factors that might be barriers to an optimal programme implementation and ongoing assessment of these factors may be necessary to inform root cause analyses and provide information on how to improve implementation and programme design moving forward **(26)**.

Process indicators reflecting areas such as risk minimisation 'exposure,' content, frequency and duration help describe the extent to which the risk minimisation plan was implemented as originally designed. Some indicators may need to be measured at one point in time, whilst others should be measured over time. Suboptimal performance in any one of these areas can provide insight into how the programme could be modified moving forward to make it more effective. Corrective actions should be taken rapidly in 'real time' (i.e. during implementation) as part of a continuous quality improvement cycle **(1)**.

Table 5.3: Key areas in the evaluation of implementation fidelity

(adapted from Knutson **(13)** and Carroll **(25)**)

AREA	DESCRIPTION	EXAMPLES OF ASSESSMENT METHODS
EXPOSURE*	Were all elements of the risk minimisation intervention fully delivered to the targeted recipients?	Mailing, web download, survey, review of programme implementation logbooks or other administrative records showing the number of hours intervention was delivered or the number of components/ elements of the intervention that were provided to targeted recipients.
CONTENT	To what extent did the information, skills, and/or knowledge that were actually delivered in the risk minimisation intervention match the specified content and purpose of the intervention as originally designed?	Focus group evaluation.
FREQUENCY	Was the risk minimisation intervention consistently delivered in the specified frequency to target recipients as originally intended?	Stakeholder behaviour survey, patient chart/diary audits, drug utilisation study, web-based interactive checklist.
DURATION	Was the risk minimisation intervention delivered consistently for the specified time period?	Timed samples of metrics through methods mentioned above.

The term 'exposure' is used by CIOMS IX to mean amount of risk minimisation intervention delivered. Also called 'dosage' according to Knutson* **(13) *and Carroll* **(25)***).*

The following example helps to illustrate these concepts and is based on a recent evaluation of a risk minimisation programme in the U.S. **(27)**. This particular risk minimisation programme included the following elements: 1) distribution of a Dear Health Care Provider (DHCP) letter; 2) distribution of a Medication Guide; 3) affixation of a sticker on each prescription by the participating physician to indicate that they had counselled the patient on product risks; and 4) education of pharmacists, including instructions not to dispense the product if the presenting prescription lacked a sticker. The evaluation was based on a survey conducted to evaluate the impact of this particular risk minimisation programme. A total of 2,052 out of 5,000 randomly selected licensed pharmacists in 20 states (1,250 from each of the four geographic regions based on U.S. Census Bureau categories) responded (response rate of 41%). Eighteen per cent (18%) of the responding pharmacists indicated that they had never received a DHCP letter. No alternative source of information (such as tracking of delivery) was collected so it was not possible to determine whether pharmacists had truly not received the letter or whether they did not remember receiving it. Twenty-nine per cent (29%) stated that they were not familiar with Medication Guides. Further, 41% of the pharmacists reported receiving a prescription without a sticker while the intervention had required the prescribers to affix a sticker to indicate that they had addressed the risk. Finally, 45% of the pharmacists dispensed the drug when the sticker was missing. Without knowledge of these gaps in the implementation of the risk minimisation interventions, an erroneous conclusion would have been drawn that the risk minimisation

programme was inadequately designed, when in fact the results indicate that risk minimisation interventions were sub-optimally implemented.

In certain circumstances, however, obtaining performance measures for each area may not be necessary **(8–9)**. This could be the case, for instance, when the structure of the healthcare system is very similar across countries or regions and the process has already been tested successfully; here, the level of scrutiny of the implementation process may not need to be as systematic or complete. Similarly, a continued process monitoring would be prohibitively expensive in the face of a programme that has demonstrated sufficient effectiveness outcomes.

• Exposure

Risk minimisation '**exposure'** refers to the extent to which the targeted recipients received, or were exposed to, all the intended elements of the risk minimisation strategy. For example, if a risk minimisation strategy specified that patients should be counselled at each monthly clinic visit, but medical chart records show that counselling actually occurred only once out of every six months, then implementation fidelity of the intervention in regard to exposure would be found to be low. Risk minimisation exposure should ideally be monitored at regular intervals starting soon after the deployment of the risk minimisation intervention to ensure that targeted recipients including specific subpopulations, are being exposed sufficiently to the intervention.

Risk minimisation exposure is based on the notion that programme participants need to be physically exposed to the relevant risk minimisation intervention materials or tool(s) in order to be impacted by them. A related concept is that of **'reach'** or 'representativeness' of programme participants as compared with the overall population of those eligible to participate. Measuring reach requires specific details on the targeted end-users. For instance, a complete list containing accurate address details is necessary in order to distribute educational materials by standard mail and/or by electronic mail to all neurologists in a country. Reach measures the proportion of all neurologists that received the educational material out of all those targeted to receive it.

A rationale describing the sampling method and explaining why the sample is believed to be adequately representative of all participants (i.e. is not a biased subset) should be provided in the risk minimisation study protocol. Evaluating the receipt of a letter targeting a broad audience of healthcare professionals could involve receiving a confirmation from all the intended recipients. Another approach might consist of using a geographically stratified sampling method to sample nurses, pharmacists, general practitioners and board-certified specialists in urban and rural settings.

• Risk minimisation content

Participants in a risk minimisation programme and in particular, the patients may have very different backgrounds and knowledge that could lead to differing levels of comprehension. User-testing the content of an intervention in a sample of targeted users and confirming its effectiveness in terms of imparting the desired level of knowledge prior to the implementation of a risk minimisation intervention to the full target audience enhances the likelihood that the material will be understood and acted upon. It can also increase 'buy-in' and commitment to risk minimisation interventions from the target audience. Other aspects of content such as risk messages and instructions about desired behavioural action could be evaluated using knowledge surveys or case studies. Content does not need to be monitored regularly unless the population being targeted should change in a fundamental way so as to require reassessment of the face and content validity of the tool.

- Risk minimisation utilisation (frequency and/or duration)

Frequency refers to the extent to which the risk minimisation intervention(s) was/were delivered as frequently as originally planned. The uptake of a new intervention depends on its acceptance by and acceptability to those receiving it **(25)**. A variety of factors (e.g. psychological, social, cultural, technical or economic) may impede or prevent the delivery of an intervention into actual 'real world' conditions. Participant utilisation ('uptake') is therefore an important consideration in any process examining implementation fidelity. Evaluating utilisation involves an assessment of how well a behavioural intent is translated into an actual behaviour (an action) by measuring the quantity (amount and/or frequency) of the interventions delivered over time (duration) to the target recipients.

Utilisation represents a different evaluation area from that of reach. When taken together, these two parameters provide an estimate of the gain that an intervention contributes to a programme. For example, one population with a higher rate of utilisation for a given degree of reach can contribute more to an intervention than another population with a lower rate of utilisation. Delivery of the risk minimisation interventions at the frequency and duration originally specified is critical to the success of an intervention and, as such, warrants being measured and monitored over time.

E. Evaluating effectiveness of a risk minimisation programme

Evaluating the overall impact of the risk minimisation strategy in the risk minimisation programme is a critically important step **(8–9)** in assessing its effectiveness. There are multiple evaluation strategies, data sources, and research designs, all of which can be considered for use either individually or in combination in order to evaluate effectiveness in terms of the characteristics of safety-related outcomes of interest (see Table 5.4 below); none of these evaluation approaches is bias-free. To this point, FDA recommends, whenever feasible, that the evaluation protocol should include at least two different quantitative, representative, and minimally biased evaluation methods for evaluating the risk minimisation programme of each critical risk.

As indicated earlier, a protocol should describe the evaluation design and a detailed analysis plan with pre-specified outcome indicators **(8–9, 19)** and threshold(s) that will be considered for determining success. The outcome indicators should provide evidence that the risk minimisation strategy is effective through clinically meaningful risk prevention or mitigation endpoints such as a desired behavioural modification and/or an improved safety-related outcome of interest (SOI). When designing studies aimed at showing the effectiveness of a risk minimisation strategy, the selection of an appropriate outcome indicator, a comparator, measures of performance and time points for analyses are key considerations. Whilst it may be desirable to include a comparator in the study, it should be recognised that this may not be feasible. The main elements to consider for the effectiveness evaluation are outlined hereafter.

Selecting appropriate outcome indicators to measure effectiveness

Outcome areas suitable for measurement include morbidity or mortality. Relevant outcome indicators refers to those specific, measureable, time-bound *safety-related outcomes of interest* (an umbrella term that groups together a variety of safety endpoints) consistent with the overall goal of the risk minimisation programme, i.e. they are the most meaningful targets, from the clinical and public health perspectives, to measure the success of a risk minimisation programme.

Outcome indicators may be a direct measurement of a hard clinical endpoint or an accepted surrogate thereof (e.g. measurement of blood pressure as a surrogate for change in cardiac risk). When the risk to be minimised is rare, a composite outcome indicator may be used as a single measure of effect, based on a combination of individual *similarly important* endpoints (e.g. 'major adverse cardiac events' combining cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke). Composite endpoints are generally used to reduce the sample size (and therefore the cost) of a study and increase feasibility when a safety-related outcome of interest is rare or when grouping together related outcome terms helps to

better understand a given risk. The weaknesses of composite endpoints should be appreciated as well and have been described elsewhere **(28–30)**. A biomarker or a lab/imaging test that is 'assumed' to represent clinical outcomes should, as much as possible, not be used as substitute for a clinical safety endpoint when the latter is readily available **(31)**.

Safety-related outcomes of interest should always be precisely defined. For example, 'hepatotoxicity' is a very broad composite term that encompasses multiple different conditions that vary in terms of incidence and severity. Considering 'hepatotoxicity' as the safety-related outcome of interest would imply evaluating 'liver enzyme test abnormalities' (a rather common laboratory test abnormality often with limited medical significance), 'hepatitis' and 'liver failure'. In this example, only the more severe conditions 'hepatitis' and 'liver failure' would constitute the risks and also the outcomes of interest.

In some cases, the measurement of a clinical safety-related outcome of interest may not be necessary if a change in certain behaviours can be expected to reduce or eliminate such an outcome. For example, a risk may result from co-prescription of two medications, and risk minimisation efforts would be aimed at avoiding such co-prescription. In this case, showing behavioural modifications through evaluating the rate of contraindicated co-prescriptions dispensed (see example on cisapride in Appendix 1 attached to this chapter) may provide enough knowledge about the desired behavioural change to sufficiently address safety concerns **(32-34)**. Similar examples include the performance of mandatory laboratory tests (see troglitazone in Appendix 1 attached to this chapter) or the rate of required therapy supplementations in a drug utilisation study **(35-37)**.

Methodologies for assessment of effectiveness of risk minimisation need to take into account any inter-relationship between adverse reactions, risks and safety-related outcomes of interest. For example, granulocytopenia is a known adverse reaction occurring in patients taking clozapine **(38–40)**. Its most severe form, agranulocytosis (i.e. the risk), is a biological condition where fatalities reflect more appropriately the safety-related outcome of interest such as an important clinical endpoint **(41)**). Consequently, the rate of agranulocytosis-related fatality has been the safety-related outcome of interest selected to evaluate the effectiveness of the clozapine controlled-distribution programme (see clozapine in Appendix 1 attached to this chapter).

As outlined earlier, selecting a clinical safety-related outcome of interest is an important decision that impacts on the sample size required to draw robust conclusions on the effectiveness of a risk minimisation intervention or programme. Very rare events would require exposing several hundreds of thousands of patients with associated time and/or financial consequences. Furthermore, the need for large cohorts may impact feasibility and delay conclusions on the effectiveness of a risk minimisation programme. Composite or surrogate endpoints could be considered when a clinical endpoint is not feasible. Surrogate endpoints may also be used to provide *interim* evaluations whilst awaiting the results of more direct risk minimisation measurements **(3)**. In very specific circumstances, the spontaneous reporting rate in the treated population could be used as an acceptable estimate of the frequency of an adverse event chosen as endpoint, for instance, when the background incidence of the endpoint in the general population is very low and there is a strong association between the medicinal product and the adverse event.

Good clinical safety-related outcomes of interest (like efficacy endpoints) need to fulfil several key characteristics which are summarised in Table 5.4. The designer or owner of a risk minimisation programme should integrate as many of these as possible and as appropriate in the (single or composite) safety-related outcome of interest that will ultimately serve to measure the effectiveness of the programme. Failure to do so may reject a risk minimisation programme that is otherwise effective due to insufficiently robust and meaningful endpoint selection.

Table 5.4: Characteristics to consider for each safety-related outcome of interest

(Used to evaluate the effectiveness of a risk minimisation programme**,** modified from Chin R. and Lee B.Y. **(42)**)

CHARACTERISTIC	DESCRIPTION OF SAFETY-RELATED OUTCOME OF INTEREST
Preventable and/or mitigable	Preventable or mitigable by the proposed risk minimisation programme.
Specific	Clearly defined, no evaluator judgment is needed.
Easy to diagnose	Easy to identify and to confirm.
Rich in information	e.g. a continuous variable is richer in information than a categorical equivalent; sampling done at two rather than one time point is also richer in information.
Responsive	Sensitive to the proposed risk minimisation programme.
Reliable	Free of measurement error; precise; reproducible, with no or low variability on repeated measures.
Internal validity	Possibly linked to the medicinal product (i.e. is preferably not a surrogate).
External validity	Generalisable to a wider population.
Clinical relevance	Has influence on the treatment choices made by physicians and/or patients.
Practical	Implementable worldwide and of low cost.

Evaluation designs: The selection of a comparator

The selection of an evaluation design is a key step in developing the evaluation protocol. Ideally, the research design should specify a comparator condition, which could be another programme or no programme at all. The strongest comparison is achieved in a concurrent prospective design where the outcome measure is compared between a cohort of patients included in a given risk minimisation programme and a similar cohort of patients not included in the risk minimisation programme. However, it may not be possible or ethical to do this in practice, especially in situations where a risk minimisation programme is required by the regulatory authority as a condition of the marketing authorisation.

Various design options however could be considered in order to address this challenge, provided that regulators are receptive to their use by MAHs. A 'dismantling' evaluation design is one such option **(43)** that would involve randomly assigning different aspects of the risk minimisation programme to be implemented in different geographic regions. An evaluation could then be conducted in which each region is compared to the others. Another option is when a risk minimisation intervention/programme has been designed to include different intervention components in different countries or regions as comparators versus each other. Open designs may also be possible comparing components required in different countries/regions and such components can be the same or different depending on the regulatory requirements. Another method can involve staggered roll-out of risk minimisation interventions. Before-after comparisons can be considered for any of these methods. In such 'before-after' comparisons, the 'before' could be chosen from the incidence of the outcome of interest in pre-approval clinical trials **(37)**; the reporting rate in the 'real world' post-approval setting prior to the implementation of a given risk minimisation programme; or some kind of predefined reference value from historical data based on a review of the medical literature in a general or specific population.

When a risk minimisation programme is introduced later in the post-authorisation phase as a consequence of an emerging safety concern, the rate which led to the need for the risk minimisation intervention can provide a good basis for the 'before-after' comparison.

Table 5.5 provides a summary of possible comparative strategies for data sources and evaluation designs, some of which are theoretical, that could be used to demonstrate the effectiveness of a risk minimisation intervention. For all of these, the designer or owner of the intervention will need to make every effort to minimise confounding and to look for biases (e.g. regarding selection or information) that may lead to incorrect conclusions. The choice of a comparator should be appropriately justified.

Table 5.5: Data sources and evaluation designs

(for studies assessing effectiveness of risk minimisation programmes)

EVALUATION STRATEGY	DESIGN	EXAMPLES OF DATA COLLECTION METHODS
Monitoring	▶ Continuous measurement of programme performance.	▶ Data collection ▶ GANTT Chart (as a reminder for the monitoring).
Trend analysis	▶ Interrupted time series	▶ Primary data collection via surveys, and/or ▶ Analyses of existing secondary data such as healthcare claims data; laboratory test data; medical charts and other programme/ records audits.
Observational	▶ Repeated cross-sectional survey design	▶ Questionnaires ▶ Interviews with recipients and other key stakeholders.
Pragmatic clinical or behavioural trial	▶ Random assignment to either intervention or 'comparator' condition. – Pre-test and post-test with multiple follow-up evaluation points. ▶ Standard of care or 'minimal intervention' as the comparator condition.	▶ Same as Trend analysis
Quasi-experimental (no randomisation)	▶ Non-random assignment to intervention or 'comparator' condition. Pre-test and post-test with multiple follow-up evaluations. ▶ Non-equivalent group design ▶ Regression discontinuity	▶ Same as Trend analysis

The choice of a 'threshold of success' for a risk minimisation programme

The safety-related outcome of interest can be considered from two perspectives: (1) the outcome measure; and (2) the magnitude or degree of the expected effect on the outcome. The former element has been discussed above; the latter will be discussed hereafter.

Despite being well-designed, risk minimisation programmes may not always achieve a sizable risk reduction during 'real world' use of the medicine. In addition, there are currently no published standards or guidance

from regulators, nor consensus within the research community on how to establish, *a priori*, threshold(s) for measuring a programme's effectiveness and determining its success. In spite of these limitations, attempts should be made to propose a threshold in the analysis plan of the protocol that formalises a risk minimisation programme.

Three factors are worth considering in order to justify the magnitude of the expected effect and therefore the choice of a threshold for determining the success of a risk minimisation programme. They include: (1) the impact of the risk (i.e. likelihood x severity of harm [see Chapter III for further details]), (2) the desired level of the risk minimisation effort in relation to the benefits provided by the medicine, and (3) what is practical and feasible given resources and time. The MAH should also assess any relevant clinical trials and published literature for any relevant information that could help define the success threshold.

Final considerations in the analytical section of the protocol should include the fact that a 'one size fits all' risk minimisation strategy may not necessarily be effective to the same extent across all patient categories or across different regions of the world. As noted above, adjustments may be required in different locations to facilitate adoption or to remove barriers to adoption of a risk minimisation programme. Similarly, the analytical section of the protocol should specify whether the evaluation of effectiveness will be performed across the entire set of countries involved in the intervention and/or whether there should be a stratified analysis according to region or country. Due consideration should be paid to variations in standards of care, regulatory requirements, healthcare systems or in the implementation of the risk minimisation programme so as to explain differences in design or observed results across countries. Further variations (such as cultural differences, genetic differences, and differences in case mix across countries) for which a control in adjusted analyses may be relevant should be considered as appropriate.

The protocol should address the issue of whether the outcome indicator(s) are expected to be equally responsive across all types of patients (e.g. adult versus elderly), healthcare professionals (e.g. nurses, pharmacists or physicians; general practitioners or specialist physicians); and localities (e.g. rural or urban). Any sub-analyses should be carefully described in the analytical section of the protocol and then followed in order to reach robust and useful conclusions on the effectiveness of the risk minimisation programme in its entirety.

At the end of this process, there is still no guarantee that a programme will reach the threshold selected for determining success despite a careful and successful programme implementation. This is because as previously stated the choice of thresholds for determining success of risk minimisation are currently not fully developed. A well-executed communication and education campaign may even induce a paradoxical increase in the reporting of an endpoint as a result of a more accurate diagnosis and a more complete reporting of the safety-related outcome of interest (surveillance bias). Such instances require good communication between the sponsor and the regulatory authorities. Based on a careful analysis of the risk minimisation programme results and of all contextual and other influencing factors, a plan for revising the risk minimisation programme may need to be developed. A rationale for further actions should be provided, documented and ideally made publicly available.

Time points for analyses and maintenance of effectiveness

Documenting effectiveness at several time points is important to demonstrate the persistence or maintenance of the risk minimisation programme impact over time. For certain types of risks and certain medicinal products, this maintenance may constitute a good argument to support the discontinuation of a risk minimisation programme, particularly if the desired safe-use behaviours become established in every day standard clinical practice. For instance, the requirements to measure the effect of an oral anticoagulant at regular intervals would no longer require any additional minimisation programme to enforce this behaviour.

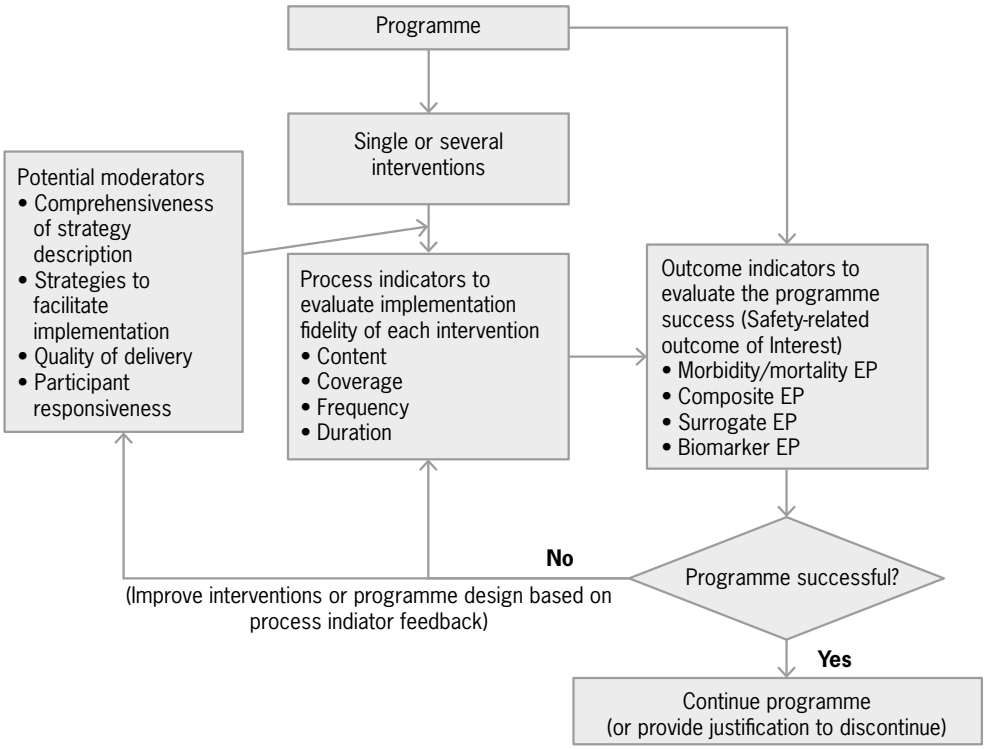
The number of time points at which an analysis of effectiveness of risk minimisation will be performed should be specified in the study protocol together with time points for submission of reports to regulatory authorities. FDA standard timetable requires the sponsors to submit an evaluation of REMS effectiveness by 18 months, three years and seven years after approval of the REMS **(1)**. However, there are no internationally accepted time points for evaluation. It could be argued that timing of assessment points should be dictated by the nature of the risk minimisation programme and different intervals may need

to be negotiated when the uptake of a medicinal product on the market is slow (e.g. in the case of an evaluation of co-prescription via a drug utilisation study), when the relevant endpoint is rare or simply when the deployment of a risk minimisation programme is complex and would take considerable time. As a general recommendation, a first time point to be selected for evaluation should avoid interference with evaluation of study outcomes. A time point which falls prior to the renewal of the marketing authorisation may be recommended so as to make sure that results on the evaluation of effectiveness will be made available for the upcoming regulatory review.

F. CIOMS IX framework for evaluation of effectiveness of risk minimisation

- A structured framework which may combine methods from social, implementation and evaluation sciences (e.g. for surveys to evaluate knowledge), behavioural science and pharmacoepidemiology (e.g. safety outcome studies, drug utilisation studies) is hereby proposed by the CIOMS IX Working Group. This framework can be considered when evaluating the effectiveness of a risk minimisation strategy as described in the risk minimisation protocol (see a non-comprehensive list with the key elements of the above mentioned framework in Annex V to this report). For each intervention, the framework should include performance indicators **(8–9, 19)** (see Fig. 5.1 below and described previously under heading B. 'Study protocol considerations'), as appropriate:
- **Process** indicators evaluate the fidelity of implementation and include such domains as coverage, content and utilisation (i.e. frequency and duration). Collecting and monitoring process indicators over time can provide (1) useful information on 'off-target' implementation or on a poor programme design that will require improvements moving forward, and (2) information critical to identifying possible reasons as to whether the programme itself or its implementation is not delivering the expected results.
- **Outcome** indicators provide the demonstration of effectiveness either through desired behavioural change or improved indicators of outcome.

Fig. 5.1: CIOMS IX risk minimisation evaluation framework



Note to Fig. 5.1: EP = endpoint. The 'CIOMS IX risk minimisation evaluation framework' outlines elements to be considered for the evaluation of a risk minimisation programme (modified from Carroll **(25)***.)*

G. Summary and conclusions

1. Risk management systems are developed to monitor, evaluate and manage risks throughout the lifecycle of a medicinal product.
2. Risk minimisation programmes should aim to ensure that, in 'real world' conditions, the right prescriber provides the right medicinal product to the right patient at the right dose and right time **(57)**. As such, they aim at reducing the impact (i.e. likelihood or severity of harm) of the most important risks through positively influencing the behaviour of patients and/or healthcare professionals.
3. Each intervention in a risk minimisation programme can provide information that may be used to improve it moving forward. Such optimisation is aimed at further reducing the risk and improving the benefit-risk balance of the medicinal product under consideration.
4. A structured framework should be considered when evaluating effectiveness of risk minimisation (see CIOMS IX risk minimisation evaluation framework above in Fig. 5.1). For each intervention, it should include process and outcome indicators as appropriate and on a case-by-case basis.
5. Marketing authorisation holders should aim at keeping the measurement of effectiveness of risk minimisation interventions as simple, pragmatic and user-friendly as possible to minimise undue burden on the patients, key participating stakeholders and on the healthcare system as a whole.
6. MAHs should consider publishing their evaluation results regarding effectiveness of risk minimisation in peer-reviewed publications in order to facilitate advances in the field.

H. The way forward: Points to consider and recommendations

Measuring the effectiveness of public health initiatives is an evolving field. Key stakeholders agree that there is still a need to develop novel, robust, more appropriate evaluation designs and methodologies to assess the effectiveness of risk minimisation programmes, including the impact, if any, of the burden on patients and the healthcare system. These methods should aim at further maximising the safe and effective medication use while minimising the burden on the healthcare system. This could be achieved through exchange of factual experience and constructive interactions between patients, healthcare professionals, marketing authorisation holders and regulators.

In order to achieve these objectives:

- **Marketing authorisation holders** should whenever possible:

1. pilot and evaluate risk minimisation interventions in the pre-approval phase,
2. incorporate metrics on implementation fidelity as a feedback loop to continuously improve the risk minimisation interventions, and
3. make available their experience on the measurement of effectiveness of risk minimisation programmes through the medical and scientific literature;

- **Key stakeholders,** including healthcare professionals and patients, should contribute to the design of the risk minimisation programmes to ensure that the programmes are feasible and acceptable;
- **Regulators** should consider:

1. defining the desired outcomes and the required actions in clear, easy to understand, unequivocal language,
2. developing harmonised guidance documents that help to ensure consistency in the evaluation of the effectiveness of risk minimisation interventions,
3. facilitating the inclusion of basic training on the principles of risk management and risk minimisation interventions in the medical curriculum for healthcare professionals with emphasis on requirements for medicines with additional risk minimisation interventions,
4. allowing MAHs to develop and utilise new types of evaluation research designs that will permit more rigorous evaluation of risk minimisation programmes,
5. developing methodologies to detect whether risk minimisation programmes have the undesired effect of shifting prescribing to other similar but perhaps less suitable medicinal products that do not have a risk minimisation programme in place, and
6. building a publicly available repository of validated and tested risk minimisation interventions.

I. Ch.V - Appendix I: Examples of effectiveness evaluation of currently-utilised risk minimisation programmes

The present section will review four selected risk minimisation programmes and put them in the context of the methodology presented previously in this chapter. All examples are related to risks that appeared in the post-authorisation phase. The reader is also referred to additional 'real world' examples which can be found in Annex III of this CIOMS report. For a complete review of all available publications on risk minimisation programmes, the reader is invited to read the publication of Nkeng L et al. **(44)**.

• Effectiveness of communication including educational material

The following two cases are examples of the use of a design to compare a 'before and after' situation in the assessment the effectiveness of DHCP letters. It is possible that DHCP letters, as a risk minimisation tool, could be effective when they reach the right recipients in the right way with the right content and the right frequency or duration. One limitation of these evaluations is that measures of success were not defined *a priori*.

Cisapride

Cisapride is a gastrointestinal tract pro-motility agent that was approved and marketed in the USA since 1993. In June 1998, the U.S. FDA contraindicated the use of cisapride in susceptible patients because of its potential to cause life-threatening ventricular arrhythmias (i.e. the risk) from QT prolongation. A risk minimisation programme consisting of communicating the risk and providing recommendations on how to prevent these life-threatening ventricular arrhythmias was initiated. Physicians were informed through three different media (the tools that have been used to communicate the intervention). Firstly, a 'Black Box' warning in the label contraindicated the use of concurrent medications interfering with cisapride metabolism or prolonging the QT interval and the use of cisapride in disorders that predispose to QT-related arrhythmias. Secondly, about 800,000 'DHCP' letters repeating the key messages were sent by the drug's manufacturer. Lastly, the warnings were also posted on the FDA website through a press release. Effectiveness was evaluated based on computerised patient medical encounter records in one of three managed care organisation sites in the one-year periods before (July 1997–June 1998, n=24,840) and after (July 1998–June 1999, n=22,459) the regulatory action **(31)**. A reduction in contraindicated use of approximately two per 100 cisapride users was observed at each site, from 26%–60% of the patient records in the year prior to the communication down to 24%–58% in the year after the regulatory action. When the analysis was restricted to new users of cisapride after regulatory action, only minor reductions in contraindicated use were found. The authors concluded that '*the FDA's 1998 regulatory action regarding cisapride use had no material effect on contraindicated cisapride use. More effective ways to communicate new information about drug safety are needed*'. Two other studies, one in the Netherlands **(33)** and another in the USA **(34)**, showed a 'gradual permanent' trend towards less contraindicated use of cisapride. In July 2000, however, Janssen Pharmaceutica in consultation with the FDA decided to discontinue the marketing of cisapride and to make it available only through an investigational limited access programme. From July 1993 through December 1999, a total of 341 cases of serious cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, Torsades de Pointes, and QT prolongation had been spontaneously reported, including 80 deaths. In approximately 85% of these cases the events occurred when cisapride was used in patients with known risk factors.

Troglitazone

Troglitazone is an oral anti-diabetic agent that was first in the new class of thiazolidinediones. It was approved in March 1997 in the US and marketed under the trade name of Rezulin®. Soon after launch, several cases of hepatitis and hepatic failure were reported through the spontaneous reporting system, leading the U.S. FDA to initiate risk minimisation activities in the form of DHCP letters requesting physicians to perform liver function test monitoring in patients treated with troglitazone. Five progressively more

stringent DHCP letters were sent in waves from 1997 (31 October 1997, 1 December 1997, 15 December 1997, 28 July 1998, and 16 June 1999) until the withdrawal of troglitazone from the market in March 2000. This withdrawal occurred after an FDA review of two similar drugs, rosiglitazone and pioglitazone, showed similar benefits to troglitazone without the same level of hepatic risk. Two studies have looked at the effectiveness of these 'DHCP' letters on the liver function test monitoring in patients prescribed troglitazone (and rosiglitazone) **(35, 36)**.

In Graham's study **(35)**, claims data from a total of 7,603 first-time troglitazone recipients in a large, multi-state managed care organisation were used to establish four cohorts representing four periods of progressively more stringent liver enzyme test monitoring. Even though baseline liver enzyme testing increased from 15% before any FDA monitoring recommendations to 44.6% following four separate FDA interventions (P<.001), less than 5% of the patients in all cohorts had all recommended liver enzyme tests performed by the third month of continuous use of troglitazone.

In Cluxton's study **(36)**, a similar methodology was used in another claims database but restricted to the U.S. State of Ohio. Patients who had received at least one troglitazone (n=7,226) or rosiglitazone (n=1,480) prescription from the beginning of April 1997 to the end of March 2000 were evaluated. The outcome of interest was the percentage of patients, based on their first treatment episode, who had baseline and post-baseline liver enzyme testing. Baseline testing was under 9% before regulatory actions, increased to 14% after the first two 'DHCP' letters issued by the FDA in October and December 1997, and peaked to about 26% thereafter. Coincident with the marketing of rosiglitazone and the fifth DHCP letter issued in June 1999, baseline testing dropped to 18%.

These two publications suggest that the DHCP letters had modest effects on the performance of baseline liver enzyme test monitoring and were insufficient to produce a sustained effect on regular monthly liver enzyme testing. Based on these data it is concluded that more effective and timely communication strategies to modify health provider behaviours need to be identified, evaluated and implemented to enhance compliance with recommended risk minimisation interventions.

• Effectiveness of restricted access

The following two cases are examples of a historical control comparison (clozapine) and pre-post comparisons (isotretinoin) of the corresponding restricted access programmes. As with the two previous examples, 'success' was not defined *a priori*.

Clozapine

The example of clozapine (Leponex® or Clozaril®, Novartis AG, Basel, Switzerland) illustrates how a laboratory-based controlled distribution programme can favourably influence an outcome in multiple countries and regions. The implementation of the programme was enforced through a mandatory registry that links the biological results on a secured monitoring platform to the dispensing of clozapine.

Clozapine is an atypical antipsychotic agent used to treat treatment-resistant schizophrenia. It was introduced in selected European countries in early 1975. Within 5 months of its introduction in Finland and over a period of about six weeks, 17 cases of neutropenia or agranulocytosis of which eight had a fatal outcome were reported by physicians to the National Drug Adverse Reaction Register at the National Board of Health **(38)**. At that time an estimated 3,000 patients had been treated with clozapine in a country with a population of about 4.6 million. According to national statistics, five to twelve cases of fatal agranulocytosis would have been expected to occur annually in Finland between 1968 and 1973 **(39)**.

In July 1975, because these adverse haematological reactions were judged by regulators as being too frequent and too severe in relation to the indications for clozapine, the National Board of Health prohibited sales of clozapine in Finland in agreement with the manufacturer. Clozapine was also withdrawn in other countries. However, because of its well-documented clinical efficacy in treatment-resistant schizophrenic patients, clozapine was subsequently reintroduced on the market but with intensified regulatory control and requirements for a special safety monitoring programme.

Clozapine has a mandatory controlled distribution (also termed restricted access in this CIOMS IX report) as the main risk minimisation programme. Its objective is to prevent the dispensing of clozapine to patients who have white blood cell/granulocyte counts below a certain threshold. This involves the prescriber and the laboratory interacting sequentially before the pharmacist can dispense clozapine. For instance, in the UK, patients must be registered with the Clozapine Patient Monitoring Service (eCPMS Internet website) before they start treatment with clozapine. Once treatment commences, patients need regular blood samples weekly in the first 18 weeks, then every two weeks up to one year and every four weeks thereafter. The blood results are accessed by the pharmacy via eCPMS. When blood samples are analysed locally, the blood sample must be followed up and phoned through to either the pharmacy or CPMS.

As far as implementation is concerned, the monitoring of granulocytes and other white blood cell lines as implemented through a mandatory registry were considered effective in the U.S. **(45)** and Australia **(46)**. In the UK, the CPMS programme put in place by Novartis is ISO 9001:2008 certified and therefore fulfils rigorous standard requirements for quality management.

In this example, the goal of the programme addressed the most clinically relevant safety-related outcome of interest to evaluate effectiveness of the controlled distribution programme, i.e. to prevent the fatal complications of agranulocytosis that may develop as a consequence of a wrong prescription of clozapine to a patient presenting with a (drug-induced) agranulocytosis. In the absence of a structured blood monitoring system, 1 to 2% of patients receiving clozapine in clinical trials develop agranulocytosis **(45, 47)** and the case fatality rate may be as high as 47% **(48)**. In comparison, when centralised monitoring systems (i.e. drug registries) of white blood cells were put in place in the UK (including Ireland) and US, the rate of agranulocytosis and of fatal agranulocytosis dropped to 0.68% and 0.016%, respectively **(49)**. In conclusion, risk minimisation measures applied through restricted access programmes of clozapine have been considered successful and the intervention is still in place today.

Isotretinoin

This example illustrates a case in which the risk minimisation restricted access programme evolved over time from being less to more restrictive. Ultimately, the final programme iteration led to iPLEDGE™, a single computer-based, controlled distribution programme and mandatory pregnancy registry which specified a closed-loop system for prescribing, dispensing, and distributing all isotretinoin products. This programme was developed with input from the FDA and is part of an approved Risk Evaluation and Mitigation Strategy (REMS).

The FDA was the first regulatory agency to approve isotretinoin (Accutane®, Hoffmann-La Roche, Basel, Switzerland) in 1982 for the treatment of severe, recalcitrant nodular acne that is unresponsive to conventional therapy, including antibiotics. Isotretinoin is a human teratogen. The drug was introduced on the U.S. market with a description of the risk of teratogenicity in the 'Contraindications', 'Warnings' and 'Precautions' sections of the package insert. It was designated as 'Category X' meaning that it must be avoided by women under all circumstances during their pregnancy. In addition to the language of the package insert, a 'patient information brochure' with warnings about avoiding pregnancy was also made available. The intended objectives of these communications were twofold: (1) preventing pregnant women from taking isotretinoin, and (2) preventing pregnancies during isotretinoin treatment. However, following the receipt of further reports of pregnancies resulting in birth defects **(50)**, two DHCP letters had to be sent. In 1983, the warning language on the teratogenic potential of isotretinoin was revised and red warning stickers were distributed to pharmacists and wholesalers to be placed on the drug bottles. Seven additional DHCP letters were issued to prescribers between 1984 and 1988 **(51)**.

In spite of all efforts to communicate Accutane's teratogenic potential through the package insert and DHCP letters, the sponsor continued to receive reports of birth defects suggesting a limited compliance with pregnancy testing prior to or during isotretinoin treatment and/or an inappropriate use of contraception. In 1988, the manufacturer instituted a voluntary restricted access programme (i.e. PPP for 'Accutane Pregnancy Prevention Program') with goals identical to those intended in 1982. The PPP is the first of three, progressively stricter, consecutive restricted access programmes (see summary in Table 5.6 hereafter).

Table 5.6: Overview of the key elements of the last three isotretinoin programmes

(modified from Abroms L, Meibach E, Lyon-Daniel K, et al., 2006 **(53)** and FDA 2004, 2007 and 2011**(54–56)**)

RISK MINIMISATION PROGRAMMES	PPP (1998 to 2000)	SMART[b] (2001 to 2005)	iPLEDGE[c] (2006 to today)
Key features of the risk minimisation programmes	1. Voluntary 2. Decentralised 3. Innovator only	4. Voluntary 5. Decentralised 6. Innovator and generic	7. Mandatory 8. Decentralised 9. Innovator and generic
Warning on label	X	X	X
Education, including contraceptive counselling	X	X	X
Red label stickers to pharmacies and wholesalers	X	X	X
"Avoid pregnancy" icon	X	X	X
Patient consent form	X	X	X
Required pregnancy test prior to start of treatment[a]	X	X	X
Required selection of two forms of birth control[a]	X	X	X
Required two pregnancy tests prior to start of treatment[a]		X	X
Limited 30-day supply/no refill		X	X
Pharmacists required to give medication guide with prescription		X	X
Required use of qualification stickers by registered prescriber[a]		X	X
Required monthly pregnancy tests[a]			X
Required registration in database by patients, prescribers, pharmacists, and wholesalers[a]			X
Qualifying questions for patient			X
Monthly identification of contraceptive methods by patients and doctors			X
Success rate: pregnancies ► **per 1,000 courses of treatment (1989 to 2001 (54))** ► **per 1,000 female users in the programme (2001 and 2010 (55–56))**	**2.8 - 4.0[d]**	**1.2 - 1.8[d]**	**1.2 - 1.4[d]**

[a] as noted on prescription package insert.
[b] and equivalent programmes SPIRIT, IMPART and ALERT (programmes initiated by generic companies upon introduction of generic isotretinoin on the U.S. market).
[c] single shared risk minimisation programme for isotretinoin.
[d] range rounded at one digit.

The main elements of the Accutane PPP include patient and prescriber education, informed consent, voluntary registration of programme participants and a tracking of pregnancy exposure. In PPP however, there was no direct link between the result of a pregnancy test and the dispensing of isotretinoin.

A telephone survey of dermatologists and primary care physicians (i.e. Accutane Prescriber Tracking Survey) was launched to determine the usage of the PPP components and evaluated compliance to PPP but its results were difficult to interpret because it was planned to track the physician's perceptions of whether the risk minimisation activities had been performed rather than the actual use of the PPP components.

From 1989 onward, effectiveness was monitored through a large-scale epidemiologic survey developed and conducted by the Slone Epidemiology Center at Boston University (i.e. the Accutane Survey). Interim results from a voluntary survey of 177,216 eligible female patients were published in 1995 **(52)**. More complete data from 1989 to 2000 obtained in nearly half a million female patients confirmed the preliminary results and indicated some success with the Accutane PPP **(51)**. Pregnancy rates in the general U.S. population were 105 pregnancies per 1,000 women year, compared with 7.4 in those taking Accutane (NHCS, 2000; women aged 15–44).

Although the awareness of the teratogenic risk was high (i.e. 99%), many weaknesses in compliance were identified; for instance, as many as 24% of female patients failed to receive a pregnancy test prior to starting therapy and 15% did not recall being told to use birth control for one month prior to starting therapy **(51)**. As a result, the FDA asked Roche to revise further this risk minimisation programme.

On 10 April 2002, Roche announced the implementation of SMART™ (the System to Manage Accutane-related Teratogenicity™), a new voluntary enhanced programme to strengthen the elements put in place previously in PPP **(54)**. First, the prescriber had to sign a letter of understanding to obtain a supply of yellow self-adhesive Accutane qualification stickers to be used as surrogate markers for appropriate pregnancy testing. Secondly, isotretinoin could only be prescribed to female patients who met three conditions: (1) two negative pregnancy tests, (2) a commitment to using two forms of birth control from one month before treatment through at least one month after treatment ceased, and (3) the signature on an informed consent form. Upon fulfilling these three conditions, the prescriber had to affix a yellow sticker with the date of the patient qualification on the prescription to trigger, within seven days of qualification, the dispensing of isotretinoin by registered pharmacies only to those patients presenting a prescription with a sticker attached. The goal set for the SMART™ programme by FDA was that no woman should begin isotretinoin therapy if pregnant and that no pregnancy should occur while a woman is taking isotretinoin. The agency however admitted that it is impossible to actually meet that goal but that it wanted to set the stage about the importance of the risk of pregnancies in women receiving isotretinoin.

The implementation and the adherence to the key elements of SMART were evaluated through a 'Prescription Compliance Survey' designed to evaluate compliance with the qualification sticker (> 94% dispensed isotretinoin prescriptions had a qualification sticker attached and correctly completed) and a voluntary 'SMART-revised Accutane Survey' designed to evaluate the compliance with the key elements of the programme and to ascertain the patient knowledge of the teratogenicity of isotretinoin. The results showed that 9% of the patients had no pregnancy testing before the prescription of isotretinoin and 34% of women at risk for pregnancy failed to receive the two recommended pregnancy tests. Eighteen percent (18%) of women reporting to be sexually active did not use two effective forms of contraception while 1% did not use any contraception at all. This suggested some weaknesses in the implementation of the programme despite the fact that 98% of women taking isotretinoin knew they had to avoid pregnancy. In addition, given the non-mandatory nature of the survey, it was difficult to ascertain whether the sample of the survey participants was reasonably representative of all female isotretinoin users.

Effectiveness measured as the rate of occurrence of isotretinoin-exposed pregnancies was also measured in the latter survey and in a 'before/after' SMART comparison. Evaluation metrics were established and agreed with FDA (see Table 5.6).

As of April 2004, the FDA was examining the need for further safeguards surrounding isotretinoin use and potential birth defects as outlined already in a letter from October 2001 to Roche. In 2005, iPLEDGE™, a *single* computer-based, controlled distribution programme and *mandatory* pregnancy registry which provides

a closed-loop system for prescribing, dispensing, and distributing isotretinoin valid for all isotretinoin products was launched **(56)**. This risk minimisation programme includes the following five mandatory components:

1. **Registration** for all patients prescribed isotretinoin, all prescribers of isotretinoin, all dispensing pharmacies via a responsible site pharmacist and wholesalers through a unique Internet website (www.ipledgeprogram.com);
2. **Education** for all isotretinoin prescribers and all patients prescribed isotretinoin;
3. **A qualification process,** i.e. for females of childbearing potential, answers to first month questions; answers to mandatory, interactive-educational questions each month about the patient's selected methods of contraception and about birth defects prior to each new prescription; and mandatory negative results to laboratory-based pregnancy tests performed in a CLIA-certified accredited laboratory. Pharmacists are authorised to dispense isotretinoin only after a patient has met all iPLEDGE™ requirements;
4. **A centralised pregnancy registry** with root cause analysis for each pregnancy that occurs; and
5. **A technical infrastructure** to support (1) the registrations, (2) collection of laboratory pregnancy test results (including a formalised process for following-up with prescribers and patients if expected pregnancy test results are not entered into the system in order to ensure that a potential pregnancy does not go unreported), and (3) verification of female patient qualifications.

A computer system checks automatically whether the patient received counselling by the prescriber, correctly answered the educational questions every month, whether patient and prescriber entries for the primary contraceptive form match and whether negative pregnancy test results have been entered by the prescriber.

A feedback loop was integrated into the risk minimisation programme. Shortly after the iPLEDGE™ programme began accepting patient registrations, the sponsors received stakeholder feedback on the operational aspects of the programme and, as a consequence, introduced several changes to facilitate the process (e.g. resetting of the prescriber's iPLEDGE password, change in the 23-day lockout period for requalification for a new isotretinoin prescription). Based on a business decision, Roche discontinued the marketing of Accutane (isotretinoin) at the end of 2010. However, iPLEDGE™ is still active in the USA supported by a consortium of generic companies. The success of the programme is still not sufficiently defined and there are no current standards about what is or should be achievable in terms of risk minimisation with the use of isotretinoin.

J. References

1. U.S. FDA. Guidance for industry. Development and use of risk minimisation action plans. 2005. www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126830.pdf, accessed 17 January 2014
2. EMEA. Action plan to further progress the European risk management strategy. Concept paper, EMEA/115906/May 2005. www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000306.jsp&mid=WC0b01ac058017e7fc, accessed 17 January 2014.
3. EMA. Volume 9A of Rules governing medicinal products in the European Union - Guidelines on pharmacovigilance for medicinal products for human use. 2008. http://ec.europa.eu/health/files/eudralex/vol-9/pdf/vol9a_09–2008_en.pdf, accessed 17 January 2014.
4. Gridchyna I, Cloutier AM, Nkeng L et al. Methodological gaps in the assessment of risk minimization interventions: A systematic review. Pharmacoepidemiol Drug Saf. 2014, *accepted for publication.*
5. Green LW, Kreuter MW. Health program planning: An educational and ecological approach. New York: McGraw-Hill. 2005, 4th edition.
6. Donabedian A. Explorations in quality assessment and monitoring. Vol. II. The criteria and standards of quality. Ann Arbor, Michigan: Health Administration Press, 1982.
7. U.S. CDC. Framework for program evaluation in public health. MMWR. 1999, 48: No. RR-11. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4811a1.htm, accessed 17 January 2014.
8. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. Am J Public Health 1999, 89(9): 1322–7. (Also see at www.re-aim.org.)
9. Glasgow RE. Evaluation of theory-based interventions: The RE-AIM model. In Glanz K, Lewis FM, Rimer BK (eds). Health Behavior and Health Education. San Francisco: Wiley. 2002, 3rd ed.: 531–544 (for latest updates see www.re-aim.org).

10. Feldstein AC, Glasgow RE. A practical, robust implementation and sustainability model (PRISM) for integrating research findings into practice. Jt Comm J Qual Improv. 2008, 34(4): 228–243.
11. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. BMJ. 2008, 337: a1714.
12. Banerjee AK, Zomerdijk IM, Wooder S et al. Post-approval evaluation of effectiveness of risk minimisation: Methods, challenges and interpretation. Drug Saf. 2014, 37: 33–42.
13. Knudson AL. Pretesting: A positive approach to evaluation. Public Health Reports. 1952, 67(7): 699–703.
14. Deniston OL, Rosenstock IM. Getting VA, Welch W. Evaluation of effectiveness. Public Health Reports. 1968, 83(4): 323–336.
15. Deniston OL, Rosenstock IM. Evaluating health programs. Public Health Reports. 1970, 85(9): 835–840.
16. U.S. FDA. Guidance for industry. Format and content of proposed Risk Evaluation and Mitigation Strategies (REMS), REMS evaluations, and proposed REMS modifications. Draft Guidance. 2009. www.fda.gov/downloads/Drugs/GuidanceCompliance RegulatoryInformation/Guidances/UCM184128.pdf, accessed 17 January 2014.
17. EMA. Guidance on format of the risk management plan (RMP) in the EU – an integrated format. EMA/465932/2013. 2013, July. www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2012/11/WC500134650.pdf, accessed 17 January 2014.
18. EMA. Guideline on good pharmacovigilance practices (GVP) ModuleVIII – Post-authorisation safety studies (EMA/813938/2011, Rev. 1) 2013. www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf, accessed 17 January 2014.
19. Prieto L, Spooner A, Hidalgo-Simon A et al. Evaluation of the effectiveness of risk minimisation measures. Pharmacoepidemiology and Drug Safety. 2012, 21: 896–899.
20. Damschroder LJ, Aron C, Keith RE, Kirsh SR, Alexander JA, Lowery JC. Fostering implementation of health services research findings into practice: A consolidated framework for advance implementation science. Implementation Science. 2009, 4:50. www.implementationscience.com/content/4/1/50.
21. Tan-Torres Edejer T, Baltussen R, Adam T et al. (Eds). Making choices in health: WHO guide to cost-effectiveness analysis. Geneva: WHO. 2003. www.who.int/choice/publications/p_2003_generalised_cea.pdf, accessed 17 January 2014.
22. Dana A, Schneider B. Program integrity in primary and early secondary prevention: Are implementation effects out of control? Clin Psychol Rev. 1998, 18: 23–45.
23. Dusenbury L, Brannigan R, Falco M et al. A review of research on fidelity of implementation: Implications for drug abuse prevention in school settings. Health Educ Res 2003, 18: 237–256.
24. Elliot D, Mihalic S. Issues in disseminating and replicating effective prevention programs. Prev Sci. 2004, Vol.5, 47–53.
25. Carroll C, Patterson M, Wood S et al. A conceptual framework for implementation fidelity. Implementation Science. 2007, 2:40. www.Implementationscience.com, accessed 17 January 2014.
26. American Pharmacists Association. 2011 REMS white paper. Summary of the REMS stakeholder meeting on improving program design and implementation. J Am Pharm Assoc. 2011, 51: 341–358.
27. Lee LY, Kortepeter CM, Willy ME et al. Drug-risk communication to pharmacists: Evaluating the impact of risk-minimization strategies on the practice of pharmacy. J Am Pharm Assoc. 2008, 48: 404–500.
28. Montori VM, Permanyer-Miralda G, Ferreira-Gonzalez I, et al. Validity of composite end points in clinical trials. BMJ 2005, 330,594–6.
29. Kleist P. Composite endpoints: Proceed with caution. Applied Clinical Trials. 2006. www.appliedclinicaltrialsonline.com/appliedclinicaltrials/article/articleDetail.jsp?id=324331, accessed 17 January 2014.
30. Tomlinson G, Detsky AS. Composite endpoints in randomized trials: There is no free lunch. JAMA. 2010, 303(3): 267–268.
31. De Gruttola VG, Clax P, DeMets DL, et al. Considerations in the evaluation of surrogate endpoints in clinical trials. Summary of a National Institutes of Health workshop. Control Clin Trials. 2001, 22(5): 485–502.
32. Smalley W, Shatin D, Wysowski DK et al. Contraindicated use of cisapride: Impact of Food and Drug Administration regulatory action. JAMA. 2000, 284(23): 3036–3039.
33. De Bruin ML, Panneman MJM, Leufkens HGM et al. Use of cisapride with contraindicated drugs in the Netherlands. Ann Pharmacother. 2002, 36: 338–343.
34. Guo JJ, Curkendall S, Jones JK et al. Impact of cisapride label changes on codispensing of contraindicated medications. Pharmacoepidemiol Drug Saf. 2003, 12: 295–301.
35. Graham DJ, Drinkard CR, Shatin D et al. Liver enzyme monitoring in patients treated with troglitazone. JAMA. 2001, 286: 831–833.
36. Cluxton RJ, Li Z, Heaton PC et al. Impact of regulatory labeling for troglitazone and rosiglitazone on hepatic enzyme monitoring compliance: Findings from the State of Ohio Medicaid program. Pharmacoepidemiol Drug Saf. 2005, 14: 1–9.
37. Kehely A, Smith C and Czarnecki A. Risk minimisation method evaluation in oncology. Drug Information Journal. 2011, 45: 77–82.
38. Idänpään-Heikkilä J, Alhava E, Olkinuora M, et al. Clozapine and agranulocytosis. The Lancet. 1975, 306: 611.
39. Idänpään-Heikkilä J, Alhava E, Olkinuora M, et al. Agranulocytosis during treatment with clozapine. Eur J Clin Pharmacol. 1977, 11: 193–198.
40. Andersohn F, Konzen C, Garbe E. Systematic review: Agranulocytosis induced by nonchemotherapy drugs. Ann Intern Med. 2007, 146: 657–665.
41. Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001, 69(3): 89–95.
42. Chin R and Lee BY. Principles and practice of clinical trial medicine. USA: Elsevier Science & Technology. 2008, Chapter 4 Measures and variables: 61–78, Chapter 7 Endpoints: 121–144.
43. Glasgow RE, Davidson KW, Dobkin PL et al. Practical behavioural trials to advance evidence-based behavioural medicine. Ann Behav Med. 2006, 31: 5–13.
44. Nkeng L, Cloutier AM, Craig C et al. Impact of regulatory guidances and drug regulation on risk minimisation interventions in drug safety: A systematic review. Drug Safety. 2012, 35(7): 535–546.
45. Alvir JM, Lieberman JA, Safferman AZ et al. Clozapine-induced agranulocytosis: Incidence and risk factors in the United States. N Engl J Med. 1993, 329: 162–167.
46. Copolov DL, Bell WR, Benson WJ et al. Clozapine treatment in Australia: a review of haematological monitoring. Med J Aust. 1998, 168(10): 495–497.

47. Rosenheck R, Cramer J, Xu W et al. A comparison of clozapine and haloperidol in hospitalized patients with refractory schizophrenia. Department of Veterans Affairs Cooperative Study Group on Clozapine in Refractory Schizophrenia. N Engl J Med. 1997, 337: 809-815.
48. Alphs LD, Anand R. Clozapine: The commitment to patient safety. J Clin Psychiatry. 1999, 60 [Suppl 12]: 39–42.
49. Schulte PFJ. Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. Ann Pharmacother. 2006, 40(4): 683–688.
50. Rosa FW. Teratogenicity of isotretinoin. Lancet. 1983, 2(8348): 513.
51. U.S. FDA. Dermatologic Drugs Advisory Committee FDA briefing information: September 21, 2000. www.fda.gov/ohrms/dockets/ac/00/backgrd/3639b1.htm, accessed 17 January 2014.
52. Mitchell AA, Van Bennekom CM, Louik C. A pregnancy-prevention program in women of childbearing age receiving isotretinoin. N Engl J Med. 1995, 333: 101–106.
53. Abroms L, Meibach E, Lyon-Daniel K et al. What is the best approach to reducing birth defects associated with isotretinoin? PLOS Medicine. 2006, 3(11): 1978–1983.
54. U.S. FDA. Joint meeting with Dermatologic and Ophthalmic Drugs Advisory Committee FDA Briefing Information: February 26–27, 2004. www.fda.gov/ohrms/dockets/ac/04/briefing/4017b1.htm.
55. U.S. FDA. Joint meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee: December 1, 2011. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM281376.pdf, accessed 17 January 2014.
56. U.S. FDA. Joint meeting of the Drug Safety and Risk Management Advisory Committee and the Dermatologic and Ophthalmic Drugs Advisory Committee: August 1, 2007. Briefing Document for iPLEDGE year one update. www.fda.gov/ohrms/dockets/ac/07/briefing/2007–4311b1–02-ipledge.pdf, accessed 17 January 2014.
57. EMA. Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (EMA/204715/2012). www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162051, accessed 1 March 2014.

CHAPTER VI:

STAKEHOLDERS

A. Introduction

The marketing authorisation holder (MAH) and regulatory authorities are partners in determining the need for a risk minimisation strategy and in defining the scope and content of any ensuing risk minimisation plan. However, a variety of other parties, particularly patients and healthcare professionals, have a stake in the success of risk minimisation efforts. As risk minimisation plans entail a significant commitment in terms of time, cost and human resources, the MAH should identify the key stakeholders that need to be involved and elicit their input in the design phase of the risk minimisation strategy in order to increase the likelihood that the strategy will be both feasible and effective. Such stakeholder involvement should be transparent. Documenting stakeholder input and providing it to the relevant regulatory authorities can greatly enhance the perceived credibility of the risk minimisation strategy and increase regulators' confidence that the proposed plan is feasible, acceptable to its target audiences, and can, most importantly, be implemented as intended.

While the importance of gaining stakeholder input is generally accepted, numerous questions remain, however, concerning how best to involve them. Such issues include: how to select individuals to represent a particular stakeholder perspective, whether (and if so, how) to train and compensate these representatives, how early in the risk minimisation planning process to engage them, and how frequently thereafter.

B. Key stakeholders

Relevant stakeholders for risk minimisation planning may include, but are not necessarily limited to, the following key groups: patients and their care partners, physicians, pharmacists and other healthcare professionals (e.g. nurses, physician assistants), and health insurers. The unique considerations involved in engaging each of these stakeholder groups are described briefly below.

• Patients and care partners

Patient representation in the development of new medicinal products is an accepted practice and one recognised as being beneficial for both patients and the drug manufacturer alike. Over the past several decades, effective models of patient-pharmaceutical company partnership have emerged for the purposes of consultation and information exchange. Examples of such partnerships are evident in the areas of cancer, HIV/AIDS, Parkinson's Disease and Paget's Disease **(1-4)**. Depending on the disease or medical condition, patients may not be physically or mentally capable of such participation; in those instances, the patient's care partner can serve as a proxy. While such patient-industry collaborations are comparatively well-established in the United States (US), Canada, the United Kingdom (UK), parts of Western Europe, and Australia, they represent an emerging phenomenon in Asian and Central European countries.

The increasing trend towards collaboration between the pharmaceutical industry and patients reflects the growing acknowledgement that patients have a unique perspective that is distinct from, but as important as, that of the medical, scientific and regulatory communities **(1)**. In fact, the lack of patient input was identified as one of the shortcomings of the European Union's (EU) pharmacovigilance system, and prompted

the inclusion of patient representatives on the EU's Pharmacovigilance Risk Assessment Committee (EU Regulation No. 1235/2010). Similarly, as part of its Prescription Drug User Fee Act - 2012 (PDUFA V) commitments, the FDA has embarked on a variety of related initiatives to elicit patient input on product benefit-risk decisions **(5)**.

In the context of risk minimisation planning, input from patients regarding the relevance, acceptability, and feasibility of a proposed initiative is critical in order to optimise the design of the risk minimisation plan, broaden support and gain cooperation for implementation. In particular, given the complexity of healthcare systems, formal solicitation of patient input regarding the design of a risk minimisation strategy may be essential to the strategy's ultimate success.

Recruiting, selecting, training and compensating patient representatives are all key issues; however, there is no consensus as to how best to address them. Patient recruits can be either 'professional' or 'grass-roots' advocates. While professionals engage in patient advocacy work on a full-time basis as their primary, paid livelihood, 'grass-roots' advocates tend to do so on an *ad hoc* basis and not necessarily for pay. As financial compensation for participation (particularly if it is provided by the pharmaceutical company) can potentially bias a patient's perspective, there is a role for an independent third party to facilitate the establishment of patient advisory boards for particular disease conditions and/or treatment regimens **(6, 7)**.

Patients who have been selected as representatives on risk minimisation planning committees may require training, particularly as regards the laws and regulations to which other stakeholders (regulators, companies) work and receive a clear description of what their responsibility as an advocate would be in the context of risk minimisation.

Once recruited and trained, input from patient representatives can be obtained through a variety of means, including focus groups, advisory board meetings, surveys or individual interviews. Input can be elicited on an *ad hoc* basis or at regular intervals throughout the risk minimisation planning process, through to implementation and evaluation. The latter approach is advantageous in that, by providing an opportunity for continued involvement, it may ensure that patients have a deeper understanding of the risk minimisation strategy for the product.

An evaluation of patient input to a risk minimisation programme can address both the *process* of obtaining such input as well as salient outcomes of such input (e.g. rate of adoption of risk minimisation strategy by target patient groups; extent to which target patients cooperated with the proposed risk minimisation efforts). Pharmaceutical manufacturers can perform such evaluations themselves, or, alternatively, this function could be performed by an independent third party.

Evidence suggests that there is a strong interest among patients to participate in risk minimisation planning. In a survey of 143 patients with a variety of different chronic health conditions, 82% expressed willingness to help design a risk minimisation programme **(8)**. In terms of preference for involvement in risk minimisation plan design, survey participants were most interested in participating in longitudinal observational studies evaluating the impact of a particular risk minimisation strategy (85% "very" or "somewhat" interested), providing feedback on how to decrease the potential 'burden' of risk minimisation activities on patients (82% "somewhat" or "very" interested), and helping improve the comprehensibility of patient drug information used in risk minimisation programmes (80% "somewhat" or "very" interested).

• Physicians and other healthcare professionals

Physicians represent another key stakeholder group for risk minimisation planning and execution. Physicians have been interacting with the pharmaceutical industry for many years in relation to clinical trials (both pre-marketing and postmarketing studies) and education in the form of detailing from sales representatives and educational events. Physicians also often serve as members of advisory boards for pharmaceutical companies. What is different about the type of input needed from physicians in regard to risk minimisation planning?

Over the last 5 years there has been an increased attention to the issue of the influence of pharmaceutical-sponsored educational events on prescribing behaviour. While this effect has been recognised for some time **(9)**, there have been recent moves by professional bodies to provide guidance on these interactions **(10-12)**.

Despite the absence of clear guidance from regulatory agencies or other professional bodies as to how and to what extent physicians should be involved in the development of these risk minimisation activities, there are potential conflicts of interest for any physician who provides advice to the pharmaceutical industry and this potential conflict should be acknowledged and documented **(13,14)**. A conflict of interest might arise, for example, in a situation where a physician is serving in some paid, advisory capacity to a pharmaceutical company (e.g. scientific advisory board member) and is, at the same time, serving as a consultant to a regulatory body or professional association in regard to risk minimisation. The physician in this situation might be potentially biased in favour of the company's proposed risk minimisation plan or programme. Consequently, some regulatory authorities apply strict codes of conduct to their experts and advisory committees **(15)**.

One way to minimise potential conflict of interest would be to have educational activities for a risk minimisation strategy be provided by a third party, such as a professional college or association, or accredited as a Continuing Medical Education (CME) activity for the relevant physician group by an academic institution or professional association. Such an approach could help ensure that the activity was seen as being public health in nature as opposed to promotional and could potentially facilitate greater cooperation from physicians.

• Health insurers and/or payers

Health insurers, whether public or private, require in-depth knowledge on the benefit-risk of medications before they will grant reimbursement coverage. Payers are decision-makers who operate in parallel with, albeit independently of, regulatory agencies. While most of their decisions are ultimately based on cost (e.g. cost of medicines, cost of resulting healthcare utilisation, and budget impact), the demonstration of the added value of a medicine is their main concern. Risk is therefore one component which contributes to the overall evaluation of benefit-risk and budget impact.

While one can appreciate the complementarity between risk minimisation and optimisation of cost-benefit and cost-effectiveness, risk minimisation plans or interventions may conflict with health policies that may be implemented concomitantly. Recent examples include the coverage of medicines that are used off-label for a given indication while the medicine approved for this specific indication is not covered because of cost. Another example is the coverage of safer but more expensive medicines only when other more affordable treatment options fail. For high-risk medicines like opioids, switching product commonly occurs to meet formulary requirements, hence placing the patient at risk of overdose. The latter consideration may not necessarily be planned in the design of the risk minimisation strategy.

Conversely, reimbursement restrictions may lessen the need for risk minimisation interventions. For example, if coverage is restricted to in-hospital dispensing, then the target population and risk factors might be less of a safety concern than if the drug were widely prescribed in the community and used off-label. Due to the Controlled Substances Act, dispensing of several psychotropic drugs is restricted in the U.S. While such restrictions minimise the risk of abuse, they mostly do not minimise the risks associated with off-label prescribing. For some payers, such as the public drug programme of Ontario (Canada), the Ontario Drug Benefit Program and the Special Drugs Program **(16)**, therapeutic intent must be specified by physicians on the prescription and reimbursement is restricted to well-defined indications. In Quebec, for example, the prescription of cholinesterase inhibitors for the treatment of dementia may only be renewed if treatment appears to be effective. While such a restriction was initially implemented for cost considerations, ultimately it also served to optimise the benefit-risk of these medicines under 'real world' circumstances.

In addition to influencing the implementation of risk minimisation interventions, health policies and third-party payers also have an impact on the methods used to evaluate the effectiveness of risk minimisation interventions. For example, absence of or delay in formulary coverage greatly hampers the uptake of

a new medicine. As a result, it may be difficult to meet the milestones set in the evaluation programme approved by the regulatory authorities. In such cases, administrative claims databases are not a viable tool to be used in the evaluation of the risk minimisation intervention. Interactions between the pharmaceutical company and third-party payers must be well communicated and as early as possible in the medicine's lifecycle so that an appropriate evaluation strategy may be designed.

C. Snapshot of stakeholder perspectives

Input on engagement in risk management planning was sought from stakeholders (n=188) who voluntarily attended a scientific session at a European Drug Information Association meeting in 2012. This real-time, interactive survey was conducted by CIOMS in order to evaluate the utilisation and content of a harmonised risk minimisation toolkit. Participants were asked to provide input regarding strategy, design, and implementation of interventions to minimise risks associated with the use of medicines. Highlights are summarised here; the survey instrument and additional details are provided in Annex IV.

- The majority (60%) of the audience self-identified as experts, while 27% and 13% categorised themselves as HCPs and patients, respectively.
- As regards selection, training and compensation, stakeholder groups supported involvement of independent third parties, regulatory authorities or professional organisations rather than companies. In particular, the patient stakeholders showed a strong preference (60%) for professional organisations to coordinate these activities.
- When asked if stakeholders, e.g. HCPs or patients, should be involved in the design of risk minimisation activities, the three groups indicated a desire for engagement, with a tendency toward appointment to an MAH's or Regulator's advisory committee.
- The majority of experts (approximately 60%), HCPs (65%) and patients (81%) thought that physician input to risk minimisation should occur after the MAH has a draft strategy. A smaller portion of the experts, HCPs and patients (approximately 18–28%) called for physician input at the beginning of the design of a risk minimisation strategy.
- As with timing of engagement, the majority recommended that pharmacists become involved only after the MAH has a draft strategy. Similarly with patient engagement, a majority of experts (approximately 63%), HCPs (45%), and patients (70%) preferred patients to be involved after the creation of a draft strategy by the MAH. With respect to geographic distribution of stakeholder advisors in the risk management planning process, the great majority (collectively greater than 90%) recommended geographic diversity at either regional or national level.

D. Conclusion

In order to develop and implement an effective risk minimisation strategy for a pharmaceutical product, there are numerous important stakeholders whose perspectives should be considered. In this chapter, we have focused on patients, physicians, pharmacists and insurers; however, depending on the risk minimisation strategy, there may be other important stakeholders that need to be consulted as well (e.g. distributors). It is the MAH's responsibility to identify appropriate representatives from the key stakeholder groups, recruit and train them, and develop a process for systematically eliciting their input, whether on an *ad hoc* or ongoing basis. It is critical that MAHs be transparent in regard to stakeholder involvement and compensation, and that efforts be made to minimise any conflict of interest.

Stakeholder involvement in risk minimisation planning is an emerging area. Other than for patients, there is limited understanding of the preferences of other stakeholder groups for involvement in the risk minimisation strategy development process. Further research is needed to ascertain when, how and in what ways to involve different types of stakeholders most efficiently and effectively in order to optimise the risk minimisation planning process and increase the likelihood that risk minimisation strategies will be successful.

E. References

1. Vogt EM. Effective communication of drug safety information to patients and the public: a new look. Drug Safety. 2002, 25(5): 313-321.
2. Maguire S, Hardy C, Lawrence T. Institutional entrepreneurship in emerging fields: HIV/AIDS treatment advocacy in Canada. Academy of Management Journal. 2004, 47(5): 657–679.
3. Collyar D. An essential partnership: patient advocates and cooperative groups. Seminars in Oncology. 2008, 35(5): 553–555.
4. Langston A, McCallum M, Campbell MK, Robertson C, Ralston SH. An integrated approach to consumer representation and involvement in a multicentre randomized controlled trial. Clinical Trials. 2005, 2(1): 80–87.
5. U.S. FDA. Working with patients to explore benefit/risk: Opportunities and challenges. Patient Network Annual Meeting, hosted by FDA's Office of Special Health Issues (OSHI) in collaboration with the Center for Drug Evaluation and Research (CDER), the Center for Biologics Research and Evaluation (CBER), and the Center for Devices and Radiological Health (CDRH). Silver Spring, MD, USA, 18 May 2012. http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/ucm298136.htm.
6. Maguire S, Phillips N, Hardy C. When "silence = death," keep talking: Trust, control and the discursive construction of identity in the Canadian HIV/AIDS treatment domain. Organization Studies. 2001, 22: 287–312.
7. Montgomery K, Oliver AL. Responses by professional organizations to multiple and ambiguous institutional environments: The case of AIDS. Organization Studies. 1996, 17: 649–672.
8. Smith MY, Wicks P, Blaser DA, Masagli M, Okun S. Incorporating the patient perspective in risk minimisation programme design and implementation: A pilot study. Under review, 2012.
9. Lexchin J. Interactions between physicians and the pharmaceutical industry: what does the literature say? Canadian Medical Association Journal. 1993, 149(10): 1401–1407.
10. Industry funding of medical education: Report of an AAMC task force. Washington, D.C., USA: Association of American Medical Colleges, June 2008.
11. Guidelines for ethical relationships between physicians and industry. Sydney, Australia: The Royal Australasian College of Physicians. 3rd edition, 2006.
12. Innovating for health: Patients, physicians, the pharmaceutical industry and the NHS. Report of a working party. London, UK: Royal College of Physicians, 2009.
13. Moynihan R. Who pays for the pizza? Redefining the relationships between doctors and drug companies. BMJ. 2003, 326: 1189-1192.
14. Mitchell JM. Do financial incentives linked to ownership of specialty hospitals affect physicians' practice patterns? Med Care. 2008, 46(7): 732–737.
15. The European Medicines Agency Code of Conduct. EMA/385894/2012. London, UK: European Medicines Agency, 23 May 2013. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004924.pdf, accessed 7 March 2014.
16. What drug programs does Ontario offer? Toronto, Ontario, Canada: Website of the Ontario Ministry of Health and Long-Term Care. 2014. http://www.health.gov.on.ca/en/public/programs/drugs/programs/programs.aspx, accessed 8 January 2014.

CHAPTER VII:

CURRENT TRENDS AND FUTURE DIRECTIONS

As the science of pharmaceutical risk minimisation matures, what future trends might be anticipated? In this chapter we highlight a number of emerging trends and future directions in the field of risk minimisation of medicinal products. We examine the ways in which existing tools or methods are delivered with new technologies, as well as how novel approaches might enhance this field now or in future. The new areas of biomarkers and genetics are also discussed as are the implications for being able to personalise risk minimisation planning.

A. Emerging trends

Risk minimisation is an inter-disciplinary science. A variety of fields offer tools and methodologies that are both relevant and applicable to risk minimisation. Such fields include, for example, medicine, genetics, behavioural science, cognitive and social psychology, quality management, health services research, public health, communications science, informatics and health systems engineering. In drawing upon this wide array of disciplines, a new generation of risk minimisation strategies will emerge. To enhance effectiveness, new risk minimisation tools may be tailored to specific aspects of the patient (e.g. genetic make-up, use of concomitant medications, disabilities), and the geographic region where the product in question is to be marketed. Regional variables to address include local disease conditions, population health status, state of the economy, and characteristics of the local regulatory and healthcare systems as well as access to communication tools and devices.

In conjunction with this trend, a new type of pharmaceutical professional with a very specific expertise, the `risk management specialist' is needed, perhaps as part of the Safety Management Team concept introduced by CIOMS VI. Core responsibilities of this professional will include the development and implementation of risk minimisation tools and strategies, and the evaluation of their impact. Continuous improvement in both risk minimisation strategies and tools would fall within the purview of the risk management specialist as well. Ideally, this new professional would be conversant in a range of areas, not only drug development, pharmacovigilance, statistics and epidemiologic methods, but also research methods, psychometrics, communication, knowledge of healthcare systems, and human factors. A team of risk minimisation professionals may be required in order to adequately represent all relevant expertise.

There is a need for more inclusive and systematic methods for identifying risks to be targeted for risk minimisation. Tools such as a Failure Mode and Effects Analysis (FMEA), which apply a systems-based approach, may be especially valuable in this regard **(1, 2)**. Increasingly, *risk minimisation strategies should be developed which seek to ensure 'safe and appropriate use' of the product within the context of the proposed healthcare system,* as opposed to focusing exclusively on the clinical risks posed by the medicine.

Similarly, there is a need to define a theoretical framework for the development of risk minimisation strategies involving medicinal products. Such theory-driven approaches can guide the selection of risk minimisation tools and activities, assist in hypothesis generation, and aid in interpretation of evaluation results **(3)**.

A number of new risk minimisation tools will be available in the near future. Many of these tools have been used previously in a variety of different healthcare settings but have had limited application in the

context of formal risk minimisation strategies. An important consideration in the future will be to identify the most effective and appropriate modalities to use in delivering these new tools and to select tools that can overcome discontinuities in the healthcare delivery system.

In the following section, we discuss some risk minimisation tools that utilise digital health technologies. A number of the tools described were originally developed for use via paper-based or in-person modalities. With the availability of the Internet, and the widespread use of computers and smartphones, it is possible to administer these tools more cheaply and more conveniently to a wider range of people in a shorter time. In the context of a product that requires a *global* risk minimisation strategy, it may be necessary to identify more than one modality for delivering risk minimisation in recognition of the fact that not all prescribers and patients world-wide will have equal access to the same types of technology.

Web-based physician checklists: The purpose of a checklist is to enhance the quality and consistency of clinical decision-making. Checklists can serve as a memory aid and decision support tool for the physician, highlighting the most critical steps that need to be followed in performing a specific medical process or procedure **(4)**. For example, a checklist might be used in a risk minimisation strategy to train physicians how to screen patients to determine whether they have a high-risk condition that would make them an inappropriate candidate for a particular drug. While currently predominantly paper-based, interactive web-based versions of checklists should represent a promising extension of this concept.

Electronic audit and feedback systems: Audit and feedback is defined as *'any summary of clinical performance of healthcare over a specified period of time' that is provided verbally, electronically or in a written format'* **(5)**. Audit and feedback is a well-established method for enhancing professional practice and has been used most frequently in the context of correcting deviations from established clinical practice or accepted clinical guidelines. With the Internet, audit and feedback techniques can be used interactively (e.g. as in an electronic medical record), thus enhancing their effectiveness. A risk minimisation strategy might utilise an audit mechanism for evaluating the impact of an educational initiative or to test the degree to which physicians are adhering to a recommended checklist or clinical guidelines for treating their patients with a particular medicine. In this manner, web-based questionnaires can be designed and used to assess effectiveness of a risk minimisation educational programme that targets healthcare professionals. Feedback systems can be built in to reinforce new behaviours and to provide guidance to the physician about specific actions that he/she needs to correct.

Computer Simulations (virtual reality, digital animations, and 'gaming'): Digital techniques using high-quality three-dimensional animations, computer graphics and virtual reality environments are now widely available and have been used successfully in a host of other industries to educate and train personnel. The power of these techniques rests in the fact that they permit visualisation of key concepts, and simulations of actual scenarios in which the patient or healthcare professional would be required to apply the newly acquired knowledge. They also offer the opportunity for 'hands on' learning.

In particular, computer-simulated virtual reality can be used to create an environment that can be shared by several people, thus permitting a teacher to provide immediate feedback during the learning process. Procedures that require the work of a team are ideally suited for practising in a virtual reality environment. As virtual reality provides the opportunity to create controllable, repeatable environments, this technology could be used in a risk minimisation strategy to educate patients and healthcare professionals about how to perform specific activities (e.g. how to self-administer the medication, how to screen patients).

In addition to simulations, digital animation approaches can be used to develop training in the form of video games, a format that is highly familiar, and attractive to younger generations of users. Digital animation approaches could be used in a risk minimisation strategy to educate children, youth and young adults about how to safely use and store a particular medication.

Technological advances will increasingly enable audio- and audio-visual based educational tools to be hosted on a variety of different platforms (e.g. data carriers, mobile phones and 'smart' phones). The optimal platform for a given set of educational materials may vary depending on such factors as patient demographics, disease condition and geographic region. More research is needed to explore the relationship between content of health communication messaging and platform type, and how to optimally translate

'paper-based' interventions to different web-based platforms. Before deciding which communication tools to use, we recommend to investigate during the planning phase the outreach of certain media to be used to apply a risk minimisation tool. For instance, smartphones may or may not be widely available in a particular country and use of computers and Internet may not be applicable to a particular patient population such as those of advancing age or comorbidities.

E-Learning and e-detailing: `E-learning' refers to the continuing education of physicians and other prescribers, using digital technology such as video conferencing and computer-based educational tools. In contrast to in-person detailing, it offers physicians the ability to access information regarding a pharmaceutical product at their own convenience, and to store the training for review at a later date. Feasibility and acceptability of e-detailing to physicians has been explored **(6)**. E-learning or e-detailing could be used, for example, in a risk minimisation strategy that seeks to educate physicians about how to appropriately screen patients to determine whether they are appropriate candidates for a particular medication.

Other digital eHealth tools: Both e-detailing and electronic decision support systems represent examples of possible applications of Internet-based activities. Other types of Internet-based activities could include: (i) strategy hub website design, (ii) expert system, and (iii) human-to-human interaction, including use of social media such as with on-line discussion or chat-line functions, messaging functions (e.g. `tweeting'), or `on-line therapists' **(7, 8, 9)**. One example of this type of capability is Netdoctor, an independent, United Kingdom-based website which offers an extensive array of health information (including medicines) as well as online medical consultation services **(10)**.

Strategy hubs are portals that offer users the opportunity to educate themselves about a particular topic using a guided information search strategy. Often the strategy is derived from a list or taxonomy of actual questions that similar users have identified as being salient **(7)**.

Web applications ('apps') with tailored, health-related feedback loops: Web apps are increasingly being developed which use an algorithm-based approach to providing expert feedback or advice that is specifically tailored to the needs and characteristics of the individual patient. Variables used to tailor the feedback include those which have been shown to be most predictive of the target behaviour and behaviour change and which are most amenable to change **(11-14)**. These apps utilize high-speed feedback loops (with option to include both positive and negative feedback) in order to encourage the desired behaviour change and keep users engaged.

These applications can also be linked to various medical devices such as blood glucose meters, blood pressure cuffs, physical activity and weight monitors to permit assessment, capture, storing and transmittal of health-related data **(15)**. In the area of pharmacovigilance, apps on mobile phones are now available for reporting adverse events, e.g. MedWatcher by the U.S. FDA **(16)**.

It is likely that in the future, these technologies may also be used to support risk minimisation strategies, for instance to deliver information or education as well as assessing effectiveness of risk minimisation interventions.

Web apps can also have various social features. For example, they can be designed to invite family, friends and/or patient 'peers' to provide encouragement or feedback. Similarly, they can be linked to different social media outlets (e.g. Facebook, Twitter) so that users can share their information or status with specified communities for support or competitions (e.g. challenge each other to consistently engage in a certain activity).

Human-to-human Interaction strategies encompass a range of computer-mediated social media–based initiatives. Examples include on-line support groups, chat-rooms, and "tweets". Such groups can be moderated by peers or professionals.

Regulations or the absence of them as well as limitations with the access (lack of resources or censorship) will have to be addressed in the risk management area as in any other areas in society. Processes for assuring accuracy and quality of content will have to be established. Regulatory authorities are already beginning to address these issues as can be seen in the recent draft guidance on Mobile Apps issued by the FDA **(17)**.

eHealth communication technologies

The rapid development of new interactive eHealth communication technologies offers another approach with their integration into a variety of different informatics systems including those used in clinical medicine, consumer health, and public health. In the near term, electronic medical record systems can be designed to accommodate a variety of risk minimisation strategies, such as clinical algorithms to guide a healthcare professional in appropriate patient selection and safe prescribing.

Packaging design: Another future trend is the implanting of information in the product bar code, QR (quick response) code or other 'data carrier' such that when the code is read the patient has access to different educational/information sites ('data clouds') to go to for more information (e.g. how to self-administer the medication, review the risk information). Other pertinent developments in product packaging include designs that promote safe storage of the medicine (e.g. medication cartons or containers that lock) or electronic reminder systems that prompt the patient at dosing time. The new 'glow cap' for pill bottles is one such example. These are cellular-connected caps that fit on standard-sized pill bottles. The caps connect wirelessly to a base station, and both the caps and the station light up at the scheduled dosing times. The cap also transmits a reminder to the patient's mobile phone via ring tone, music and/or instant message **(18)**.

Biomarkers and genetics: Other 'near future' risk minimisation tools may include extending the role of genetics to customise pharmaceutical products to patients with specific DNA profiles. Pharmacogenetics, pharmacogenomics and pharmacoproteomics may be increasingly employed to predict an individual's likelihood of experiencing benefits or harms from a particular medicine. 'Pharmacogenetics' and 'pharmacogenomics' are the study of the interaction between genetics and therapeutic drugs. The difference between these two disciplines is the initial approach of the science, although the terms are sometimes used interchangeably.

- Pharmacogenetics starts with an unexpected drug response result and looks for a genetic cause.
- Pharmacogenomics begins with looking for genetic differences within a population that explain certain observed responses to a drug.

`Pharmacoproteomics,' is the study of the interaction between tissue proteins and therapeutic drugs and complements pharmacogenetics and pharmacogenomics by using a more functional approach to identifying and characterising patients likely to experience benefits or harms as a result of a particular treatment.

Gene variants with sufficient specificity/sensitivity for identifying drug-associated adverse events may offer promising ways to identify and classify patient subgroups at increased risk of adverse reactions. An example is the use of the human leukocyte antigen HLA-B*57:01 to predict hypersensitivity to abacavir. Biomarkers in immune genes (e.g. human leukocyte antigen HLA) have been identified for other drug hypersensitivities (cutaneous, liver, agranulocytosis and lupus), but they need to have sufficient predictive value for routine, simple clinical application. There are also a number of hurdles between discovery and clinical application that need to be taken into account such as empirical demonstration, test availability and cost effectiveness.

Gene variants for drug efficacy are promising, but there are similar issues to be overcome before they can be adopted in clinical practice. Pharmacogenetic examples that are included in the product information include: (a) Warfarin and VKORC1 (vitamin K pathway) and CYP2C9 (metabolism for inactivation) variants; (b) Clopidogrel and CYP2C19 variants (prodrug conversion); and (c) Tamoxifen and CYP2D6 variants (prodrug conversion). An example of pharmacogenomics is the use of KRAS mutation status (tumour DNA), as a response predictive biomarker for cetuximab treatment for colorectal cancer (KRAS mutated tumours do not respond). An example of pharmacoproteomics is the use of tumour HER2 protein expression as a response predictive biomarker for herceptin and lapatinib in breast cancer (HER2 over-expressors respond better).

Genetic profiling should be integrated in pre- and postmarketing study protocols to be able to look for patterns in patients such as susceptibility to adverse effects or likelihood of therapeutic responses.

B. Long-term trends

Motivating both healthcare professionals and patients to take responsibility for learning how to safely and appropriately use medications is a key challenge in risk minimisation. To address this issue, the traditional roles of patient and healthcare professional may need to be re-defined and new approaches identified for motivating and empowering patients. This is particularly the case for developing world settings where healthcare resources are scarce. A 'peer-to-peer' model, currently used for public health and health promotion initiatives in Africa and other developing regions or countries, could be applied to risk minimisation interventions as well. Such models rely upon information and education being transmitted from one patient to another, aided by social media and the increasingly cheap and ubiquitous mobile (cell) phone technology.

Behaviour can also be changed by incentives such as virtual monetary rewards, social reinforcement, or visualisations that quantify or otherwise display patient progress. Examples of the latter can be seen in the popularity of such virtual games as MyLand (by Striiv, Inc. in which patient progress translates into the growth of new wildlife and plants on an individual's 'enchanted island'), or MindBloom.com (in which each step in a patient's progress results in growth of a flower).

For the treating physician, rewards (for learning how to safely and appropriately prescribe medications) could take the form of continuing medical education credits supporting marketing authorisation renewal, reduction in professional insurance rates, being listed or announced publically as supporting public health (in regional papers, respective homepages, phone books), provision of scientific literature or support/training in using (electronic) communication tools with their patients. Also, physicians could be motivated with added functionality in any technological tools that can help them with their day-to-day clinical practice.

For patients, rewards can include reimbursement of treatment, offer of free or reduced rates for health services (professional dental hygiene, vaccination, travel medicine consultation), a healthy recipes cook book, free hours or preferential rates at the public swimming pool, fitness centre or other memberships.

Compliance with local legislation may be an issue in some countries (e.g. Sunshine Laws in the U.S.), which makes diligent planning with input of all relevant stakeholders necessary.

Paper-based prescribing and patient information, currently the foundation of routine risk minimisation for medicines, may be replaced or enhanced in future by other communication strategies. Such strategies will be aimed at more effective provision of information to healthcare professionals and patients taking into account healthcare systems as well as scientific and technological advances.

Risk minimisation interventions should be evidence-based. New evaluation methods and paradigms will be needed to accompany new technologies and intervention approaches in risk minimisation. It will be critical that those engaged in risk minimisation work contribute to the evidence base by assessing the effectiveness of interventions and publishing results. The success of a risk minimisation strategy will need to be assessed not solely in terms of process measures but also in terms of impact on knowledge, attitudes, behaviour, and patient outcomes. Other important dimensions to assess are the extent to which the risk minimisation strategy prevents certain risks from occurring and the extent to which the risk minimisation strategy places a burden on the healthcare system. Standards need to be developed in regard to setting goals and defining success in this context, and these standards should be subject to peer review and periodic re-evaluation.

Risk minimisation activities can occur in a variety of settings (e.g. outpatient, community-based). Studies will, therefore, be needed to address the dissemination of effective risk minimisation interventions. To date, there has been no recognition of the appropriate methodologies for planning, evaluating and reporting on dissemination efforts for risk minimisation plans that occur in different settings and locations. There is a need for better understanding of the barriers and facilitators for implementing evidence-based risk minimisation activities and for methods to address these dissemination challenges (i.e. issues of design, outcomes, and external validity; balance between fidelity and adaptation to local settings; and funding of dissemination science). For example, methodological challenges to disseminating evidence-based interventions to promote physical activity have been reported **(19)**.

As risk minimisation becomes a more mature science and as tools become more effective, there will be a growing acceptance of risk minimisation as a distinct discipline within the pharmaceutical industry and better integration of risk minimisation efforts within the drug development process. In particular, there will be increased recognition of the value of piloting risk minimisation strategies and tools during Phase III trials.

There will be compelling reasons for various key stakeholders to engage and cooperate in new ways (e.g. regulatory agencies with sponsors, and between and among pharmaceutical companies), to develop, implement and evaluate risk minimisation interventions. Possible initiatives may include: class-wide REMS; 'core risk management plans' in the EU (e. g. bisphosphonates); risk mitigation tailored to the risk, not to the individual compound; more collaboration on understanding and better characterisation of certain medicine-related risks as currently done by the Progression Multifocal Leukoencephalopathy (PML) Consortium, composed of several companies working with an academic network. Research networks with existing codes of conduct and methodological standards and public private partnerships that may be able to contribute specifically to risk minimisation in the future are already established in some regions (e.g. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance – ENCePP **(20)** and Innovative Medicines Initiative – IMI **(21)** in the EU).

In the future, regulatory agencies should be open to new types of implementation models and programme evaluation designs that are more methodologically rigorous.

In addition, regulatory agencies in conjunction with trusted third parties (academia) on their behalf, may actively facilitate co-operative arrangements between sponsors (e.g. patient registries), and harmonise risk minimisation requirements for medicines within the same therapeutic class. In addition, regulatory agencies may further facilitate this process by developing generic educational packages that focus on the need to read the product information prior to prescribing and highlighting specific requirements for medicines with additional risk minimisation strategies through their communication channels with prescribers. Regulators may take a more active role in providing incentives to physicians, other prescribers and dispensers, to facilitate the uptake of risk minimisation strategies that are dependent on specific types of healthcare provider behaviours. Regulatory agencies may need to develop communication strategies, particularly around those activities that may limit consumer access (such as limiting prescribing to specific patient populations) which emphasise the overall benefit to the consumer of the strategy and encourage patient adherence.

The developing field of `implementation science' will provide methods and `lessons learnt' that should be integrated into the design of risk minimisation strategies. `Implementation science' describes the study of methods to promote optimal implementation of health interventions in 'real world' contexts. Consequently, there will be a pressing need for culturally sensitive approaches so as to enhance the adoption of risk minimisation strategies in different geographic locations. Evaluation of the implementation process is necessary in order to facilitate interpretation and generalisability of the tool's effectiveness. In addition it could shed light on the processes and causal mechanisms involved in modifying the behaviour of physicians and patients.

The implementation science approach may involve the following considerations recognised as important for influencing practice behaviour and the feasibility and sustainability of practice change:

- gathering data on **attitudes** about the new tool;
- subjective norms (perceived **pressures from colleagues** and peers to adopt or not adopt the tool);
- perceived **behaviour control** (perception of having or not having control over their behaviour);
- characteristics of the **physician-patient relationships**;
- features of their **practice environment** and of the broader **healthcare system**; and
- **HCP understanding** of the clinical problem itself.

Another promising direction involves combining different risk minimisation tools together to create a synergistic effect. This synergistic approach could involve utilising several different tactics and designing

interventions that intervene at different levels (e.g. societal, community, familial, individual), or utilising different tools collectively to target a particular topic or behaviour (e.g. specific types of patient screening) including electronic media (mixture of 'real' and electronic interaction). Ideally, evaluating the effectiveness of such strategies should include an assessment of which components of the risk minimisation intervention are the 'active' ones, and determining the independent contributions of each element on specified outcomes of interest.

In order to maximise sustainability and effectiveness, risk minimisation needs to be viewed as not the exclusive purview of the pharmaceutical companies but as a shared responsibility of pharmaceutical manufacturers, healthcare professionals, patients and the healthcare system itself. Such integration can be realised via advances in information technology (IT) coupled with education for both healthcare professionals and patients concerning their role in ensuring that drug products are used appropriately. Regulators will have a role in encouraging this shift in culture and in supporting increased collaboration of the various relevant stakeholders. Regulators and academia should facilitate the inclusion of basic risk management, including risk minimisation, in the educational curricula of physicians, nurses, pharmacists and other healthcare professionals.

Another valuable option could be to establish 'third party' organisations to conduct research on risk minimisation tools, practices, strategies, implementation and effectiveness evaluation. An independent third party in this context would be important for credibility purposes. One viable model would involve sponsors joining as fee-paying members. Membership would confer specific prerogatives, including serving on a governance board, and prioritising the research agenda.

Risk minimisation research results should be published and disseminated in the peer-reviewed literature.

C. Recommendations

- A new risk management specialist with specific expertise including risk minimisation is required. Pharmaceutical companies and regulators need to foster cross-functional collaboration of their respective expertise and acquire new skill sets currently not necessarily available in traditional settings. There is a pressing need to improve how 'risks' are identified for the purposes of additional risk minimisation;
- Risk minimisation strategies should be guided by the principles of 'safe and appropriate use' of the medicine in the healthcare system as opposed to clinical risks in isolation;
- Consideration should be given to the incorporation of digital (e-health) tools into risk minimisation strategies;
- Current and future development and use of biomarkers and genetic approaches are recommended aiming at risk prevention;
- It is important to encourage research, and generation of appropriate data to enable data-driven, evidence-based decisions; tools with proven effectiveness should be used;
- Conversely, tools with questionable effectiveness should NOT be used; if doubt exists regarding effectiveness it is imperative to carry out pilot studies;
- Companies should work with regulators to test/employ more rigorous approaches to evaluating the impact of risk minimisation strategies;
- Increased collaboration is necessary between stakeholders such as companies with regulators and between regulators in different regions;
- More efficient approaches are recommended for different products in the same class and similar risk profiles and for different classes of drugs in the same disease area. These approaches may reduce burden created by multiple programmes tackling the same risk or the same class;

- Medical education should foster a culture of risk awareness and responsibility. Risk management and risk minimisation should be integrated into healthcare professional curricula so that they eventually become standard practice and part of the healthcare system(s);
- A higher level of transparency in risk minimisation is to be encouraged. Relevant data to all stakeholders should be accessible in a common repository; and
- There is a special need for sharing data relating to assessment of effectiveness of risk minimisation. The CIOMS Working Group IX recommends having an independent 3rd party holding the data repository, with maintenance through a vendor funded by the industry as a potential model.

D. References

General references:

Alkhateeb FM, Doucette WR (2009). Influences on physicians' adopting of electronic detailing (e-detailing). Informatics for Health and Social Care (Informa Healthcare journal portfolio and online book collection). 2009, 34 (1): 39–52. (http://informahealthcare.com/page/resources/readers.)

Avorn J, Soumerai SB. Improving drug therapy decisions through educational outreach: A randomized controlled trial of academically-based detailing. N Engl J Med. 1983, 308(24): 1457–1463.

Bryman A. Quantity and quality in social research. London: Routledge; 1988.

Charmaz K. Grounded theory: Objectivist and constructivist methods. Edited by Denzin NK, Lincoln YS. Thousand Oaks, CA, USA: Sage Publications Inc. 2000: 509–535.

Denzin NK, Lincoln YS (Eds). Handbook of qualitative research. Thousand Oaks, CA, USA: Sage Publications, Inc. 2000: 835–850.

Eakin JM, Mykhalovskiy E. Reframing the evaluation of qualitative health research: Reflections on a review of appraisal guidelines in the health sciences. J Eval Clin Pract. 2003, 9: 187–194.

Farmer AP, Legare F, Turcot L, Grimshaw J, Harvey E, McGowan JL, Wolf F. Printed educational materials: Effects on professional practice and healthcare outcomes. Cochrane Database of Systematic Reviews. 2008, Issue 3. Art. No.: CD004398.

Kvale S. InterViews: An introduction to qualitative research interviewing. Thousand Oaks, CA, USA: Sage Publications. 1996.

McLellan H. Virtual environments and situated learning. Multimedia Review. 1991: 30–37.

O'Connor AM, Bennett CL, Stacey D, Barry M, Col NF, Eden KB et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database of Systematic Reviews. 2009, Issue 3. Art. No.: CD001431.

Robson C. Real world research: A resource for social scientists and practitioner-researchers. Oxford, UK: Blackwell Publishers Ltd. 1993.

Ryan GW, Bernard HR. Data management and analysis methods. Edited by Denzin NK, Lincoln YS. Thousand Oaks, CA, USA: Sage Publications Inc. 2000: 769–802.

Shah BR, Bhattacharyya O, Yu C, Mamdani M, Parsons JA, Straus SE et al. Evaluation of a toolkit to improve cardiovascular disease screening and treatment for people with type 2 diabetes: Protocol for a cluster-randomized pragmatic trial. Trials. 2010, 11:44. (http://www.trialsjournal.com/content/11/1/44.)

Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: Increasing the value of clinical research for decision making in clinical and health policy. JAMA. 2003, 290: 1624–1632.

Expanding the reach and impact of consumer e-health tools. Report by the Office of Disease Prevention and Health Promotion (ODPHP), U.S. Department of Health and Human Services. June 2006. (http://www.health.gov/communication/ehealth/ehealthTools/executivesummary.htm.)

Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B et al. for the CONSORT and Pragmatic Trials in Healthcare (Practihc) groups. Improving the reporting of pragmatic trials: An extension of the CONSORT statement. BMJ. 2008, 337: a2390.

ICH E2E guideline: Pharmacovigilance planning, Step 4 – November 2004. (http://www.ich.org).

Management of safety information from clinical trials. Report of CIOMS Working Group VI. Geneva, Switzerland: CIOMS. 2005.

References Chapter VII endnotes

1. Fetterman JE, Pines WL, Nickel WK, Slatko GH. A framework for pharmaceutical risk management. Washington, DC, USA: Food and Law Institute Press. 2003.
2. Stamatis DH. Failure mode and effect analysis: FMEA from theory to execution. (2nd ed). Milwaukee, WI, USA: ASQ Quality Press. 2003.
3. Morrato EH. Social science theory as a framework for designing and evaluating pharmaceutical risk mitigation dissemination and implementation strategies. In Risk management principles for devices and pharmaceuticals: Global perspectives on the risk-benefit assessment of medicinal products. Sietsema WK, Sprafka JM (Eds.) Rockville, MD, USA: Regulatory Affairs Professionals Society.2012.
4. Gawande A. The checklist manifesto: How to get things right. New York: Metropolitan Books. 2009.
5. Jamtvedt G, Young JM, Kristoffersen DT, O'Brien MA, Oxman AD. Audit and feedback: Effects on professional practice and health care outcomes. Cochrane Database of Systematic Reviews. 2006, Issue 2. Art. No.: CD000259.
6. Alkhateeb FM, Doucette WR. Physicians' attitudes toward e-detailing: (A pilot study). Value in Health. 2007, 10, A34-A34.
7. Strecher, V. Internet methods for delivering behavioral and health-related interventions (eHealth). Annual Review of Clinical Psychology. 2007, 3: 53–76.
8. Bhavnani SK, Bichakjian CK, Johnson TM, Little RJ, Peck FA et al. Strategy hubs: Domain portals to help find comprehensive information. J. Am. Soc. Inform. Sci. Technol. 2006, 57(1): 4–24.
9. Claypool M, Gokhale A, Miranda T, Murnikov P, Netes D, Sartin M. Combining content-based and collaborative filters in an online newspaper. Paper presented at Association for Computing Machinery (ACM) Special Interest Group on Information Retrieval (SIGIR) Workshop on recommender systems: Algorithms and evaluation. University of California, Berkeley, CA, USA. 19 August, 1999.
10. Netdoctor.co.uk. The UK's leading independent health website. www.netdoctor.co.uk, accessed on 9 March 2014.
11. Lancaster T, Stead L, Silagy C, Sowden A. Effectiveness of interventions to help people stop smoking: findings from the Cochrane Library. BMJ. 2000, August 5, 321(7257): 355–358.
12. Brug J, Campbell M. and Van Assema P. The application and impact of computer-generated personalized nutrition education: a review of the literature. Patient Education and Counseling. 1999, 36: 145–156.
13. Strecher VJ. Computer-tailored smoking cessation materials: A review and discussion. Patient Education and Counseling. 1999, 36: 107–117.
14. Unrod M, Smith M, Spring B, DePue J, Redd W, Winkel G. Randomized controlled trial of a computer-based, tailored intervention to increase smoking cessation counseling by primary care physicians. J Gen Intern Med. 2007, 22(4): 478–484.
15. Mobihealth news 2012 report: Healthy feedback loops: Devices, apps and portals. Prepared by Akamai Technologies. Boston, Massachusetts, USA: Chester Street Publishing, Inc. 2012. http://mobihealthnews.com/offers/healthy_feedback_loops/.
16. U.S. FDA. MedWatcher mobile application in medical device reporting. U.S. Food and Drug Administration. www.fda.gov/MedicalDevices/Safety/ReportaProblem/ucm385880.htm, accessed 9 March 2014.
17. U.S. FDA. Mobile medical applications: Guidance for industry and Food and Drug Administration staff. U.S. Department of Health and Human Services Food and Drug Administration, Center for Devices and Radiological Health, Center for Biologics Evaluation and Research Staff. 2013. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM263366.pdf, accessed 9 March 2014.
18. GlowCap, a comprehensive way to manage medication and get reminders for what matters most. www.glowcaps.com/, accessed 9 March 2014.
19. Rabin BA, Brownson R, Kerner JF, Glasgow RE. Methodologic challenges in disseminating evidence-based interventions to promote physical activity. Am J Preventive Medicine. 2006, 31(4): 24–34.
20. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). www.ema.europa.eu/, Home >Partners & Networks>Networks>ENCePP, accessed 9 March 2014.
21. Innovative Medicines Initiative (IMI). www.imi.europa.eu/, accessed 9 March 2014.

ACRONYMS

ACS	All-cases surveillance
ADR	Adverse drug reaction
AE	Adverse effects
AFFSAPS	Agence française de sécurité sanitaire des produits de santé
ANSM	L'Agence nationale de sécurité du médicament et des produits de santé
ATMP	Advanced therapy medicinal products
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (The German Federal Institute for Drugs and Medical Devices)
CA	Competent authority
CAPA	Corrective action and preventive action
CBC	Complete blood count
CHMP	Committee for Medicinal Products for Human Use (EU)
CIOMS	Council for International Organizations of Medical Sciences
CPMP	Committee for Proprietary Medical Products (Australia)
DHCP	Dear health care provider (U.S. FDA)
DSUR	Development safety update report
E2E	ICH pharmacovigilance plan
EEA	European Economic Area
EMA	European Medicines Agency (its acronym since 2010, formerly EMEA)
EPPV	Early postmarketing phase vigilance
ETASU	Elements to assure safe use
EU	European Union
FDA	Food and Drug Administration (U.S.)
FMEA	Failure mode and effects analysis
GVP	Good pharmacovigilance practices
HTA	Health technology assessment
HCP	Healthcare professional
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
INN	International Nonproprietary Name
KFDA	Korean Food and Drug Administration
MA	Marketing authorisation
MAH	Marketing authorisation holder

MG	Medication guide
MHLW	Japan's Ministry of Health, Labour and Welfare
NDA	New drug applications
PAES	Post-authorisation efficacy studies
PBRER	Periodic benefit-risk evaluation report
PI	Product information
PMDA	Japan's Pharmaceuticals and Medical Devices Agency
PPI	Patient package insert
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
PV	Pharmacovigilance
RE-AIM	Reach, Efficacy, Adoption, Implementation, Maintenance
REMS	Risk evaluation and mitigation strategy
RMP	Risk management plan (e.g. EU-RMP)
RMin	Risk minimisation (used herein for figures and graphs as an abbreviation)
RMinP	Risk minimisation plan (used by Health Canada)
SFDA	China's State Food and Drug Administration
SMT	Safety management team
TGA	Australia's Therapeutic Goods Administration
WG	Working group
WHO	World Health Organization

ANNEX I

GLOSSARY

Additional risk minimisation activity

An intervention intended to prevent or reduce the probability of an undesirable outcome, or reduce its severity should it occur, which is in addition to the routine risk minimisation activities defined as requirements applied to all medicinal products in the regulations of a particular territory.

Proposed by CIOMS WG IX. See also definition of 'Routine risk minimisation activities.'

Adoption

One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance). Adoption refers to the participation rate and representativeness of both the settings in which an intervention is conducted and the intervention agents who deliver the intervention. Adoption is usually assessed by direct observation or structured interviews or surveys. Barriers to adoption should also be examined when nonparticipating settings are assessed.

Modified from:

Glasgow RE, Linnan LA. Evaluation of theory-based interventions. In Glanz K, Rimer BK, Viswanath K (eds). Health Behaviour and Health Education (4th Ed.), San Francisco: Wiley. 2008: 496–497.

Glasgow RE, Vogt TM, Boles SM. Evaluating the Public Health Impact of Health Promotion Interventions: The RE-AIM Framework. Am J Public Health. 1999, 89(9)*: 1322–1327.*

Adverse Event (AE) (synonym: Adverse Experience)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (08 January 2014).

Adverse Reaction (synonyms: Adverse Drug Reaction (ADR), suspected adverse (drug) reaction, adverse effect, undesirable effect)

A response to a medicinal product which is noxious and unintended.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse and medication errors.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (08 Januar 2014).

Advocate / Patient advocate

A person who helps a patient work with others who have an effect on the patient's health, including doctors, insurance companies, employers, case managers, and lawyers. A patient advocate helps resolve issues about health care, medical bills, and job discrimination related to a patient's medical condition.

National Cancer Institute at the National Institutes of Health: http://www.cancer.gov/dictionary?cdrid=44534, *accessed on 21 March 2014.*

Benefit

An estimated gain for an individual or a population.

WHO 2002: The Importance of Pharmacovigilance. (Safety monitoring of medicinal products). http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf, accessed on 9 March 2013.

Biomarker

A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001, 69: 89–95.

Burden of a risk minimisation activity

Burden is defined as the additional load that a risk minimisation activity imposes on (1) patients, (2) carers, (3) the healthcare system including health care professionals, (4) others such as regulatory authorities, pharmaceutical companies, the supply chain and those involved in access and supervision of the use of medicines.

The burden may impact, for example:

- Patients by adversely affecting their access to prescribed medicines and/or needed healthcare services, daily activities or routines;
- Healthcare providers by adding steps or services that are normally not required in the day-to-day management of their medical area;
- The health care system by requiring extra human and/or financial resources;
- Other entities of the healthcare system by including additional scientific evaluation of the risk minimisation plan, its implementation, and its effectiveness.

Proposed by CIOMS WG IX.

Clinical endpoint

A characteristic or variable that reflects how a patient feels, functions, or survives.

Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001, 69: 89–95.

Cohort study (prospective / retrospective)

Cohort studies are studies that identify subsets of a defined population and follow them over time, looking for differences in their outcome. Cohort studies can be performed either prospectively, that is simultaneous with the events under study, or retrospectively, that is after the outcomes under study had already occurred, by recreating those past events using medical records, questionnaires, or interviews.

Strom, BL. Pharmacoepidemiology. 4th ed., Wiley. 2005, p. 23.

Coverage

See **Reach**

Cross-sectional study, prevalence study (see also Survey)

Study in which the prevalence of a variable (e.g. exposure, an event, a disease) is measured in a population at a given moment; this can also be termed a prevalence study. In pharmacoepidemiology, cross-sectional studies can be used to measure, for example:

- The prevalence of a disease or an event in a population;
- The prevalence of exposure to a risk factor such as the use of a drug.

Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

Direct Healthcare Professional Communication (DHPC)

A direct healthcare professional communication (DHPC) is a communication intervention by which important information is delivered directly to individual healthcare professionals by a marketing authorisation holder or by a competent authority, to inform them of the need to take certain actions or adapt their practices in relation to a medicinal product. For example, a DHPC may aim at adapting prescribing behaviour to minimise particular risks and/or to reduce the burden of adverse reactions with a medicinal product.

EU Guideline on good pharmacovigilance practices: Module XVI Risk-minimisation measures: selection of tools and effectiveness indicators (28 April 2014).

Educational tool

Material designed to impart awareness, knowledge and aid comprehension of specific information.

Proposed by CIOMS WG IX.

Effectiveness

Extent to which an intervention when used under the usual clinical circumstances does what it is intended to do for a defined population.

Hartzema AG, Porta MS, Tilson HH. Pharmacoepidemiology: An introduction. 2nd Edition. Harvey Whitney Books. 1991.

Effectiveness of risk minimisation

Measure of effect of risk minimisation in a setting allowing for meaningful conclusions with regard to the use of a medicinal product.

Proposed by CIOMS WG IX.

Effectiveness threshold

Minimum acceptable level of risk minimisation to be achieved in order for the intervention to be rated a success. The effectiveness threshold is determined subjectively taking into account the impact of risk, the vulnerability of the target population, the drug's benefit in a given indication as well as aspects of practicality and feasibility.

Proposed by CIOMS WG IX.

Efficiency

Results achieved in relation to the resources invested.

Hartzema AG, Porta MS, Tilson HH. Pharmacoepidemiology: An Introduction. 2nd Edition. Harvey Whitney Books. 1991.

Failure modes and effects analysis (FMEA)

Failure modes and effects analysis (FMEA) is a systematic method for evaluating a process to identify where and how it might fail and to assess the relative impact of different failures, in order to identify the parts of the process that are most in need of change. FMEA includes review of the following:

- Steps in the process
- Failure modes (What could go wrong?)
- Failure causes (Why would the failure happen?)
- Failure effects (What would be the consequences of each failure?)

Modified from: *Institute for Healthcare Improvement (IHI), Cambridge, Massachusetts, USA: http://www.ihi.org/knowledge/Pages/Tools/FailureModesandEffectsAnalysisTool.aspx, accessed on Jun 16th, 2013.*

Harm

Damage qualified by measures of frequency of occurrence, severity or duration.

Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety. 2007, 30: 825–830.

Hazard

A situation or given factor that under particular circumstances could lead to harm. A source of danger.

Modified from: *Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals, Report of CIOMS Working Group IV, Geneva: Council for International Organizations of Medical Sciences. 1998.*

Healthcare professional (HCP) (also: health professional)

A person who is qualified and trained to provide healthcare to humans. This includes doctors, physician assistants in some jurisdictions, nurses, dentists, pharmacists and midwives. For the purposes of reporting suspected adverse reactions the definition of healthcare professional additionally includes coroners and medically-qualified persons otherwise specified by local regulations.

Adapted from: *Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety. 2007, 30: 825–830* and *ICH Harmonised Tripartite Guideline post-approval safety data management: Definitions and standards for expedited reporting E2D (Nov 2003).*

Identified risk

An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples include:

- an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;
- an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group, on a parameter of interest suggests a causal relationship;
- an adverse reaction suggested by a number of well-documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site reactions.

In a clinical trial, the comparator may be placebo, active substance or non-exposure.

EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 Apr 2014).

Implementation

One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance). In this context implementation refers to the extent to which a programme is delivered as intended (*see Implementation fidelity*). There are both individual-level and programme-level measures of implementation.

Modified from: *Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. Am J Public Health. 1999, 89*(9)*: 1322–7.*

Implementation fidelity

The degree to which an intervention or programme is delivered as intended.

Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implementation Science 2007, 2:40. http://www.implementationscience.com/content/2/1/40, accessed on 10 November, 2013.

Important identified risk and important potential risk

An identified risk or potential risk that could impact on the benefit-risk profile of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product information should be considered important.

Adapted from: *ICH Harmonised Tripartite Guideline Periodic Benefit-Risk Evaluation Report (PBRER) E2C (R2) (Dec 2012).*

Important missing information (see Missing information)

Incidence

Number of new cases of an outcome which develop over a defined time period in a defined population at risk. In an epidemiologic sense incidence is a measure where the numerator refers to the number of events (counting only the initial event in each patient) and the denominator often refers to the total person-time at risk during exposure to the study drug.

Combined and modified from:

Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30: 825–830. Strom, BL. Pharmacoepidemiology. 4th ed., Wiley, 2005, p.395.

Indicator

An indicator provides evidence that a certain condition exists or certain results have or have not been achieved or provides a measure to determine the extent they have been achieved.

Modified from: *Brizius, J. A., & Campbell, M. D. Getting results: A guide for government accountability. Washington, DC: Council of Governors Policy Advisors. 1991.*

Informational tool

Material that is applied to bring attention or focus on information relevant to meeting risk minimisation objectives.

Proposed by CIOMS WG IX.

Labelling

The definition of this term varies by regulatory jurisdiction. In EU legislation the term refers to the information given on the immediate or outer packaging. In other medicinal product legislation, including that of the US, labelling may refer more broadly to the approved content of product information (*see* Product information).

Proposed by CIOMS WG IX, includes definition taken from EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Maintenance

One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance). At the individual level, it refers to the long-term results of an intervention (a minimum of six months following the last intervention contact).

At the setting level, Maintenance refers to the continuation (short-term) or institutionalization (long-term) of a programme (Goodman and Steckler, 1987). This is the extent to which intervention settings will continue a programme (and which of the original components of the intervention are retained or modified), once the formal research project and supports are withdrawn.

Modified from: *Glasgow RE, Linnan LA. Evaluation of theory-based interventions. In Glanz K, Rimer BK, Viswanath K (eds). Health Behaviour and Health Education (4th Ed.), 497, San Francisco: Wiley, 2008.*

Medication guide (Med guide or MG)

A paper handout intended for patients that are distributed as part of drug labeling at the point of dispensing of certain prescription medicines in the U.S. Medication Guides address issues that are specific to the safe and appropriate use of particular drugs and drug classes, and they contain FDA-approved information that can help patients avoid serious adverse events and assist health professionals in counseling patients about the correct use when prescribing or dispensing a drug.

Modified from: *http://www.fda.gov/Drugs/DrugSafety/ucm085729.htm, accessed on 17 March 2013.*

Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant.

It is noted that there is an ICH definition for important missing information, which is: critical gaps in knowledge for specific safety issues or populations that use the marketed product (see Annex IV, ICH-E2C (R2) Guideline).

EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

Outcome indicators

Outcome indicators provide an overall measure of the level of risk control that has been achieved with any risk minimisation measure in place. For example, where the objective of an intervention is to reduce the frequency and/or severity of an adverse reaction, the ultimate measure of success will be linked to this objective.

EU Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (28 April 2014).

Over–the–counter (OTC) drug / medicine

Medicinal product available to the public without prescription.

Glossary of terms used in Pharmacovigilance. The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala. http://who-umc.org/Graphics/24729.pdf, accessed on 17 March 2013.

Package leaflet

Patient product information in the EU. A leaflet containing information for the user which accompanies the medicinal product [Dir 2011/83/EC Art 1(26)].

Modified from: *EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).*

Patient alert card

A small leaflet or card, designed to be carried by the patient at all times, which provides critical information, about a medicine prescribed to the patient, which a healthcare professional needs to know if treating the patient.

Proposed by CIOMS WG IX.

Patient brochure

Patient brochures are specific communications, in addition to the routine product information, designed to enhance patient (or carer) awareness of a particular risk (or risks) associated with a medicinal product and the actions (s)he should take to manage the risk including reporting specific signs or symptoms.

Proposed by CIOMS WG IX.

Patient package insert (PPI)

Patient product information in the U.S., distinct from a Medication Guide. A patient package insert contains information for patients' understanding of how to appropriately use a drug product.

Modified from: *Drugs@FDA Glossary of Terms:* http://www.fda.gov/drugs/informationondrugs/ucm079436.htm#P*, accessed on 19 November 2013.*

Periodic safety update report (PSUR)

Format and content for providing an evaluation of the benefit-risk balance of a medicinal product for submission by the marketing authorisation holder at defined time points during the post-authorisation phase.

Adapted from: *EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).*

Pharmacoepidemiology

The application of epidemiologic methods, measurements, analysis and reasoning to the study of uses and effects, both intended and unintended, of medicinal products including biologicals and vaccines in defined human populations.

Proposed by CIOMS WG IX.

Pharmacovigilance

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem.

Glossary of terms used in Pharmacovigilance. The World Health Organization (WHO) Collaborating Centre for International Drug Monitoring, Uppsala. http://who-umc.org/Graphics/24729.pdf, accessed on 17 March 2013.

Pharmacovigilance system

In general, a pharmacovigilance system is a system used by an organisation to fulfill its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorised medicinal products and detect any change to their risk-benefit balance.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Post-authorisation safety study (PASS)

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.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014) [DIR 2001/83/EC Art 1(15)].

Potential risk

An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples include:

- toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies;
- adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed group), on a parameter of interest raises a suspicion of, but is not large enough to suggest a causal relationship;
- a signal arising from a spontaneous adverse reaction reporting system;
- an event known to be associated with other active substances within the same class or which could be expected to occur based on the properties of the medicinal product.

EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

Prevalence

Number of existing cases of an outcome in a defined population at a given point in time.

Adapted from: *Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30: 825–830.*

Prevalence focuses on existing states. Prevalence of a state at a point in time may be defined as the proportion of a population in that state at that time.

Rothman KJ, Green land S, Lash T. Modern Epidemiology. 3rd edition. Lippincott Williams & Wilkins. 2008:46.

Process indicators

Process indicators are measures of the extent of implementation of the original risk minimisation plan, and/or variations in its delivery.

Modified from: *EU Guideline on good pharmacovigilance practices: Module XVI Risk-minimisation measures: selection of tools and effectiveness indicators (28 April 2014).*

Product information (PI)

Documents proposed by marketing authorisation holders / applicants, amended if required and agreed by regulatory authorities which provide information to prescribers / healthcare professionals or patients on the appropriate and safe use of a medicinal product. As such the product information constitutes the main tool used for routine risk minimisation. For examples regarding terminology used in different regulatory jurisdictions see Fig. 1.1 in Chapter I. The EU labelling on the immediate or outer packaging is a part of product information.

Proposed by CIOMS WG IX.

Reach

One of 5 dimensions in the RE-AIM evaluation model (Reach, Efficacy, Adoption, Implementation, Maintenance), also referred to as 'coverage' or 'distribution'. Reach refers to the percentage of potential participants who are exposed to an intervention and how representative they are.

Glasgow RE, Linnan LA. Evaluation of theory-based interventions. In Glanz K, Rimer BK, Viswanath K (eds). Health Behaviour and Health Education (4th Ed.), 496, San Francisco: Wiley, 2008.

Reference risk (baseline risk)

Risk measured in a population, called the reference population, which resembles the exposed population in all respects except that its members have not been exposed to the factor under study. The reference risk can be very different from the risk measured in the general population.

Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

Registry

An organised system that uses observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

REMS (Risk evaluation and mitigation strategy)

FDA enforceable document required when necessary to ensure that the benefits of a drug outweigh the risks. It describes the elements that an applicant is required to implement.

Modified from: *FDA Draft Guidance for Industry 'Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications' (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf)*

Restricted access programme (May be known as managed or controlled access in some jurisdictions.)

Restricted access programmes aimed at medicinal product risk minimisation consist of interventions seeking to restrict access to a medicine on the market beyond the level of control ensured by routine risk minimisation measures.

Examples of interventions that can be linked to restricted access programmes, alone or in combination may include:

- Documentation of specific testing and/or examination of the patient to ensure compliance with strictly defined clinical criteria before the patient can receive the medication;
- Documentation of prescriber, dispenser and/or patient documenting their receipt and understanding of information on the serious risk/s associated with the medicinal product;
- Explicit procedures for systematic patient follow-up through enrolment in a specific data collection system e.g... patient registry;
- The medicine being made available for dispensing only through pharmacies or other appropriate distribution channels that are registered and approved to dispense the medicinal product (controlled distribution).

Note: Since restricted access programmes for risk minimisation have significant implications and possible burden for all concerned stakeholders, their use should be limited and guided by a clear therapeutic need for the medicinal product based on its demonstrated benefit-risk profile, the nature of the associated risk and whether this risk is expected to be managed by additional risk minimisation interventions.

Proposed by CIOMS WG IX; modified from EU Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (21 February 2014).

Risk

The probability of developing undesirable outcomes relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health or any undesirable outcomes with regard to the environment.

Combined from:

Lindquist, M. The need for definitions in pharmacovigilance. Drug Safety, 2007, 30: 825–830 and EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Risk assessment

Risk assessment consists of identifying and characterising the nature, frequency, and severity of the risk associated with the use of a product. Risk assessment occurs throughout a product's lifecycle, from the early identification of a potential product, through the pre-marketing development process, and after approval during marketing. Note: Risk assessment can be subdivided into risk estimation and risk evaluation

FDA Guidance for Industry. Premarketing Risk Assessment. March 2005. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf, accessed 11 December 2009).

Risk avoidance

An informed decision not to become involved in activities that lead to the possibility of the risk being realized.

Risk Management and Decision Making Glossary: http://www.argospress.com/Resources/risk-management/.

Risk-benefit balance

An evaluation of the positive therapeutic effects of the medicinal product in relation to the risks, i.e. any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Risk communication

Any exchange of information concerning the existence, nature, form, severity or acceptability of health or environmental risks. Effective risk communication involves determining the types of information that interested and affected parties need and want, and presenting this information to them in a useful, accessible and meaningful way.

Modified from: *Decision-making framework for identifying, assessing and managing health risks, Health Canada, 1 August 2000. (http://www.hc-sc.gc.ca/ahc-asc/pubs/hpfb-dgpsa/risk-risques_cp-pc_e.html, accessed 11 December 2009) Note: The Erice Declaration on Communicating Drug Safety Information lays out key principles for ethically and effectively communicating information on identified or potential risks. See Current Challenges in Pharmacovigilance: Report of CIOMS Working Group V. Geneva, Switzerland: CIOMS. 2001. Appendix 1: 219–220.*

Risk elimination

'Absolute' or complete prevention of risk, i.e. reduction of the frequency of an undesirable outcome to zero.

Proposed by CIOMS WG IX.

Risk estimation

Risk estimation includes the identification of outcomes, the estimation of the magnitude of the associated consequences of these outcomes and the estimation of the probabilities of these outcomes.

Risk analysis, perception and management, The Royal Society, UK. 1992.

Risk evaluation

Risk evaluation is the complex process of determining the significance of value of the identified hazards and estimated risks to those concerned with or affected by the decision. It therefore includes the study of risk perception and the trade-off between perceived risks and perceived benefits. It is defined as the appraisal of the significance of a given quantitative (or where acceptable, qualitative) measure of risk.

Risk analysis, perception and management, The Royal Society, UK. 1992.

Risk factor

Characteristics associated with an increased probability of occurrence of an event or disease.

Bégaud B. Dictionary of Pharmacoepidemiology. Wiley 2000.

Risk identification

Determining what risks or hazards exist or are anticipated, their characteristics, remoteness in time, duration period, and possible outcomes.

http://www.businessdictionary.com/definition/risk-identification.html (accessed on 16 June 2013).

Risk level / level of risk

Characterisation of an undesirable outcome by severity and likelihood of occurrence.

Proposed by CIOMS WG IX.

Risk management

Reiterative activities or interventions associated with the identification, characterisation, prevention or mitigation of risks and the measurement of the effectiveness of the risk minimisation measures.

Proposed by CIOMS WG IX.

Risk management plan (RMP)

A detailed description of the risk management system [DIR 2001/83/EC Art 1(28c)]. To this end, it 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.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Risk management system

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 activities and interventions [DIR 2001/83/EC Art 1(28b)].

EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

Risk minimisation

In a broader sense the term risk minimisation is used as an umbrella term for prevention or reduction of the frequency of occurrence of an undesirable outcome (see *risk prevention*) and reduction of its severity should it occur (see *risk mitigation*).

Proposed by CIOMS WG IX.

Risk minimisation action plans (RiskMAPs)

FDA approved strategic safety programme designed to meet specific goals and objectives in minimising known risks of a product while preserving its benefits. RiskMAPs were developed for products that had risks that required additional risk management strategies beyond describing the risks and benefits of the product in labeling and performing required safety reporting. Prior to REMS being introduced through the

Food and Drug Administration Amendments Act of 2007, in 2005, FDA had issued a guidance for industry on Development and use of risk minimisation action plans (the RiskMAP guidance), that described how to develop RiskMAPs, select tools to minimise risks, evaluate and monitor RiskMAPs and monitoring tools, and communicate with FDA about RiskMAPs.

Modified from: *FDA Draft Guidance for Industry 'Format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications'* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf).

Risk minimisation exposure

One of several measures of the fidelity of implementing a risk minimisation intervention. It describes the amount of risk minimisation delivered to the risk minimisation target (e.g. healthcare professional, patient) in terms of content, frequency and duration of an intervention.

Modified from: *Carroll C, Patterson M, Wood S, Booth A, Rick J, Balain S. A conceptual framework for implementation fidelity. Implementation Science 2007, 2:40 available at* http://www.implementationscience.com/content/2/1/40, *accessed on 19 January 2014.*

Risk minimisation-burden balance

A measure of the effectiveness of risk minimisation relative to the burden it imposes. (see *Effectiveness of risk minimisation* and *Burden*).

Proposed by CIOMS WG IX.

Risk minimisation intervention / risk minimisation activity / risk minimisation measure (synonyms)

Application of one or more risk minimisation tools with the intent to reduce the frequency of occurrence of an undesirable outcome or to reduce its severity should it occur.

Proposed by CIOMS WG IX.

Risk minimisation plan

Part of the risk management plan which details the risk minimisation activities which will be taken to reduce the risks associated with an individual safety concern. It includes both routine and additional risk minimisation activities.

Modified from: *Eudralex, Volume 9a, of the Rules governing medicinal products in the European Union. Guidelines on pharmacovigilance for medicinal products for human use. Final, September 2008: 1.3.*

Risk minimisation programme

A system of risk minimisation action(s) that are described and derived from a risk minimisation plan.

Proposed by CIOMS WG IX.

Risk minimisation strategy

Direction and scope of planned risk minimisation as specified by objective(s) and target(s) to reach defined goal(s).

Proposed by CIOMS WG IX.

Risk minimisation target

Recipient or audience for a risk minimisation intervention instrumental to its implementation, e.g. healthcare providers.

Proposed by CIOMS WG IX.

Risk minimisation tool

A risk minimisation tool is a method for delivering an intervention intended to minimise specific/specified risks.

Modified from: *FDA Guidance for Industry Development and Use of Risk Minimization Action Plans, March 2005 http://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf, accessed on 16 June 2013.*

Risk mitigation

Reduction of the severity of an undesirable outcome should it occur.

Proposed by CIOMS WG IX.

Risk prevention

Reduction of the frequency of occurrence of an undesirable outcome in a population, population subset or an individual patient.

Proposed by CIOMS WG IX.

Risks related to use of a medicinal product

Any risk relating to the quality, safety or efficacy of the medicinal product as regards patients' health or public health and any risk of undesirable effects on the environment [DIR 2001/83/EC Art 1(28)].

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Routine pharmacovigilance

Set of activities required by applicable regulations as a minimum standard of pharmacovigilance to be conducted for all medicinal products.

Proposed by CIOMS WG IX.

Routine risk minimisation activities

Risk minimisation activities that apply to all medicinal products and relate to standard activities such as product labelling, limitations on drug pack size and the legal status of the product (e.g., drug scheduling).

Modified from: *EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).*

Safety concern

An important identified risk, important potential risk or missing information.

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Safety-related outcome of interest (see also definition for outcome indicator).

Clinical outcome indicator closely linked to the goal(s) of a risk minimisation programme which has been selected as suitable indicator of relevance for measuring its effectiveness.

Proposed by CIOMS WG IX.

Serious adverse event

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Article 2(o) of Directive 2001/20/EC.

Serious adverse reaction *(see also definition for adverse reaction)*

An adverse reaction which results in death, is life-threatening, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect [DIR 2001/83/EC Art 1(12)].

EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).

Signal

Information that arises from one or multiple sources (including observations and experiments), which suggests a new potentially causal association or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial.

Adapted from*: Hauben M, Aronson J.K. Defining "signal" and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Safety. 2009, 32: 1–12.*

Signal detection

The act of looking for and/or identifying signals using event data from any source.

CIOMS WG VIII.

Signal management

A set of activities including signal detection, prioritisation and evaluation to determine whether a signal represents a risk which may warrant further assessment, communication or other risk minimisation actions in accordance with the medical importance of the issue.

CIOMS WG VIII.

Sponsor

An individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial [DIR 2001/20/EC Art 2(e)].

Eudralex Volume 9a (Sep 08 YEAR?), Glossary 1.3.

Standard of care

Diagnostics and/or treatment provided by healthcare professionals that are based on scientifically accepted evidence and comply with common current professional practice in given circumstances.

Proposed by CIOMS WG IX.

Summary of product characteristics (SmPC)

Part of the marketing authorisation of a medicinal product in the EU setting out the agreed position of the product as distilled during the course of the assessment. It is the basis of information for healthcare professionals on how to use the product safely and effectively.

Adapted from: *EU Guideline on good pharmacovigilance practices (GVP) – Annex I - Definitions (28 April 2014).*

Surrogate endpoint

A surrogate endpoint is an endpoint that is intended to relate to a clinically important outcome but does not in itself measure a clinical benefit or harm or lack of benefit or harm, e.g. a biomarker. A surrogate endpoint is expected to predict clinical outcome based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence and may be used as a primary endpoint when appropriate.

Combined from: *ICH Harmonised Tripartite Guideline - General considerations for clinical trials E8 (Jul 1997)* and *Biomarkers definitions working group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther. 2001, 69: 89–95.*

Survey

Patient or healthcare professional surveys are designed to gather information to assess a safety signal, knowledge about a labeled adverse event, use of a product as labeled, particularly when the indicated use is for a restricted population or numerous contraindications exist, or confusion in the practicing community over sound-alike or look-alike trade (or proprietary) names. A written protocol should include objectives for the survey and a detailed description of the research methods.

Modified from: *FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. 2005, March.*

Targeted follow-up questionnaire

A questionnaire used to capture specific follow-up/further information from a reporter for an adverse event of special interest. It is part of routine pharmacovigilance.

Proposed by CIOMS WG IX.

Target population

While generally referring to the patients who might be treated with the medicinal product in accordance with the indication(s) and contraindications in the authorised product information or specifically to populations as defined in epidemiologic studies, in the context of risk minimisation in this book target population refers to the patients targeted by a risk minimisation activity which may be a subset of or overlap with the former.

Proposed by CIOMS WG IX and based on EU Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (28 April 2014).

ANNEX II

MEMBERSHIP AND MEETINGS OF THE WORKING GROUP

The CIOMS Working Group IX on Practical approaches to risk minimisation for medicinal products met in a series of eight meetings from May 2010 through March 2013 with a final Editorial Meeting in November 2013. This Working Group report was reviewed in draft form by participating members at the final meeting in March 2013 and following a review by the editorial team and team members was finalized thereafter for publication. The members of the Editorial Team were: Panos Tsintis, Philippe Close, Jane Cook, Gerald Dal Pan, Bill Gregory, Stephen Heaton, and Meredith Smith, supported by Gunilla Sjölin-Forsberg and Karin Holm.

During the course of its work, the Working Group recognised its membership to represent the following broad groups of stakeholders (or interested parties) in risk minimisation approaches: regulatory authorities; pharmaceutical industry; international organizations; and academia. Members, their institutional affiliations and stakeholder groups (as defined above) as well as a chronological summary of the Working Group meetings are listed below.

Name	Organisation (Stakeholder group)	Duration of membership*
Arlett, Peter	European Medicines Agency (*Regulatory authority)*	Partial
Auclert, Laurent	Sanofi S.A. *(Pharma industry)*	Full
Berthiaume, Marc	Health Canada (*Regulatory authority)*	Full
Blackburn, Stella	European Medicines Agency (*Regulatory authority)*	Full
Blum, Michael**	MedImmune *(Vaccine industry)*	Partial
Broich, Karl	BfArM, Germany *(Regulatory authority)*	Partial
Bülow, Birgitta	Medical Products Agency, Sweden *(Regulatory authority)*	Partial
Castot, Anne	Affsaps, France *(Regulatory authority)*	Partial
Close, Philippe	Novartis *(Pharma Industry)*	Partial
Cook, Jane	TGA, Australia *(Regulatory authority)*	Full
Dal Pan, Gerald	FDA, U.S. *(Regulatory authority)*	Full
Denayer, Marc	Johnson & Johnson *(Pharma industry)*	Full
Fiore, Gregory	Merck *(Pharma industry)*	Partial
Garg, Rekha	Amgen *(Pharma industry)*	Partial
Geary, Stewart	Eisai *(Pharma industry)*	Full
Goh, Kah Lay	Amgen *(Pharma industry)*	Partial
Gregory, William	Pfizer *(Pharma industry)*	Full
Hammett, Rohan	TGA, Australia *(Regulatory authority)*	Partial

Name	Organisation (Stakeholder group)	Duration of membership*
Heaton, Stephen	Bayer HealthCare *(Pharma industry)*	Full
Hidalgo-Simon, Ana	European Medicines Agency *(Regulatory authority)*	Partial
Hobbiger, Steven	GSK *(Pharma industry)*	Full
Hogan, Vicky	Health Canada *(Regulatory authority)*	Partial
Idänpään-Heikkilä, Juhana	CIOMS (Senior Adviser, Past Secretary-General) *(International organization)*	Full
Kurokawa, Tatsuo	MHLW/PMDA, Japan (*Regulatory authority)*	Full
Kouchakji, Elias	Amgen *(Pharma industry)*	Partial
Kusche, Katja	Roche *(Pharma industry)*	Full
Le Louet, Hervé	Pharmacovigilance Department, Hôpital Henri Mondor, Creteil, France (*Academia*) and ISoP	Partial
Moride, Yola	University of Montreal, Canada *(Academia)*	Partial
Naim, Karen	Johnson & Johnson *(Pharma industry)*	Partial
Petracek, Jan	European Medicines Agency *(Regulatory authority)*	Partial
Rägo, Lembit	World Health Organization (*International organization*)	Partial
Raine, June	Medicines and Healthcare Products, UK *(Regulatory authority)*	Partial
Sachs, Bernhardt	BfArM, Germany *(Regulatory authority)*	Full
Sato, Junko	MHLW/PMDA, Japan *(Regulatory authority)*	Full
Schubert, Mary-Frances	Merck *(Pharma industry)*	Partial
Simmons, Val	Eli Lilly *(Pharma industry)*	Full
Smith, Meredith	Abbott *(Pharma industry)*	Full
Gunilla Sjölin-Forsberg	CIOMS (Secretary-General, since 2010) *(International organization)*	Full
Tsintis, Panos	NDA Group (consultant)	Full
Weismantel, Stefan	Boehringer-Ingelheim *(Pharma industry)*	Full
Zander, Judith	AstraZeneca *(Pharma industry)*	Full

** "Partial" denotes membership in the Working Group for a portion of the 3-year period while "Full" denotes membership for the full period.*

*** Annex VI concerning vaccine risk minimisation was authored by a Subgroup of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance led by Michael Blum (MedImmune) with members Novilia Bachtiar (Bio Farma Indonesia), Priya Bahri (EMA), Adrian Dana (Merck), Barbara Law (Public Health Agency of Canada), Paulo Gomes dos Santos (Bio-Manguinhos), and Françoise Sillan (Sanofi Pasteur). The Annex was endorsed by the full CIOMS/WHO Working Group on Vaccine Pharmacovigilance. The Subgroup worked in parallel to and interactively with CIOMS WG IX.*

CIOMS IX Working Group meetings***

Date	Location	Host
March 2010	London, UK	European Medicines Agency (EMA)
June 2010	Leuven, Belgium	Janssen Pharmaceutica N.V
October 2010	Windlesham, UK	Lilly UK
February 2011	Berlin, Germany	Bayer-Schering Pharma AG
October 2011	Wilmington, Delaware, USA	AstraZeneca Pharmaceuticals
February 2012	Bonn, Germany	BfArM
July 2012	Paris, France	Sanofi
March 2013	Upplands Väsby, Sweden	The NDA Group
November 2013	Geneva, Switzerland	CIOMS (Editorial Board)

**** Costs for travel and accommodation were covered by each Working Group member's parent organization or by CIOMS as per rules, and were not covered by the meeting hosts.*

ANNEX III

REAL-LIFE EXAMPLES

For this section we include both the International Nonproprietary Name (INN) or generic name and the proprietary, brand or registered name ® for a particular pharmaceutical company's product if it is significant to the example.

A. Bosentan (INN), Tracleer®

Pharmacology	Endothelin ETA/ETB receptor agonist.
Indication/Disease treated	Pulmonary Arterial Hypertension (PAH).
Risks targeted for additional risk minimisation	Liver toxicity, teratogenicity.
Risk minimisation tools (beyond routine)	Liver enzyme tests – regular monitoring stipulated. Birth control and pregnancy monitoring for women of child-bearing potential. Tracked and controlled distribution (US). Postmarketing surveillance system (EU).
Effectiveness measurement methods	ADR reporting rates (true event rate as denominators were known). Annual review of fulfilling commitment (see Table 1).
Conclusion	Both the US and the EU systems confirmed clinical study data with regard to product safety and the benefit-risk balance in the postmarketing setting.

Bosentan/Tracleer® Case Study – US and EU experiences

Background

Bosentan (Tracleer®) is an oral dual endothelin ETA/ETB receptor agonist. It was approved in 2001 with orphan drug status in the US and the EU for the treatment of pulmonary arterial hypertension (PAH). PAH is a rare disease involving endothelin that has a poor prognosis. At the time of approval, it was therefore difficult to collect comprehensive data on clinical safety due to limited patient exposure (59 patient-years).

Main safety concerns: The main safety concerns at the time of product approval were liver toxicity and teratogenicity.

In a pooled analysis of the placebo-controlled clinical trials, elevated liver transaminases occurred primarily in the first 4–6 months and were noted to be dose-related and reversible without sequelae either during continued or discontinued treatment. (ALT and/or AST elevation of > 3 x ULN – 11.2% active vs. 1.8% placebo – was observed.)

In preclinical studies, the potential risk of teratogenicity was reported.

Risk minimisation measures and tools

To address these potential safety issues, the following risk minimisation measures were proposed:

Prescribing information: US package insert (PI) or EU Summary of product characteristics (SmPC) included:

- Liver enzyme tests – regular monitoring stipulated
- Birth control and pregnancy monitoring for women of child-bearing potential

In the US, a system (Tracleer® Access Program) was instituted to track and control the distribution of the product and in the EU, a postmarketing surveillance system (Tracleer Excellence) was implemented to monitor the safety of the product. An overview of the features of the US and EU postmarketing programmes are shown in Table 1 below **(1)**.

Annex III - Bosentan Table 1: Post-approval commitments in the US and EU

Type	US	EU
Postmarketing surveillance	No	Yes, TRAX PMS system
Controlled distribution	Yes T.A.P.	Yes
Medical information	Yes, medication guide, USPI	Yes, patient reminder card, prescriber kit, SPC
Regular reporting	Yes, annually	Yes, semiannually
Safety reporting	Yes, USPR[a] (courtesy PSUR)	Yes, PSUR[b] (courtesy USPR)
Annual review of fulfilling commitments	Yes	Yes
Patient identity known by system	Yes	No
Patient demographics	Yes	Yes (partial)
Prescriber details	Yes	Yes, if legally possible
Information on bosentan discontinuation[c]	Yes	Yes
Capture of AEs relating to the liver	No	Yes
Capture of AEs relating to pregnancy	No	Yes
Reminder about liver function tests	Yes, to patient	Yes, to prescriber

[a] *Reported quarterly X 12 quarters, then annually (waiver received from the US FDA to provide USPRs annually after 12 quarterly reports submitted.*

[b] *Reported semi-annually.*

[c] *When bosentan is discontinue, no survival status is captured thereafter unless spontaneously reported by the prescriber to the Actelion Global Drug Safety (GDS) department.*

AEs = *adverse events;* **PSUR** = *periodic safety update report;* **SPC** = *summary of product characteristics;* **T.A.P.** = *Tracleer®* **Access Program; TRAX PMS** = *Tracleer® Excellence;* **USPI** = *US package insert;* **USPR** = *US periodic report*

In the United States

In the US, bosentan is only available through the Tracleer Access Program (TAP) and only specialty distributors are licensed to distribute the product.

The practitioner is required to provide certification that:

1. Bosentan is prescribed for appropriate use of PAH treatment as per PI.
2. The physician has reviewed liver and pregnancy warnings and is committed to appropriate monitoring.

A key feature of TAP was the monthly calls from distributor to patient to assess:

1. If the patient has had liver enzyme blood test and pregnancy test (if appropriate).
2. If the patient was unsure, the distributor had to remind the physician.
3. At time of call, if the patient did not want to continue or had died, the physician would be contacted. The company drug safety department would perform further follow-up with the physician. Any discontinuations due to liver test abnormalities were captured.

According to the MAH, the proportion of distributor calls requiring physician notification was around 3–7% in the US TAP and these were mostly due to the patients forgetting the required blood work.

In the US, most of the liver transaminase abnormalities were collected as part of discontinuation data in TAP. However, the number of patients who experienced transient liver transaminase elevations without discontinuation was not routinely collected in TAP. The data on pregnancies were captured either from spontaneous reports or as part of discontinuation data.

Features of the Tracleer Access Program:
1. Complete registration of all patients receiving Tracleer.
2. Complete registration of practitioners who prescribe Tracleer.
3. Distribution of Tracleer through a controlled specialty distribution network.
4. Distribution of the medication guide to patients with each shipment of Tracleer.
5. Initial distribution of Tracleer is to occur only after receipt of appropriate prescribing form by the distributor.
6. Patient reminder monthly regarding liver and pregnancy tests.
7. Notification of discontinuation of patient to prescriber; collection of data relating to liver function, pregnancy or related adverse event or death.

In the European Union

Tracleer Excellence (TRAX PMS) System

TRAX PMS was set up as a European non-interventional prospective, Internet-based postmarketing surveillance (PMS) database. However, each country had a different way of managing the system which was approved by the national competent authority in each country. At the time of the 2005 publication, data from 18 countries were being collected through this system.

The objectives of the programme **(1)** were to:

- Ensure that prescribing physicians were aware of the safety-related information.
- Supplement under-reporting of spontaneous AEs from prescribers by soliciting reports through a series of prompts by the system (monthly for liver function test potential signals and quarterly for other potential safety signals).

- Provide regular and timely comprehensive postmarketing experience reports to the regulatory agencies.

However, in a separate publication **(2)**, the objectives of the programme were defined as:

- Education of practitioners on the appropriate use of bosentan and encouragement of the reporting of adverse drug reactions (ADR).
- Collection of potential safety signals, including the incidence of elevated liver aminotransferase levels during bosentan treatment in clinical practice.
- Assessment of the practicality and appropriate use of the algorithm developed in registration studies for managing aminotransferase elevations in daily clinical practice, including the re-introduction of bosentan where appropriate.

In this programme, the prescribing physicians were contacted and given a prescriber kit describing TRAX PMS. The participation was voluntary. Once the physician was registered, they are requested to enter patient data into the system on a regular basis, with secure transfer to the central database.

The data collected in this system included demographics, aetiology of PAH, New York Heart Association (NYHA) classification status at baseline and the use of specific medications. The aggregate data collated was reviewed by the MAH to determine if potential safety signals were present.

Data handling procedures:

The MAH introduced a classification system in the handling of the safety information gathered in the TRAX PMS; the data were classified as either potential safety or non-safety signals.

- Potential safety signals: death, hospitalisation, pregnancy, SAEs/ADRs, ADRs not listed in the SmPC, liver test abnormalities, other lab abnormalities, transplantation, atrial septostomy or initiation of prostacyclin.
- Non-safety signals: reasons for discontinuation such as patient request, loss to follow-up or non-medical reasons.

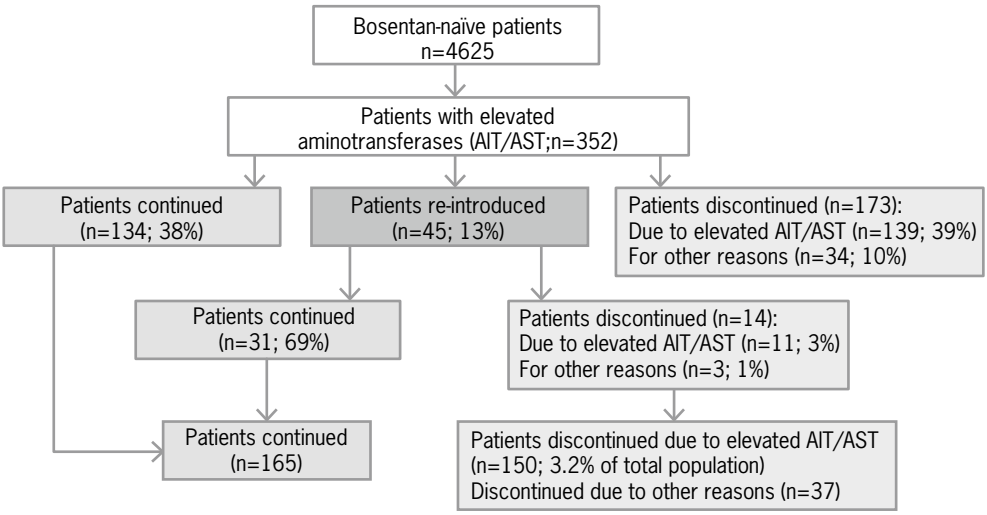
Any persons reporting information that was classified as a potential safety signal in TRAX PMS would prompt the reporter to complete an AE/ADR form, which would be forwarded to the Safety department to be entered into the company safety database. If despite prompting, no additional information was forthcoming from the physician, minimal information on the case would be captured in the safety database.

By convention, the term 'liver function test abnormality' was used to denote increases in the serum levels of ALT and/or AST and not to isolated bilirubin or alkaline phosphatase level elevations. The liver disorders were regularly reviewed by an International Liver Safety Board established by the company, particularly with respect to a regulatory authority's request to focus particularly on patients who had systemic symptoms attributable to liver injury. At the time of the publication **(1)**, none of the patients identified to have met the Zimmerman criteria had fatal liver failure due to the use of bosentan.

Analysis of the TRAX PMS data

An analysis of the data gathered through the EU postmarketing surveillance programme was published in 2007 and shown in Fig. 1. **(2)**. Data for 4,994 patients enrolled between May 2002 and November 2004 in 17 countries were included in this review. This represented 79% of the 6,318 patients who received bosentan in Europe during that period of time. Of these 4,994 patients, 93% (n= 4,625) were naïve to bosentan at database entry. The total patient exposure was 3,416 patient yrs. The mean age of the bosentan-naïve patients were 52+/- 18.8 years, 67.1% were female and 22.9% male, and the majority were assessed as NYHA Functional Class III status (67.8%).

Annex III - Bosentan Fig. 1: Analysis of the TRAX PMS data



From Humbert M et al. Eur Resp J, 2007 **(2)**. Management of patients with elevated liver aminotransferases. ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Of these 4,625 patients, 352 were found to have experienced elevated liver aminotransferases. This corresponds to a crude rate of 7.6% and an annual rate of 10.1%, which is consistent with the observed rate from clinical trials (12.8% in pivotal studies and 11.2% in 8 placebo-controlled studies).

Discontinuation of bosentan treatment occurred in 1,286 (27.8%) of the 4,625 patients. The most common discontinuations were due to death (9.1%) and hospitalisation (4.1%; mainly due to worsening of PAH). Discontinuation due to elevated liver transminases was reported in 150 patients, representing 3.2% of all bosentan-naïve patients. In clinical trials, the discontinuation rate due to elevated liver transminase values was 1.5%. The authors indicated that it was unclear whether the observed differences may simply be a reflection that patients in the postmarketing setting may have discontinued more readily, or that patients treated for longer period in the postmarketing setting still had the potential to develop liver test abnormalities. It was noted however that liver transaminase elevations occurred mainly in the first 6 months and after one year, this probability was reduced.

Discusssion

In general, operational challenges were noted in both the US and EU programmes. Both systems were found to be labour-intensive and costly.

In the US TAP system, intensive training was required for distributors to understand reporting requirements. The intensity of the active queries and follow-up were also thought to be cumbersome by the treating physicians. The large amount of solicited information, such as deaths (since PAH is a life-threatening condition), required follow-up for additional information. The cases of death were mostly due to disease progression and resulted in an increased number of unrelated deaths populating the safety database ('noise'). The company had to change their data handling process and to actively query for reasons for drug discontinuation in the programme and verify the relationship to bosentan. Only the related events were entered in the company safety database and the unrelated events were recorded in the speciality distribution listings.

Under the EU TRAX postmarketing surveillance system, the experience was that the data reconciliation exercise between the TRAX system and the global safety database was labour-intensive. It also required a lot of effort to remind physicians to complete AE/ADR forms where these were required and also setting up a tracking system in order to maintain records of inquiries. The company also reported that information

may reach them via different routes (may be minimal or incomplete information) and at different times, and had faced challenges in determining the 'day zero' date for expedited reporting of safety information. The design of the surveillance programme also had to take into account the legal data protection requirements in the EU member states. Patients were assigned random numbers on the web databases and the prescriber information is kept in a separate database. Thus patients are identifiable to the safety department only by patient number on the AE/ADR forms. Cross-referencing between cases received by the safety department on the AE/ADR forms versus the TRAX PMS listing were done via the TRAX PMS numbers and year of birth (no initials or full date of birth were collected in TRAX PMS).

Both the US and EU systems appeared to confirm the clinical trial safety data, particularly with regard to liver safety. The EU TRAX PMS system, which functioned as a large simple survey, and the US controlled distribution system both ensured patients were appropriately monitored. The systems facilitated the collection of more extensive patient datasets than would have been expected in the usual spontaneous post-marketing system. It was reported that the ADR reporting rate was approximately 10% in patients not enrolled in TRAX PMS versus 30% in those enrolled in the programme **(1)**. The TRAX PMS also helped to determine the true event rate (as opposed to the reporting rate) since the actual number of events and the number of exposed patients were both known. It also facilitated the assessment of the suitability of the algorithm developed in the clinical trial setting to manage the monitoring of elevations in liver transaminases in the postmarketing setting.

In the EU, after enrolling almost 5,000 patients in 2.5 years, the European Medicines Agency permitted the discontinuation of the TRAX PMS programme and agreed that it had fulfilled its objectives.

Conclusion

Overall, both the US TAP and the EU TRAX PMS systems confirmed that clinical study data with regards to product safety and the favourable benefit-risk balance of bosentan was maintained in the postmarketing setting. Due to the orphan characteristics of the treatment indication, only limited clinical safety data was available prior to approval and hence such orphan drugs require particular safety monitoring and attention in the postmarketing setting. However, the operational challenges in the implementation of such postmarketing surveillance or controlled distribution systems are considerable and may only be deemed acceptable for stakeholders (e.g. prescribers, pharmacists, patients) if the drug offers substantial benefits to the patients.

References

1. Segal ES, Valette C, Oster L, Bouley L, Edfjall C, Herrman P et al. Risk management strategies in the post-marketing period. Drug Safety. 2005, 28(11): 971–980.
2. Humbert M, Segal ES, Kiely DG, Carlsen J, Schwierin B and Hoeper MM. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. Eur Respir J. 2007, 30: 338–344.

B. Clozapine (INN), Clozaril®

Pharmacology	Atypical antipsychotic, sedative.
Indication/Disease treated	Treatment-resistant schizophrenia.
Risks targeted for additional risk minimisation	Agranulocytosis, leukopenia, (low white blood cell counts that could lead to serious infections and fatal outcomes.)
Risk minimisation tools (beyond routine)	Global "no blood, no drug" policy by original manufacturer requiring patient monitoring systems varying by country. Patient and prescriber registration, required brand adherence (UK), national registry system (US), original manufacturer has to keep a 'non-rechallengeable database,' generic manufacturers must cross-check and inform.
Effectiveness measurement methods	UK: Review of data collected over 4.5 years by manufacturer. US: Analysis and assessment of national registry system by manufacturer.
Conclusion	The centralised blood monitoring systems in combination with routine risk minimisation measures reduced the incidence of agranulocytosis and deaths.

Pharmacology

Clozapine (brand name Clozaril®) is an anti-psychotic agent that is classified as a tricyclic dibenzodiazepine derivative. It has only weak dopamine-receptor-blocking activity at D1, D2, D3 and D5 receptors, but shows high potency for the D4 receptor, in addition to potent anti-alpha-adrenergic, anticholinergic, antihistaminic, and arousal-reaction-inhibiting effects. It has also been shown to possess anti-serotoninergic properties. Its therapeutic effects are probably mediated by dopaminergic and serotonergic activity **(1)**.

Clinically, clozapine produces rapid and marked sedation and exerts antipsychotic effects in schizophrenic patients resistant to other drug treatment. In such cases, clozapine has proven effective in relieving both positive and negative schizophrenic symptoms.

Due to its unique dopamine receptor binding profile, its effects on various dopamine mediated behaviours and the paucity of extrapyramidal adverse effects, it is classified as an atypical anti-psychotic agent.

Background

The efficacy of clozapine in the treatment of patients with schizophrenia was well-established; however, its use was also associated with potentially serious adverse reaction of granulocytopenia and agranulocytosis. Agranulocytosis is clinically defined as the absence of granulocytes, which may lead to serious infections and fatal outcomes. In view of this risk, the initial indication for clozapine was limited to treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Clozaril® was first introduced in Europe in the early 1970's (in selected countries) but quickly withdrawn due to fatalities, notably in Finland. Cases of neutropenia and agranulocytosis emerged as a strong signal and resulted in voluntary withdrawal from the market by the MAH. The incidence of agranulocytosis in Europe prior to monitoring was estimated to be 1–2% per year **(2, 3)**. The incidence of agranulocytosis during Clozaril clinical trials prior to US approval (1989) was 1.3% at 1 year. Mortality among agranulocytosis cases (worldwide) prior to1989 was estimated to be 32% **(4)**.

However, due to its clinical benefits, there was pressure from psychiatrists to reintroduce Clozaril into the market. Clinical trials in patients with treatment-resistant schizophrenia, where close haematological

monitoring was devised, showed significant improvement in 30% of patients after six months **(5)**. Subsequent studies showed improvement in 61% of patients if treatment was continued for up to one year **(6, 7)**.

Clozaril was subsequently granted marketing product approval in the US in 1989 and in the UK in January 1990, with the adoption of additional risk minimisation measures to reduce the risk of agranulocytosis and its serious sequelae. Novartis, the manufacturer of Clozaril, adopted a global policy of 'no blood, no drug' applied to all Clozaril-treated patients, through national centralised haematology monitoring services, or institutional/physician oversight. At the time, there was a lack of known predictors for patients likely to develop agranulocytosis and the rationale of monitoring was to aid early detection of leukopenia, i.e. identify patients at a point prior to agranulocytosis and minimise the development of agranulocytosis. The rationale for the frequency of monitoring was based on the premise that a relationship existed between frequency of the tests and the probably of early detection. Thus the global objective of the monitoring systems was to facilitate the early detection of moderate leukopenia, in order to reduce or prevent the occurrence of severe leukopenia, agranulocytosis and death.

The monitoring systems vary somewhat from country to country and have also undergone some modifications in the schedule over time. The elements of the UK and US monitoring systems are described below.

Risk minimisation measures in the UK

Summary of product characteristics (SmPC)

As a consequence of a recent European regulatory initiative, the Clozaril SmPC has been harmonised across Europe. The SmPC states that blood monitoring should be carried out in accordance with national-specific official recommendations.

In the UK, the treatment indication for Clozaril is restricted to the following patient population:

- patients with schizophrenia who are non-responsive to or intolerant of antipsychotic medication, or with psychosis in Parkinson's disease when other treatment strategies have failed;
- patients who have initially normal leukocyte findings (white blood cell count $\geq 3500/mm^3$ (3.5x109/l), and ANC $\geq 2000/mm^3$ (2.0x109/l)); and
- patients in whom regular white blood cell (WBC) counts and absolute neutrophil counts (ANC) can be performed as follows: weekly during the first 18 weeks of treatment, and at least every 4 weeks thereafter throughout treatment. Monitoring must continue throughout treatment and for 4 weeks after complete discontinuation of Clozaril.

The SmPC provides warning and precautions on agranulocytosis and also details of the UK haematological monitoring services.

Patient Information Leaflet (PIL)

The Clozaril PIL contains warnings on the risks of low white cells, information on symptoms suggestive of infection (that should prompt notification of their physicians) and the need for medical check-ups and blood tests prior to starting, during and after treatment.

Clozaril Patient Monitoring Service (CPMS)

The UK CPMS was developed in order to manage the risk of agranulocytosis associated with clozapine. It is available 24 hours a day. It provides for the centralised monitoring of leucocyte and neutrophil counts, which is a mandatory requirement for all patients in the UK who are treated with Clozaril. The use of Clozaril is restricted to patients who are registered with the CPMS. In addition to registering their patients, prescribing physicians must register themselves and a nominated pharmacist with the CPMS. All Clozaril-treated patients must be under the supervision of an appropriate specialist and supply of Clozaril is restricted to hospital and retail pharmacies registered with the CPMS. Clozaril is not sold to, or distributed through wholesalers.

In the UK, a white cell count with a differential count must be monitored. From 1990–1995, the monitoring schedule was:

- At least weekly for the first 18 weeks of treatment; and
- Every two weeks thereafter.

From 1995 onwards (current system), the monitoring schedule is:

- At least weekly for the first 18 weeks of treatment;
- At least at two-week intervals between weeks 18 and 52;
- After one year of treatment with stable neutrophil counts, patients may be monitored at least at four week intervals; and
- Monitoring must continue throughout treatment and for at least four weeks after discontinuation.

Additionally, the CPMS maintains a database which includes all patients who have developed abnormal leucocyte or neutrophil findings and who should not be re-exposed to Clozaril. Of note, prescribers and pharmacists had to adhere to brand prescribing and dispensing of clozapine in order to prevent the disruption to effective monitoring that may be caused if patients switch brands. Furthermore, in order to protect patient safety, at any one time patients should only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand.

Patients must have a satisfactory pre-treatment blood count before starting Clozaril. The monitoring service also analyses blood samples to detect falling counts of white blood cells, neutrophils and platelets. However, the full range of haematological parameters is also measured and communicated to the patient's psychiatrist. For ease of interpretation, the results are divided into three colour bands:

- Green: WBC>3.5x109/l and neutrophils>2.0x109/l
- Amber: WBC 3.0–3.5x109/l and/or neutrophils 1.5–2.0x109/l
- Red: WBC <3.0x109/l and/or neutrophils <1.5x10/l and/or platelets, <50x109/l

In the event of a red result, the hospital or other blood sampling venue is contacted immediately to ask for a confirmatory blood sample. The patient's psychiatrist, hospital ward staff and pharmacist would be informed that the patient must stop clozapine immediately and advice for the management of neutropenia and agranulocytosis would also be provided.

Prescribing physicians must comply fully with the required safety measures. At each consultation, a patient receiving Clozaril must be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention must be paid to 'flu-like' complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia.

Effectiveness assessment

A review was undertaken of the data collected in the CPMS over a period of four and a half years after the programme inception **(8)**. It should be noted that the CPMS was developed for safety monitoring purposes and not for research or explanatory assessment.

During the period from 7 January 1990 to 3 July 1994, a total of 6,316 patients were registered in CPMS and received at least one blood test; 2,825 (45.2%) of these patients received clozapine for at least one year and 1,625 (25.7%) were on treatment for at least two years.

The cumulative incidence over the four and the half year period was 0.8% for agranulocytosis. The frequency of agranulocytosis and neutropenia was highest in the first 6–18 weeks of treatment and the incidence of both was significantly reduced after the first year.

The incidence of agranulocytosis was 0.7% (n=46) in the first year and 0.07% (n=2) in the second year. There were no reported cases of agranulocytosis in the third and fourth year. The incidence of fatal

agranulocytosis was 0.03% in the first year (n=2). The two fatalities occurred due to complications of agranulocytosis (uncontrolled sepsis despite antibiotic treatment). In both cases, the fatalities occurred within the first twelve weeks of treatment.

The incidence of neutropenia in the first, second, third and fourth year were 2.3%, 0.7%, 0.7% and 0.5% respectively. The analysis identified increasing age as the only risk factor for the development of agranulocytosis. Increasing daily dose was not a risk factor for either agranulocytosis or neutropenia.

A further analysis was also conducted by the company in 2002. As of April 2002, a total of 29,298 patients were registered in CPMS. Those who were enrolled but never started treatment with Clozaril were excluded from the analysis. Thus, 27,894 CPMS patients were ultimately included in the analysis. Of note, generic clozapine was not available in UK at the time of this analysis.

The results are summarized in the table below:

Annex III - Clozaril Table 1: Results of effectiveness monitoring

	Weeks 0–18 Weekly	Weeks 19–52 Bi-weekly	Weeks >52 Weekly/ bi-weekly	
Moderate Leukopenia {per 1,000 patient yrs. (N)}				
Incidence: pre-1995 (initial system)	105.1 (182)	30.5 (79)	11.8 (77)	
Incidence: patients enrolled post-1995 (current system)	82.5 (482)	20.7 (177)		7.4 (228)
Severe Leukopenia {per 1,000 pt. yrs. (N)}				
Incidence: pre-1995 (initial system)	33.5 (58)	4.3 (11)	2.6 (17)	
Incidence: patients enrolled post-1995 (current system)	31.9 (186)	4.0 (34)		1.9 (58)
Agranulocytosis {per 1,000 pt. yrs. (N)}				
Incidence: pre-1995 (initial system)	24.8 (43)	1.2 (3)	0.3 (2)	
Incidence: patients enrolled post-1995 (current system)	20.4 (119)	1.5 (13)		0.6 (18)

Source: Clozaril briefing document for PDAC, 2003 **(8)**

Although the incidence of agranulocytosis was higher for Weeks >52 under the monthly monitoring system (0.6 per 1000 patient-years) compared to bi-weekly monitoring (0.3 per 1,000 patient-years), this was not statistically significant. Of note, with the change to at least monthly monitoring after 52 weeks, some patients continued to be monitored on a weekly or bi-weekly basis. In fact, the incidence rate of agranulocytosis in the group of patients who continued to be monitored on a weekly (4.6 per 1,000 patient-years) or bi-weekly basis (0.9 per 1,000 patient-years) after 52 weeks was greater than those who were monitored on a monthly basis (0.35 per 1,000 patient-years).

Risk minimisation in the US

Prescribing Information (PI)

Clozaril was initially approved in 1989 for use in treatment-resistant schizophrenia and in 2002; it was also approved for the treatment for patients at risk of recurrent suicidal behaviour in schizophrenia or schizoaffective disorder.

This risk of development of agranulocytosis in patients treated with Clozaril is described in the boxed warning, warning and adverse reaction sections of the PI. Additionally, the use of Clozaril simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function is also contraindicated.

Physicians are advised to discuss the significant risk of developing agranulocytosis with patients for whom they prescribe Clozaril. Patients should be advised to report immediately any symptom suggestive of infection. Patients should be informed that Clozaril tablets will be made available only through a special programme designed to ensure the required blood monitoring in order to reduce the risk of developing agranulocytosis. The details of the monitoring schedules are described in the PI.

Clozaril National Registry (CNR) and effectiveness monitoring

In the US, the initial haematology monitoring system established in 1990 required weekly monitoring for the entire duration of testing.

The incidence rates of agranulocytosis based upon a weekly monitoring schedule rose steeply during the first two months of therapy, peaking in the third month. Among Clozaril patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree. After six months, the weekly incidence of agranulocytosis declines still further, however, it never reaches zero.

Novartis presented an analysis of the CNR data to the Psychopharmacological Drugs Advisory Committee (PDAC) in 1997 **(8)**. The PDAC recommended that the monitoring frequency should be reduced after six months of treatment to every two weeks and, after implementation, an impact analysis of this change in monitoring frequency should be evaluated.

In 1998, Novartis implemented the current monitoring system that was recommended by the PDAC members (i.e. weekly for the first 26 weeks of treatment and every two weeks thereafter). At the time, the US CNR collected only white blood cell (WBC) counts systematically (while the UK CPMS routinely collected absolute neutrophil counts in addition). However, cases of agranulocytosis were identified through MedWatch as well as by Novartis Clinical Safety and Epidemiology and were entered into the CNR. In the US, Clozaril is only temporarily discontinued when WBC falls below 3.00x109/l and ANC is between 1 and 1.50x109/l and not permanently discontinued until WBC <2.00x109/l or ANC <1.50x109/l; in the UK CPMS, Clozaril was discontinued when the WBC falls below 3.0x109/l and/or neutrophils were <1.5x109/l.

Also, shortly thereafter the first generic version of Clozaril became available in US and patients treated with generic clozapine became subject to a monitoring system. Manufacturers of generic clozapine are responsible for ensuring adherence to the current monitoring frequency schedule by maintaining a registry database with functionality identical to the CNR. Novartis, however, is responsible for maintaining a database of patients who should not be rechallenged with clozapine ('non-rechallengeable database') and generic manufacturers are responsible for:

1. Contacting Novartis prior to initiating patients to cross-check them against the 'non-rechallengeable database'; and
2. Informing Novartis of patients who should be added to this database.

In 2001, the FDA contacted Novartis to follow up on the 1997 PDAC recommendation.

In September 2002, Novartis provided a report analysing patients enrolled in the CNR that addressed two issues: (1) an analysis of the effect of biweekly monitoring of WBC after six months of treatment on the incidence rate of agranulocytosis and severe leukopenia; and (2) an assessment whether the current

biweekly blood monitoring system after six months could be changed to a less frequent monitoring regimen. The analysis was based on a total of 203,818 patients who were enrolled in the CNR as of 1 September 2001. The report also included information on the haematology monitoring system in place in the UK and Australia at the time.

The key findings of the analyses were:

1. Demographic characteristics of the patients treated under the initial and the revised monitoring systems were similar;
2. Rates of moderate leukopenia during and after the first 6 months were similar in both systems: initial vs. revised: 31 per 1,000 patient-years vs. 28 per 1,000 patient-years for the first 6 months, 9.0 per 1000 patient-years vs. 8.0 per 1,000 patient years after the first 6 months;
3. During the first 6 months, rates of severe leukopenia (initial vs. revised: 7 per 1,000 patient-years vs. 3 per 1,000 patient-years for first six months) and agranulocytosis (initial vs. revised: 7 per 1,000 patient-years vs. 3 per 1,000 patient-years for first six months) were less in the revised system than in the initial system;
4. After the first six months, the rates of severe leukopenia (0.5 per 1,000 patient-years vs. 0.3 per 1,000 patient years after the first six months) and agranulocytosis (0.4 per 1,000 patient-years vs. 0.4 per 1,000 patient years after the first six months) were similar in both monitoring systems;
5. The unexpected finding of a decrease in observed rates of leukopenia and agranulocytosis in the revised system was not clear, but may in part be related to the following:
   5.1. Patients who received generic clozapine were not considered in these analyses when exposure to more than six months of clozapine treatment was known. This resulted in an exclusion of data during the period of highest risk for agranulocytosis i.e. the first six months;
   5.2. Patients switching to alternative atypical antipsychotics treatments prior to developing severe leukopenia or agranulocytosis; and
   5.3. The greater proportion of patients who discontinued during the first six months of therapy under the revised monitoring system (58%) compared to the initial monitoring system (40%).
6. The change in the frequency of monitoring in the US was not associated with an increase in fatal outcomes related to agranulocytosi; and
7. Overall, the data demonstrated that the CNR effectively detects moderate leukopenia and reduces the occurrence of severe leukopenia, agranulocytosis and death.

After reviewing recommendations provided by the PDAC of June 2003 regarding the white blood cell monitoring schedule required for all clozapine users, the Food and Drug Administration (FDA) concluded that the current monitoring schedule should be modified. The major changes regarding the frequency and parameters of the monitoring schedule are summarised below:

- Requirement that the absolute neutrophil count (ANC) be determined and reported along with each WBC count;
- New parameters for initiation of Clozaril treatment: WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$;
- Initiation of monthly monitoring schedule after one year (six months weekly, six months every two weeks) of WBC counts and ANCs in the normal range (WBC $\geq 3500/mm^3$ and ANC $\geq 2000/mm^3$);
- Addition of cautionary language to prescribers describing the increased risk of agranulocytosis in patients who are rechallenged with clozapine following recovery from an initial episode of moderate leukopenia ($3000/mm^3 >$ WBC $\geq 2000/mm^3$ and/or $1500/mm^3 >$ANC $\geq 1000/mm^3$); and
- After recovering from such an episode, these patients are now required to undergo weekly monitoring for 12 months if they are re-challenged.

Discussion

The original manufacturer for Clozaril, Novartis, adopted a strict global policy of 'no blood, no drug', which was implemented in each region/country in accordance with national health systems and local medical practices.

The principle of a centralised monitoring system, as illustrated in the UK and US programmes, enabled patients to be tracked, regardless of any changes in healthcare practitioners or move to different healthcare institutions during their period of treatment. The patients are not able to receive a new prescription for Clozaril until the confirmation of a satisfactory blood test result.

In both programmes, the possibility of patients being treated with generic products is also taken into account when designing these monitoring systems. In the UK, prescribers and pharmacists have to adhere to brand prescribing and dispensing of clozapine in order to prevent the disruption to effective monitoring that may be caused if patients switch brands. At any one time, patients should only be prescribed one brand of clozapine and only registered with the monitoring service connected to that brand. In the US, the generic companies are also expected to set up their own haematological monitoring system, but also to work with the product originator, who maintains a central 'non-rechallengeable database' to ensure the sharing of information on patients who must not be rechallenged.

In these systems, treating physicians and pharmacists are provided with simple and concise algorithms to follow in terms of the monitoring process and frequency, so that there is little ambiguity in terms of data interpretation and actions required. For example, in the UK CPMS, a traffic light system was used to categorise the blood results and linking these directly to any follow-up actions required.

There were criticisms of the systems, particularly the CNR, during its initial set-up. The intensive weekly monitoring in the CNR was considered cumbersome and costly. The steps taken by the manufacturers, PDAC and FDA to review the data arising from the CPMS and CNR over time enabled the further characterisation of the risk for developing leukopenia and agranulocytosis (incidence of leukopenia and agranulocytosis is highest during the first 6 months and decreases thereafter), which led to the later modification of the monitoring schedule. Similarly in the UK, the monitoring schedule was modified following evaluation of the data from CPMS a few years after initial implementation.

Conclusion

Overall, the Clozaril central haematology monitoring systems and in combination with routine risk minimisation measures (i.e. product information) are considered an example of a successful risk minimisation programme for the reduction in incidence of agranulocytosis and deaths resulting from complications of agranulocytosis associated with the use of clozapine. This case study also illustrates that a periodic review of the programme post-implementation is important for the assessment of the appropriateness of the proposed blood monitoring algorithm in real-life settings and allows adjustment of the monitoring regime and threshold laboratory values as required.

References

1. Clozaril UK Summary of product characteristics. Novartis Pharmaceuticals UK Ltd. Rev 15 Jan 2010.
2. Honigfeld G, Arellano F, Sethi J, Bianchini A, Schein J. Reducing clozapine-related morbidity and mortality: Five years of experience with the Clozaril National Registry. J Clin Psychiatry. 1998, 59(Suppl 3): 3–7.
3. Clozaril US Prescribing information. Novartis Pharmaceuticals Corporation. Rev Jan 2010.
4. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1998, 45: 789–796.
5. Meltzer HY, Bastani B, Kwon KY, Ramirez LF, Burnett S, Sharpe J. Psychopharmacology (Berl). 1989, 99 Suppl:S68–72.
6. Meltzer HY. Dimensions of outcomes with clozapine. Br J Psych 1992;160(Suppl 17): 46–53.
7. Atkin K, Kendall F, Gould D, et al. Neutropenia and agranulocytosis in patients receiving clozapine in UK and Ireland. Br J Psych. 1996, 169: 483–488.
8. Clozaril briefing book for Psychopharmacological Drugs Advisory Committee Meeting. Novartis Pharmaceutical Corporation. 16 Jun 2003.

C. Isotretinoin (INN), Accutane®

Pharmacology	Retinoid which reduces the production of sebum and shrinks the sebaceous glands.
Indication/Disease treated	Severe forms of acne.
Risks targeted for additional risk minimisation	Teratogenicity.
Risk minimisation tools (beyond routine)	Pregnancy Prevention Programmes (PPPs) controlled by national regulatory authorities with objectives to: 1) prevent pregnant woman from taking drug, and 2) prevent women taking drug from becoming pregnant. PPPs differ by country, some stricter than others, and can include: educational requirements for patients, prescribers, pharmacists; mandatory contraception and pregnancy testing; limited validity prescriptions.
Effectiveness measurement methods	Inherent pregnancy register in US and spontaneous reporting of pregnancies in EU.
Conclusion	No studies have yet formally or comprehensively evaluated the various PPPs effectiveness in reducing the rate of isotretinoin-induced birth defects.

Isotretinoin Case Study

Background

Pharmacology. Isotretinoin (13-cis-retinoic acid) is a retinoid compound and a derivative of vitamin A **(1, 2)** originally marketed by Roche under the brand name Accutane®. It is relatively long-acting with mean elimination half-lives of isotretinoin and of its metabolite, 4-oxo-isotretinoin, being on average, 29 and 22 h, respectively **(3)**. Isotretinoin is available in 10, 20 and 40 mg capsules **(4)**. The exact mechanism of action is unknown, but it is assumed that it alters DNA transcription, similar to other retinoids **(2)**.

Marketing authorisation and approved indications. Isotretinoin has been approved in the US since 1982 and in all European countries except Sweden since 1983 **(1)** for the treatment of the most severe forms of acne which have failed to respond to other treatments such as antibiotics **(5)**. This second line indication in the EU deviates from the US indication. Isotretinoin is considered an efficacious and cost-effective anti-acne drug since it leads to lasting remissions in the majority of acne patients with a relatively short treatment course of up to six months **(6, 7)**. Since 2001 several generic formulations of isotretinoin have been authorised in the EU and the US targeting the same indication **(4)**.

Isotretinoin prescriptions. Women account for 50% of isotretinoin prescriptions **(8)**, and 90% of users are young people between 13 and 45 years of age **(9)**. In recent years, it has also been used for mild to moderate forms of acne. In a population-based study, 64% of first isotretinoin prescriptions were given to patients who did not have a history of other anti-acne medication use **(8)**.

Adverse drug reactions. Like all retinoids, isotretinoin is highly teratogenic **(1)**. Other risks associated with its use include depression and suicide, liver damage, and musculoskeletal symptoms **(4, 10)**.

Teratogenicity. From animal experiments it has long been known that retinoids are highly teratogenic. Thus, when isotretinoin was initially marketed in the US, it was, therefore, labelled as being contraindicated in pregnancy **(11, 12, 13)**. Isotretinoin embryopathy in humans was first described by Lammer et al. in 1985. It consists of anomalies of the ears, facial and palatine defects, micrognathia, cardiovascular defects, and developmental defects of the thymus and central nervous system **(14, 15)**.

Epidemiological data on isotretinoin-induced teratogenicity. Schäfer summarised spontaneous abortion rates of up to 40%, an increased rate of premature births, and up to almost 30% major birth defects **(2)**. The psychological burden to the mother following her awareness of a foetal exposure may also be important, although it is difficult to determine. High rates of pregnancy terminations (84%) were reported by some authors **(7)**.

Objectives of the pregnancy prevention programmes

Foetal exposure to isotretinoin is an international problem and pregnancy prevention programmes (PPPs) have been set up by regulators around the world **(16)**. Children born with major malformations will require continuous healthcare services throughout their life **(7)**. Hence, the safe use of isotretinoin in women of childbearing age is an important public health issue. In this paragraph we will focus on the EU- and the US-PPP, called iPLEDGE.

The objectives of PPPs encompass **(17)**:

- preventing pregnant women from beginning isotretinoin therapy; and
- preventing pregnancies among women who are taking isotretinoin.

PPP in the EU

The European Medicines Agency released guidelines for prescribers, pharmacists and patients regarding the safe use of isotretinoin in 2003 **(1)**. These guidelines required harmonised, consistent and accurate product information as the increasing marketing of generic drugs with varying product information has caused uncertainty and confusion amongst users. The European guidelines had to be implemented under national responsibility in the European Member States with a supporting PPP. This PPP consists of the following key elements as described in the guidelines:

- *Educational programme*
- *Therapy management*
- *Distribution control*
- *Additional measures*

Educational programme

The aim of the educational programme is

- enhanced understanding of the teratogenic risk by both patients and physicians
- enhanced female patient information, awareness and acknowledgement

The key components of the educational programme are the provision and informed acknowledgement of the following documents:

- Physician's Guide to prescribing isotretinoin
- Pharmacist's Guide to dispensing isotretinoin
- Checklist for prescribing to female patients
- Patient Information Brochure
- Brochure on contraception
- An acknowledgement form for female patient, if locally required

Therapy management

1. Mandatory pregnancy testing

It is mandatory to have medically supervised pregnancy testing before, during and five weeks after the end of treatment. Negative pregnancy tests with a sensitivity of at least 25mIU/ml are a precondition and have to be carried out on a monthly basis, from one month before starting therapy until after its completion. Five weeks after stopping treatment, women should undergo a final pregnancy test to exclude pregnancy. The dates and results of all pregnancy tests should be documented.

2. Mandatory contraception

Use of at least one method of effective contraception and preferably two complementary forms of contraception including a barrier method before initiating therapy is mandatory. Contraception should be continued for at least one month after stopping treatment with isotretinoin, even in patients with amenorrhea.

3. Obligation of the prescriber

The prescriber must ensure that the patient complies with the conditions for pregnancy prevention as listed above.

Distribution control

Prescribing and dispensing restrictions include:

1. limitation of the prescriptions of isotretinoin for women of childbearing potential to 30 days of treatment (continuation of treatment requires a new prescription); and
2. limited validity of the prescription to seven days.

Additional precautions

Patients are instructed never to give the medicine to another person and to return any unused capsules to their pharmacist at the end of treatment. There is no evidence to suggest that the fertility or offspring of male patients will be affected by them taking isotretinoin. However, male patients are also reminded not to share their medication with anyone, particularly females. Patients should not donate blood during therapy and for one month following discontinuation of isotretinoin because of the potential risk to the foetus of a pregnant transfusion recipient.

Registration of isotretinoin exposed pregnancies

Any case of pregnancy or suspected embryo-foetal exposure of a treated patient brought to the attention of the MAH should be reported, by the MAH, immediately to the competent authority of the Member State in whose territory the incident occurred. All exposure should be carefully monitored and followed-up using a specific form collecting all relevant information.

PPP in the US

Isotretinoin was labelled as being contraindicated in pregnancy when first marketed in the US in 1982 **(11, 12, 13)**. In 1983, a revised warning in bold was placed in the package insert and red warning stickers were sent to pharmacists. In 1988, a PPP was developed by Roche, which was strengthened in 2001 and was called SMART. This programme now targeted both healthcare providers and patients. In 2003, this programme was dismissed as 'ineffective'. The failure was partially attributed to the lack of mandatory record-keeping and the fact that slightly different PPPs were started by the registration holders of three newly released generic isotretinoin brands. Consequently, in the US, the so-called iPLEDGE programme was launched in March 2006. In 2007, some changes to iPLEDGE have been approved which were considered to reduce the burden to stakeholders.

iPLEDGE is a compulsory single pregnancy risk management programme for prescribing and dispensing all isotretinoin products (branded and generic) in the US. iPLEDGE is a closed system and requires registration of all wholesalers distributing isotretinoin, all healthcare professionals prescribing isotretinoin, all pharmacies dispensing isotretinoin, and all male and female patients prescribed isotretinoin **(17)**. Key elements of iPLEDGE as listed by Schonfeld et al. are **(18)**:

- Physicians and pharmacies must be registered members of the iPLEDGE programme to prescribe and dispense isotretinoin;
- all patients receiving an isotretinoin prescription must be registered in the system, visit their provider monthly, and fill their prescription within seven days of the office visit;
- additional requirements for patients of childbearing potential include:
  - The requirements to use two forms of contraception while on isotretinoin therapy, these methods must be disclosed to the prescribing provider, who enters them into the iPLEDGE system;
  - Patients must successfully complete a monthly assessment of their understanding of the risks of pregnancy before filling a prescription for isotretinoin;
  - Patients of childbearing potential are required to have a negative pregnancy test no more than seven days before filling a 30-day-prescription for isotretinoin;
  - Patients of childbearing potential also receive extensive educational information about the teratogenic risk of isotretinoin and the requirements; and
  - Prescribers receive detailed information about this contraceptive counselling for their patients on isotretinoin therapy.

Other patient groups. Unlike female patients of childbearing potential, male patients and female patients who cannot become pregnant (e.g. postmenopausal women) do not need to access iPLEDGE each month. They must be registered in the iPLEDGE system initially by the prescriber, and the prescriber must confirm that the patient understands the key safety aspects on a monthly basis to iPLEDGE **(19)**.

Pregnancy Registry. iPLEDGE includes a pregnancy registry. As part of activation in the system, pharmacies, prescribers and patients all agree to report any exposure to isotretinoin during pregnancy and its outcome to the registry.

Annex III - Isotretinoin Table 1: Comparison of selected requirements of EU- and US-PPPs

	EU-PPP	US-PPP 'iPLEDGE'
Indication	treatment of the most severe forms of acne which have failed to respond to other treatments such as antibiotics	treatment of severe recalcitrant nodular acne
Contraceptive measures	use effective continuous contraception with one, preferably two, forms (of which one is a barrier method such as a condom) from one month before treatment initiation until one month after cessation of isotretinoin	two forms of birth control; abstinence may be one (registered at pharmacy)
Pregnancy testing	pregnancy testing before, during (monthly) and five weeks after cessation of treatment	two pregnancy testing before, monthly pregnancy testing, monthly identification of contraceptive methods by patients and controls

	EU-PPP	US-PPP 'iPLEDGE'
Informed consent	signed informed consent on understanding the risks and agreement on the necessary ongoing precautionary measures with isotretinoin treatment	patient consent form
Prescribing by specialists	isotretinoin should be prescribed by physicians experienced in treating patients with this drug	pharmacists required to give medication guide with prescription
Limited validity of prescription	the maximum duration of a prescription is 30 days and dispensing of the drug by the pharmacy should take place within seven days after prescription	for female patients who can get pregnant, prescriptions must be filled and picked up within the 7-day prescription window counting the day of the blood draw or urine sample as day 1
Efficacy measurement by inherent register	no mandatory registry but obliged reporting to national authorities	pregnancy registry

Differences between the EU- and US-PPP

Table 1 lists key elements of the EU- and the US-PPP. Within the EU-PPP only one effective contraceptive form is obligatory, and the concomitant use of a second form is only a recommendation. Hence, it is less stringent than the iPLEDGE, which explicitly demands two contraceptive methods for female users of isotretinoin who are of reproductive age. In the case of iPLEDGE, the additional contraceptive method should have been registered at the pharmacy, even as regards the use of a condom.

Effectiveness assessment

It should be borne in mind that even a very strict risk-management programme will not be able to completely prevent exposed pregnancies. These may occur due to contraceptive failure or human error **(16, 19)**. Hence, the question concerning the efficacy of a PPP will probably not be if pregnancies occur but how many. Ideally, the PPP itself enables regulators to assess this efficacy, for instance by an inherent pregnancy register as it is the case with iPLEDGE.

The outcome measure for assessing the effectiveness of the PPP is the number of pregnancies that occur within the programme. Factors that may influence effectiveness include programme compliance by key stakeholders, i.e. patients, physicians and pharmacists. Among these the patient is key, since she actually takes the drug and performs the contraceptive measures. Therefore, ensuring that the patient understands the necessity of the programme for her own benefit is crucial. Studies investigating the effectiveness of a PPP have thus focussed on these aforementioned parameters.

a) Effectiveness in terms of prevented pregnancies

With regard to the former PPPs in the US, some publications **(7, 10, 20)** indicated that pregnancies still occurred in an unacceptable manner, that finally led to the implementation of the current strict iPLEDGE programme. Under iPLEDGE, pregnancy rates are reported to be 0.13/100 per isotretinoin users, i.e. 122 pregnancies per 91,894 females of childbearing potential **(18)**. This figure may suggest that iPLEDGE is effective. However, the decrease in the number of observed pregnancies may also reflect that isotretinoin has been removed from the therapeutic options of many women who might not be able to comply with

the PPP, even if the drug might potentially be very beneficial to them **(16)**. To date the programme's effectiveness in reducing the rate of isotretinoin-induced birth defects has not formally and comprehensively been evaluated in the literature. A recent study found no evidence that iPLEDGE significantly decreased the risk of fetal exposure in female patients of childbearing potential compared to the previous SMART program, based on 29 fetal exposures and 9,912 isotretinoin courses **(21)**.

Similarly, the PPP set up in the EU has also not formally been evaluated. However, spontaneous reporting indicated that pregnancies during isotretinoin use still occurred in a number which triggered initiatives to enhance the efficacy of the PPP in EU countries **(22)**. It may be assumed that the EU PPP, which is not as rigorous as the iPLEDGE, is not as effective as iPLEDGE. However, there are currently no studies directly comparing these two programmes.

b) Effectiveness in terms of stakeholder compliance with the PPP

With regard to the European PPP, Teichert et al. investigated the compliance with the Dutch isotretinoin PPP, in women of reproductive age, between January 2005 and December 2008 **(23)**. This was a retrospective cohort study in females of reproductive age using pharmacy dispensing data. The study clearly showed that concomitant use of isotretinoin and contraceptives was too low (60%). Furthermore, isotretinoin use was not restricted to cases of severe acne.

An earlier survey in the Netherlands had already shown that the pharmacists regarded the prescribers as primarily responsible for the safe use of isotretinoin. However, because of current legislation and standards, pharmacists and prescribers are equally responsible for patient counselling **(24)**.

Robertson et al. conducted a survey among women who called teratology information services throughout North America from 2002 to 2004, that is before iPLEDGE was in place in the US **(25)**. Women with an isotretinoin-exposed pregnancy were prospectively interviewed before the outcome of the pregnancy was known. In this investigation, almost one-fourth of the women surveyed (24%; 8/34) did not recall having contraception counselling before starting their medications. Monthly pregnancy tests were not always conducted during treatment, as recalled by the surveyed women (56%; 19/34). Once therapy was initiated, 62% (21/34) recalled using a birth control method, but only 29% (6/21) recalled using two forms of birth control, as specified by the voluntary pregnancy prevention programmes.

c) Effectiveness in forms of patients understanding the information

LaPointe et al. investigated patients' receipt and understanding of written information provided with isotretinoin prescription in 2004–2005, that is before iPLEDGE was in place in the US. Among 186 isotretinoin patients, the mean score on five questions assessing recognition of medication risks was only slightly better than the score expected from guessing (3.1 vs. 2.5; $p<01$) **(26)**. In the example of a case report, Robertson et al. pointed out the importance of fully informing a patient about her pregnancy risk at a level that she can understand **(25)**.

Discussion

In general, a PPP should decrease targeted adverse outcomes without limiting access for those users of the drug who can benefit from it. In addition, the efforts of a PPP must be adequate to address the targeted goal and it must be easy for key stakeholders to understand and comply. Furthermore, the implementation of a PPP should consider the feasibility to implement the programme in particular countries and regions where it is launched, taking into account cost-benefit where relevant **(18)**.

It is not realistic that a PPP can decrease pregnancies to zero. In addition, foetal malformations in an isotretinoin-exposed pregnancy may not wholly be attributable to isotretinoin, as they may also occur sporadically in normal pregnancies, whether they are isotretinoin exposed or not **(18)**. Finally, individuals who cannot get access to the medication within the PPP may still find ways to circumvent the PPP, for instance by obtaining the medicine via the Internet.

iPLEDGE seems to be a rigorous and effective PPP **(18)**, however, it involves such strict risk minimisation measures that may increase burden on the healthcare system and reduce access to some patients that could benefit from isotretinoin. In this respect iPLEDGE has been criticised by some dermatologists for

its inflexibility and multiple administrative and time-consuming requirements **(27, 28)**. Furthermore, with iPLEDGE, the primary responsibility for making decisions about therapy is shifted from the usual physician-patient relationship to a third party **(18)**. In Canada the regulatory authorities have decided to adhere to the original PPP **(16)**. In comparison, under the PPP in the EU, which seems to be less strict than iPLEDGE, pregnancies are still being reported.

When considering both programmes, the behaviour of the patients when taking the drug seems crucial for an effective PPP. Providing adequate information to patients is pivotal in order to positively influence their behaviour and must be communicated in a way that the patient will understand and comply of their own accord. Besides healthcare providers, companies have key responsibilities for providing information and education which they should be obliged to fulfil.

Critical technical elements of an effective PPP include contraceptive measures (ideally two) and screening for pregnancy prior to the start of therapy with isotretinoin and regular pregnancy testing thereafter. Implementation of a PPP might also be improved by explicit statements of responsibilities for prescribers as well as for pharmacists regarding patient counselling.

Conclusions

The effectiveness of isotretinoin Pregnancy Prevention Programmes (PPPs) has not been sufficiently investigated. Hence, it cannot be shown conclusively that a more rigorous programme is superior to a less restrictive one. Prevention of exposed pregnancies and the availability of isotretinoin for patients who really need this medication must be balanced. Any PPP may only be as good as the stakeholders' compliance with it, which is particularly influenced by adequate information and education.

References

1. European Medicines Agency, Committee for Proprietary Medicinal Products (CPMP). Summary information on a referral opinion following an arbitration pursuant to article 29 of EU Directive 2001/83/EC, for isotretinoin lurantal/ trivane/rexidal/ scheritonin, 17 October 2003, http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Isotretinoin_29/WC500010882.pdf, and Annex I, II, III in WC500010881.pdf, accessed 30 April 2014.
2. Schaefer C et al. Isotretinoin exposure and pregnancy outcome: An observational study of the Berlin Institute for Clinical Teratology and Drug Risk Assessment in Pregnancy. Arch Gynecol Obstet. 2010, 281:221-7.
3. Nulman I et al. Steady-state pharmacokinetics of isotretinoin and its 4-oxo metabolite: Implications for fetal safety. J Clin Pharmacol. 1988, 38:926–930.
4. Ganceviciene R and Zouboulis C. Isotretinoin: State of the art treatment for acne vulgaris. JDDG. 2010, supplement 1:S47-S59.
5. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Isotretinoin/human_referral_000258.jsp&mid=WC0b01ac05805c516f, accessed 30 April 2014.
6. Brelsford M, Beute TC. Preventing and managing the side effects of isotretinoin. Semin Cutan Med Surg. 2008, 27:197-206.
7. Bérard A et al. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Clin Pharmacol. 2007, 63:196-205.
8. Azoulay L et al. Patterns and utilization of isotretinoin from 1984 to 2003: is there need for concern? Eur J Clin Pharmacol. 2006, 62:667–674.
9. Moskop JC et al. Ethical aspects of teratogenic medications: the case of isotretinoin. J Clin Ethics. 1997, 8:264–278.
10. Abroms L et al. What is the best approach to reducing birth defects associated with isotretinoin? PLoS Med. 2006, 3:e483.
11. Fantel AG et al. Teratogenic effects of retinoic acid in pigtail monkeys (Macaca nemes trina): I. General features. Teratology. 1977, 15:65-71.
12. Kochhar D. Teratogenic activity of retinoic acid. Acta Pathol Microbiol Scand. 1967, 70:398-404.
13. Shenefelt RE. Morphogenesis of malformations in hamsters caused by retinoic acid: relation to dose and stage at treatment. Teratology. 1972, 5:103-18.
14. Lammer EJ et al. Retinoic acid embryopathy. N Engl J Med. 1985, 313:837–841.
15. Lammer EJ et al. Unusually high risk for adverse outcomes of pregnancy following fetal isotretinoin exposure. Am J Hum Genet. 1988, 43:A58.
16. Garcia-Bournissen F et al. Fetal exposure to isotretinoin—An international problem. Reproductive Toxicology. 2008, 25:124–128.
17. https://www.ipledgeprogram.com.
18. Schonfeld TL et al. iPLEDGE allegiance to the pill: evaluation of year 1 of a birth defect prevention and monitoring system. J Law Med Ethics. 2009, 37:104-107.
19. Honein MA et al. Can we ensure the safe use of known human teratogens? The iPLEDGE test case. Drug Safety. 2007, 30:5-15.
20. Honein MA et al. Continued occurrence of Accuatene-exposed pregnancies. Teratology 2001;64:142-7.
21. Shin J et al. The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care sytem. J Am Acad Dermatol. 2011, 65:1117-1125.
22. Crijns I et al. Implementation of the harmonized EU Isotretinoin Pregnancy Prevention Programme. Drug Safety. 2012, 35:27-32.
23. Teichert M et al. Isotretinoin use and compliance with the Dutch Pregnancy Prevention Programme. Drug Saf. 2010, 33:315-326.
24. Smeets JG et al. NHG-standard acne. Huisarts Wet. 2007, 50:259-268.
25. Robertson J, Polifka JE, Avner M et al. A survey of pregnant women using isotretinoin. Birth Defects Res A Clin Mol Teratol. 2005, 73:881–887.

[26] La Pointe NMA et al. Patient receipt and understanding of written information provided with isotretinoin and estrogen prescriptions. J Gen Internal Med. 2007, 22(1), 98-101.
[27] Boodmann SG. Too hard to take: A strict new acne drug programme may prevent birth defects. The Washington Post. 2006, 5 Sept. (EH01).
[28] Darves B. Dermatologists frustrated with problematic iPLEDGE programme. Medscape Med News. 2006, 9 March.

D. Oxycodone hydrochloride (INN), OxyContin®

Pharmacology	Opioid analgesic
Indication/Disease treated	Chronic moderate to severe pain.
Risks targeted for additional risk minimisation	Opioid misuse and abuse, resulting in morbidity and mortality.
Risk minimisation tools (beyond routine)	▶ FDA Warning Letter to marketing authorization holder (MAH) holder re: advertisements. ▶ Submission of risk management plan to FDA, featuring an active surveillance entitled the Researched abuse, diversion and addiction-related surveillance system (RADARS) which collected real-time data. ▶ Educational materials developed for HCPs, and patients regarding safe and appropriate use of the product and the potential for abuse and addiction. ▶ Other risk minimisation initiatives included strict manufacturing and distribution controls (including identification ID chips on the drug shipment pallets), revision of promotional materials, additional training of sales force, support of local law enforcement efforts to combat prescription drug abuse, education and training to healthcare professionals about drug screening tests and patient opioid contracts. ▶ Distribution of tamper-resistant prescription pads and pens to physicians. ▶ The manufacturer submitted RiskMAP to the FDA. A new tamper resistant formulation was approved by the FDA in 2010 (the new tamper-resistant formulation represented a form of risk minimisation). ▶ In addition, the FDA requested that OxyContin be part of a "Class-Wide REMS" for extended-release opioid analgesic products. The Class-Wide REMS was subsequently developed and implemented by 2012.
Effectiveness measurement methods	No formal evaluation of the effectiveness of the RiskMAP was ever conducted. However, attendant with the launch of the new, tamper-resistant formulation, the MAH undertook several epidemiological studies to assess the effectiveness of the new formulation in reducing levels of nonmedical use of the re-formulated product. Results from several of these studies have been published (see citations below). As of the date of publication of this book, results from the impact of the Class-Wide REMS had not yet been released.
Conclusion	Results from several epidemiological studies show that there was a significant drop in preference for OxyContin as the primary drug of abuse among drug abusers, as well as a decrease in diversion, and rates of abuse. The effectiveness of other elements of the OxyContin REMS educational programme remains to be demonstrated empirically.

OxyContin®: A Case Study in the evolution of a risk minimisation strategy for a drug with abuse potential

Introduction

OxyContin® (oxycodone hydrochloride) is a controlled-release semisynthetic oral opioid analgesic with a Schedule II designation under the Controlled Substances Act (CSA). The CSA defines Schedule II drugs as those which have an accepted medical use but also a high potential for abuse that could lead to severe psychological or physical dependence **(1)**.

At the time of OxyContin's 1995 approval by the Food and Drug Administration (FDA), undertreatment of chronic pain was recognized as a major public health problem and long-acting opioid analgesics were acknowledged as offering important benefits to pain patients as described in the landmark publication on cancer pain relief of the World Health Organization in 1986 **(2)**. Specific benefits offered by OxyContin included continuous relief from pain over an extended (twelve hours) time period, reduction in pain fluctuations, improved convenience in the form of fewer daily doses, and increased ease of dose adjustment to respond to increasing pain levels.

OxyContin was indicated for 'moderate to severe pain where use of an opioid analgesic is appropriate for more than a few days.' Because of its controlled-release formulation, OxyContin was labelled as having less abuse potential than other oxycodone products due to the fact that, when taken properly, a controlled-release formulation ensures that a drug is absorbed slowly without an immediate rush or high. However, precisely because OxyContin contained more active ingredient than other, non-controlled-release oxycodone-containing drugs, the label's Warning section advised patients not to crush the tablets because of the possible rapid release of a potentially toxic amount of oxycodone.

Following market launch in 1996, OxyContin's sales increased rapidly from $44,790,000 in 1996 to $1,536,816,000 in 2002 **(3)**. Commensurate with this rise, reports of nonmedical use, abuse and diversion of OxyContin began appearing in the media, some dating from as early as 1999 **(3)**. While reports were received from all across the US, the majority emanated from socio-economically depressed communities, particularly those in rural areas such as the Appalachians, Ohio, Pennsylvania, Virginia and Maine **(3, 4, 5)**.

Efforts to mitigate the risks of nonmedical use, abuse and diversion of OxyContin

Between 2001 and 2004, a host of different initiatives was launched to mitigate the risks associated with the nonmedical use, abuse and diversion of OxyContin. These initiatives involved a variety of participants, including such governmental agencies as the FDA, Drug Enforcement Administration (DEA), and the Department of Justice (DOJ), professional organisations; non-profit pain and patient advocacy groups; and OxyContin's sponsor, Purdue Pharma L.P. Specifically, efforts included:

- Extensive revisions to the OxyContin label in 2001, including:

1. addition of a black box warning stressing the opioid nature of oxycodone and risks for abuse and diversion of the drug;
2. addition of a subsection to the Warning section on misuse, abuse and diversion of opioids;
3. expanded wording in the clinical pharmacology regarding the pharmacological properties and side effects (e.g. respiratory depression) of opioids in general, and oxycodone in particular;
4. a statement in the Drug Abuse and Addiction section regarding the fact that oxycodone can be abused and is subject to criminal diversion; and,
5. in the Safety and Handling section, an alert to healthcare professionals that OxyContin could be targeted for theft and diversion and instructions to contact their State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of OxyContin.

- FDA issuance of a Warning Letter in January 2003 to Purdue Pharma regarding two professional medical journal advertisements for OxyContin. The Warning Letter stated that the advertisements

failed to present information from the boxed warning on the potentially fatal risks associated with OxyContin's abuse liability. Purdue pulled the offending advertisements and revised the content to address the FDA concerns.

- Development and FDA submission of a formal risk minimisation plan for OxyContin in 2004 **(6)**. The elements of this plan included establishing a surveillance programme entitled the Researched abuse, diversion and addiction-related surveillance system (RADARS), a set of studies collecting real-time data on the nonmedical use, abuse and diversion of OxyContin and other comparator opioid analgesics at the 3-digit ZIP code level in selected locales in the U.S. Other elements of the risk minimisation plan included: development and dissemination of educational materials for healthcare professionals concerning the potential for abuse and diversion; education of patients about the possibility of abuse associated with OxyContin, and the importance of safe storage of all opioid medication, including OxyContin; revision of all OxyContin promotional materials to reflect the labelling changes; training of the sales force on the label revisions; and distribution of tamper-resistant prescription pads and pens to physicians prescribing opioid analgesics.
- Issuance of a "Dear Healthcare Professional Letter" by Purdue alerting physicians to the changes in the label;
- Development of an OxyContin Patient Package Insert (PPI) with information regarding the potential for the drug's abuse and diversion;
- Initiation of a multi-pronged national action plan by the Drug Enforcement Administration (DEA) which involved: 1) coordinating enforcement and intelligence operations with other law enforcement agencies to target people and organizations involved in the abuse and diversion of OxyContin; 2) pursuing regulatory and administrative action to limit abusers' access to OxyContin; 3) initiating national outreach efforts to educate the public on the dangers related to the abuse and diversion of OxyContin; and 4) the lowering of Purdue's procurement quota for oxycodone at levels lower than that requested by Purdue.
- Increased federal government funding to provide grants to states for the establishment of prescription drug monitoring programmes;
- Issuance of a consensus statement from the DEA and 21 national pain and health organizations that called for a balanced policy on prescription medication use, one in which healthcare professionals and DEA share responsibility for ensuring that prescription medications, such as OxyContin, are available to patients who need them and for preventing these drugs from becoming a source of abuse and diversion.
- Voluntary withdrawal by Purdue of the highest dose (160 mg) of OxyContin from the market.

OxyContin Risk Minimisation Action Plan (RiskMAP)

Despite these efforts, the abuse and diversion of OxyContin continued to escalate **(7, 8)**. Between 2003 and 2006, published surveillance data indicated that OxyContin was being used non-medically by a growing percentage of Americans, particularly those between the ages of 18 and 44 (National Survey on Drug Use and Health). Ethnographic studies in recreational drug abusers and drug addicts revealed that OxyContin was being crushed, melted, smoked, injected, snorted for abuse purposes **(9, 10)**. OxyContin was also associated with an increasing number of abuse-related calls to poison control centres **(11)**.

In 2006, the FDA issued a tripartite set of guidances on risk management of pharmaceutical products. The third guidance, which addressed postmarketing activities, introduced the concept of a Risk Minimisation Action Plan or RiskMAP **(12)**. Although development of a RiskMAP was voluntary, Purdue's risk minimisation plan was revised to conform to the RiskMAP template **(8)**. The OxyContin RiskMAP was structured to include goals and objectives, identification of the specific risks to be minimized and product benefits to be preserved under the RiskMAP, postmarketing reporting commitments, an implementation schedule, and a discussion of any potential unintended consequences of RiskMAP activities. Many of the specific risk minimisation tools to be deployed, however, remained the same or similar to those included in the original risk minimisation programme.

Effectiveness of RiskMAP in combating abuse and diversion of OxyContin

Little publicly available data are available to determine the effectiveness of the RiskMAP tools, and the overall RiskMAP in combating the nonmedical use, abuse, diversion of OxyContin. One exception was a published analysis of the adoption of free, tamper-resistant prescription pads by prescribers of OxyContin **(13)**. Results showed that uptake of these pads was limited and essentially stabilized after initial introduction. No data were available to determine, however, the extent to which these tamper-resistant prescription pads actually deterred the writing of forged prescriptions for OxyContin. Publicly available epidemiological data, however, indicated that the nonmedical use and abuse of OxyContin continued unabated after the introduction of the RiskMAP **(14)**.

In May 2008, Purdue presented a revised RiskMAP to the Joint Meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee as part of a new drug application for a new formulation of OxyContin **(6)**. The new formulation was designed to have with greater tamper-resistant properties in terms of being more difficult to physically manipulate the pill and to extract the active pharmaceutical ingredient (e.g. crush, dissolve, and to extract the oxycodone).

While the goals of the revised RiskMAP remained similar to those of the original, a key difference included the explicit use of the revised formulation as a new type of risk minimisation tool, and the inclusion of an epidemiological study to assess the effectiveness of the RiskMAP in reducing levels of nonmedical use, and abuse of OxyContin **(6)**. In particular, the epidemiological study was designed to compare the prevalence of OxyContin abuse, by site, among enrollees to opioid treatment programmes (OTP) before and after availability of the new formulation. The study design involved conducting a cross-sectional assessment of drug abuse behaviours in adults (≥18 years old) seeking admission to one of 68 OTPs for addiction to opioids using data from the RADARS OTP study. Based on the results of the Advisory Committee meeting, however, the FDA requested Purdue to conduct additional studies regarding the new tamper-resistant formulation. Notably, in publicly-posted correspondence with Purdue, however, the FDA acknowledged that drug re-formulation could be recognized as a risk minimisation tool. The original RiskMAP remained in effect during this period.

With the passage of the Food and Drug Administration Amendment Act (FDAAA) in September, 2007, the FDA introduced a mandatory risk management plan referred to as a 'Risk Evaluation and Mitigation Strategy' (REMS). OxyContin's RiskMAP was subsequently modified into a REMS **(15)**. A comparison of the RiskMAP and REMS for OxyContin is presented in Table 1.

Annex III - OxyContin Table 1: Comparison of the RiskMAP and REMS.

	RiskMAP
Goal	1. To minimize abuse of OxyContin. 2. To minimize diversion of OxyContin. 3. To minimize exposure to OxyContin among those under age 18.
A. Risk minimisation elements	1. Package insert. 2. Controlled distribution via Schedule II status. 3. Patient Package Insert (PPI). 4. Sales force training on key messages. 5. Education of healthcare professionals (via brochures available on Internet and hard copy) concerning: a) appropriate prescribing of opioid analgesics; b) appropriate patient selection; c) prevention of diversion; d) proper storage and disposal of opioid analgesics; e) targeted education of law enforcement and/or healthcare professionals in the affected community. 6. Targeted education of law enforcement professionals in communities affected by prescription drug abuse. Education delivered via printed materials and in-person lectures. Topics covered included: understanding prescription drug addiction; investigating and preventing drug diversion; and identification of different opioid drug products. 7. Free tamper-resistant prescription pads and pens to OxyContin prescribers. 8. Tamper-resistant formulation.
B. Elements to assure safe use	Not applicable.
C. Implementation system	Specification of a timetable for implementing and distributing risk minimisation tools.
D. Timetable for submission of assessments	Annually.
	REMS*
Goal	1. To inform patients and healthcare professionals about the potential for abuse, misuse, overdose, and addiction of OxyContin; 2. To inform patients and healthcare professionals about the safe use of OxyContin.
A. Risk minimisation elements	1. Package Insert 2. Controlled distribution via Schedule II status 3. Medication Guide- 3 copies to be packaged with each bottle of OxyContin (delivered by pharmacist; Sales representatives, through an Internet presence, and from Purdue's Medical Services Department).

	RiskMAP
B. Elements to assure safe use	Healthcare providers who prescribe OxyContin will receive training. To become trained, each prescriber will be provided with the OxyContin educational materials. The training includes the following: 1. Proper patient selection; 2. Appropriate OxyContin dosing and administration; 3. General principles of safe opioid use, including information about opioid abuse and how to identify patients who are at risk for addiction; 4. Potential abuse, misuse, overdose and addiction from exposure to opioids, including OxyContin; 5. Risks of OxyContin, including: ► The risk of overdose caused by exposure to an essentially immediate-release form of oxycodone by consuming broken, chewed, crushed or dissolved OxyContin tablets; ► The risk of addiction from exposure to OxyContin; and ► The risk of overdose in patients who have not developed tolerance to the sedating or respiratory-depressant effects of opioids from exposure to a single dose of OxyContin greater than 40 mg; 6. Information to counsel patients and caregivers on the need to store opioid analgesics safely out of reach of children and household acquaintances and the need to properly dispose of unused drugs when no longer needed by the patient; 7. Importance of providing each patient a Medication Guide with each prescription and instructing the patient to read the Medication Guide; and 8. Dear Healthcare Professional letter: within at least 3 weeks prior to first availability of OxyContin to healthcare professionals, the letter will be mailed to prescribers most experienced in treating chronic pain with opioid agonists, including pain specialists, physiatrists, and primary care physicians. This letter is designed to convey and reinforce the risks of abuse, misuse, overdose and addiction of OxyContin as well as the need to complete the OxyContin REMS Educational Program. This letter will be available on the Purdue website (www.oxycontinrems.com) for 1 year from the date of mailing. The mailings will include the following OxyContinREMS Educational Program materials: ► Prescribing OxyContinTablets CII: A Guide for Healthcare Providers; ► Additional printed educational material will be available through field-force distribution and by calling the toll-free number at Purdue; ► The educational material will also be available for download at www.oxycontinrems.com. Prescribers will be re-trained every two years or following substantial changes to the OxyContin REMS. Substantial changes may include changes in the OxyContin Full Prescribing Information, OxyContin Medication Guide, or OxyContin REMS that require substantial modification of the educational materials.

	RiskMAP
C. Implementation system	Because OxyContin can be approved without the Elements to Assure Safe Use described under FDCA 505–1(f) (3) (B), (C), and (D) of the Act, an implementation system is not required.
D. Timetable for submission of assessments	Receipt of education will be verified via an OxyContin® Education Confirmation Form that healthcare professionals will be asked to complete and submit to Purdue. Purdue will maintain a list of all prescribers who have completed the OxyContin® REMS Educational Program. Purdue Pharma L.P. will submit REMS Assessments to FDA every 6 months for the first year from the date of approval of the REMS and annually thereafter. To facilitate inclusion of as much information as possible, while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment will conclude no earlier than 60 days before the submission date for that assessment. Purdue L.P. will submit each assessment so that it will be received by the FDA on or before the due date.

***Class REMS** *that applies to extended release opioids in the US.*

Conclusion

Following the introduction of REMS, the OxyContin risk minimisation efforts were significantly scaled back in terms of scope. While the RiskMAP goals had targeted reducing abuse and diversion of the product, REMS goals' specified a more modest, and arguably more realistic, target of educating patients and healthcare professionals regarding the safe use and potential for addiction and abuse of OxyContin. Such an approach is consistent with the viewpoint that prescription drug abuse is a societal problem best addressed by a coordinated effort between a host of public and private stakeholders **(16)**. The effectiveness of the OxyContin REMS educational programme remains to be demonstrated empirically. The emphasis on raising awareness about drug risks is consistent with that found in REMS for other opioid analgesic products. A larger question, however, is whether raising awareness alone is sufficient and if REMS goals should focus on changing healthcare professional behaviour (e.g. appropriate patient selection, appropriate prescribing, and counselling of patients concerning drug risks) as well.

General references

Black R, Coplan P, Cassidy T, Chilcoat H et al. Effects of reformulated OxyContin® among patients assessed for substance abuse treatment in the NAVIPPRO sentinel surveillance network. Journal of Pain. 2012, April Vol. 13, Issue 4, Supplement: S58.

Davis J, Severtson SG, Bartelson BB, Munoz A et al. Changes in diversion rates following the introduction of a reformulated extended release oxycodone product. Annals of Emerg Med. 2012, October Vol. 60, Issue 4, Supplement: S35.

Graham A, Smith MY, Haddox JD, et al. Reducing the potential for diversion of prescription opioids: Tested interventions. Poster presented at College on Problems of Drug Dependence. Orlando, Florida, June 2005.

Manchikanti L, Fellows B, Damron KS et al. Prevalence of illicit drug use among individuals with chronic pain in the Commonwealth of Kentucky: An evaluation of patterns and trends. J Kentucky Med Assoc. 2005, 103: 55–62.

National Institute of Drug Abuse. Research report series: Prescription drugs abuse and addiction. NIH Pub No 05–4. L881. Bethesda, MD: National Institute of Drug Abuse, 2005.

OxyContin (oxycodone hydrochloride controlled-release) Tablets REMS: Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm, accessed on 8 March 2014.

Severtson SG, Bartelson BB, Davis JM, Muñoz A et al. reduced abuse, therapeutic errors, and diversion following reformulation of extended-release oxycodone in 2010. Journal of Pain. 2013, Vol. 14, Issue 10: 1122–1130.

Severtson SG, Bartelson BB, Davis JM, Muñoz A et al. Difference in rates of abuse following reformulation of extended release oxycodone using data from the RADARS® System Poison Center Program, Annals of Emerg Med. 2012, Vol. 60, Issue 4, Supplement: S34-S35.

Smith M, Colucci S, Haddox JD. Diffusion of tamper-resistant prescription pad usage among opioid analgesic prescribers in the U.S.: 2001–2005. J Pain. 2006, 7(4): S98.

Young D: Federal reports say oxycodone abuse is on the rise. J Health Syst Pharm. 2001, 58: 1175,1178–1179.

References

1. Controlled Substances Act. Title 21 - Food and Drugs, Chapter 13 - Drug abuse prevention and control, Subchapter I - Control and enforcement. U.S. Food and Drug Administration. http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm.
2. World Health Organization. Cancer pain relief with a guide to opioid availability (second edition). Geneva, Switzerland: WHO, 1986.
3. U.S. Government Accountability Office. Prescription drugs: Oxycontin abuse and diversion and efforts to address the problem. Report to Congressional Requesters. 2003, December. http://www.gao.gov/products/GAO-04–110. Last accessed on 8 April 2014.
4. Drug Enforcement Administration. OxyContin®. Pharmaceutical division. Drug Intelligence Brief. Arlington, VA, USA. 2002.
5. Hutchinson A. OxyContin Testimony. House Committee on Appropriations, Commerce, Justice, State, and Judiciary. 2001.
6. Purdue Pharma L.P. A new formulation of OxyContin® (oxycodone HCl controlled-release) tablets. Presentation to joint meeting of the Anesthetic and Life Support Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee, May 5, 2008. www.fda.gov/ohrms/dockets/ac/08/slides/2008–4356s1–05-Purdue.pdf . Last accessed on 8 April 2014.
7. Zacny J, Bigelow G, Compton P, Foley K, Iguchi M, Sannerud C. College on problems of drug dependence Taskforce on prescription opioid non-medical use and abuse: Position statement. Drug and Alcohol Dependence. 2003, 69: 215–232.
8. Compton WM, Volkow ND. Major increases in opioid analgesic abuse in the United States: Concerns and strategies. Drug Alcohol Dep. 2006, 81: 103–107.
9. McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. Addict Behav. 2007, 32(3): 562–575.
10. Young AM, Havens RJ, Leukefeld CG. Route of administration for illicit prescription opioids: a comparison of rural and urban drug users. Harm Reduct J. 2010, 7(24).
11. Smith MY, Schneider MF, Wentz A, Hughes A, Haddox JD, Dart R. Quantifying morbidity associated with the abuse and misuse of opioid analgesics: A comparison of two approaches. Clin Toxicol. 2007, 45(1): 23–30.
12. U.S. Food and Drug Administration. Guidance for industry: Development and use of risk minimisation action plans. 2005. http://www.fda.gov/downloads/RegulatoryInformation/guidances/ucm126830.pdf, accessed 8 April 2014.
13. Smith, MY. PRISMAP®: A risk management program for drugs with abuse potential. Oral presentation presented at: 42nd Annual Meeting of the Drug Information Association. June 2006. Philadelphia, PA, USA. June 2006.
14. Substance Abuse and Mental Health Services Administration. Results from the 2006 national survey on drug use and health. Nonmedical use of prescription pain relievers. Rockville, MD, USA: Office of Applied Studies. 2008.
15. Food and Drug Administration. Guidance for industry: Format and content of proposed risk evaluation and mitigation strategies (REMS), REMS assessments, and proposed REMS modifications. 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM184128.pdf, accessed on 8 April 2014.
16. Smith MY, Kleber HD, Katz N, Houck L, Sabo S. Reducing opioid analgesic abuse: Models of successful collaboration among government, industry and other key stakeholders. Drug Alcohol Depend. 2008, 95(1–2): 177–181.

E. Paracetamol (INN) in UK, acetaminophen (INN) in US

Pharmacology	Over-the-counter mild analgesic (pain reliever) and antipyretic (fever reducer).
Indication/Disease treated	Pain and fever.
Risks targeted for additional risk minimisation	Paracetamol poisoning and/or deliberate self-harm by overdose.
Risk minimisation tools (beyond routine)	Reduced pack size to 16 x 500mg tablets. Pharmacies restricted to sell packets up to 32 tablets. Warnings printed on packets and leaflets in packets. (Legislation passed in the UK only.)
Effectiveness measurement methods	Numerous observational studies with various parameters assessed.
Conclusion	Very difficult to draw any firm conclusions as to whether product pack size limitation had significant impact on mortality, severity of poisoning, or sales data, and only slight reduction in hospital admissions or liver transplantations.

Paracetamol case study – UK experience

Background

Deliberate self-harm with over-the- counter analgesics is common in the UK and paracetamol poisoning accounts for approximately 48% of all poisoning admissions to the hospital annually **(1)**. Between 1993 and 2000, paracetamol was detected in about 150–200 deaths per year in England &Wales **(2)**. Paracetamol overdose is the most common cause of acute liver failure in the UK.

Risk minimisation approach

Paracetamol poisoning has been closely linked to its availability **(3)**. In 1998, legislation was introduced in the UK to limit the pack sizes for paracetamol or salicylate products sold over the counter. The objective was to reduce the mortality and morbidity associated with deliberate overdose of analgesics, especially paracetamol.

Summary of the legislative changes affecting paracetamol packs:

1. Reduce pack size of paracetamol in general sales to 16 x 500mg tablets (8g in total).
2. Pharmacies may sell packets of up to 32 tablets or capsules.
3. Warnings about the dangers of paracetamol overdose must be printed on packets and leaflets in packets.

Analysis of effectiveness of reduction in pack size on paracetamol overdose

Two systematic literature reviews to assess the impact of the reduction in pack size of paracetamol are presented below, one was published in 2004 and the other in 2007.

Summary of the literature review by Morgan et al. (4)

Search criteria**:**

- Database - EMBASE, Medline, CINHAL and evidence-based medicine reviews.
- Literature search – English publications 1998–2003.
- UK studies that assessed changes in any aspects of paracetamol poisoning due to 1998 regulations.

Twelve studies were included in the review; nine studies met the criteria and three additional studies were recommended for inclusion by the referees. These were all observational studies, reporting outcomes before and after 1998. In the majority of the studies, the follow-up period after the implementation of the legislation in1998 was short (around 1–2 years).

Seven studies were conducted at local level (wholly or partly) and only three compared results of paracetamol with other medicines. Several different outcomes were assessed across the studies: admissions to liver transplant units (three studies), severity of paracetamol poisoning (eight studies), hospital admissions (six studies), mortality trends (three studies) and OTC sales (two studies).

Annex III - Paracetamol Table 1: Comparison of seven studies outcomes

Study	Period and setting	Parameters assessed
Prince et al. **(5)**	1995–1999; Freeman liver unit, Newcastle-upon-Tyne. UK transplant special support authority (UKTSSA).	Referrals to specialist liver units, transplantation requests, amount of paracetamol ingested, biochemical data, and clinical features.
Turvill et al. **(6)**	1995–1999; Royal Free Hospital, London UK	Number of overdoses and severe overdoses, those where acetylcysteine or methionine was indicated, benzodiazepine overdose (control).
Robinson et al. **(7)**	1998–1999; five general hospitals in the Belfast area, Northern Ireland.	Amount of paracetamol ingested, serum paracetamol concentrations, liver enzyme levels, International Normalised ratio (INR) level, antidote administration.
Hawton et al. **(8)**	1996–1999; E&W (mortality), 5 liver units (England) and 7 general hospitals (England). UK (sales data).	Mortality, liver transplants and referrals to specialist liver units, number of overdoses and tablets taken, blood concentrations of drugs, prothrombin times, sales data.
Sheen and Dillon **(9)**	1995–2000; Ninewells Hospital, Scotland.	Paracetamol assay (serum concentration) requests.
Sheen et al. **(10)**	1998–2000; UK (sales data)	Sales (mass) of aspirin, paracetamol and ibuprofen
Bateman et al. **(11)**	1990–1999; Scotland	Discharge rates, mortality
Sheen et al. **(12)**	1994–2000; Scotland	Number and annual incidence of paracetamol-related deaths.
Hughes et al. **(13)**	1995–2002; University hospitals and the Queen Elizabeth Hospital liver unit, Birmingham, UK	Hospital admissions for paracetamol overdose, admissions to the specialist liver unit with paracetamol-induced hepatotoxicity.

Study	Period and setting	Parameters assessed
Donohoe and Tracey **(14)**	1997–1998; National Poisons Information Unit, Ireland.	Cases of reported acute paracetamol overdose and number of tablets ingested.
Laing et al. **(15)**	1996–2000; Scottish Poisons Information Bureau, Scotland.	Telephone enquiries made to a poisons centre involving paracetamol.
Thomas and Jowett **(16)**	1998–1999; Withybush General Hospital, Wales,	Hospital admissions for all paracetamol and non-paracetamol overdoses.

Liver units

All three studies that considered referrals to the liver units reported a reduction in number of referrals.5,8,13

Severity of poisoning

A variety of different criteria were used in the assessment of severity of poisoning across the studies. The overall indication is that the severity of poisoning does not appear to have been changed. Key findings from the published studies are summarised below:

Annex III - Paracetamol Table 2: Assessment of severity of poisoning

Study	Key findings
Prince et al. **(5)**	Assessed severity in terms of overdose size, substance taken or criteria for transplant amongst the referrals – no change was reported pre- and post–legislation.
Turvill et al. **(6)**	Reduction in severity (measures by N-acetylcysteine), with 64% fewer severe paracetamol poisoning.
Robinson et al. **(7)**	Reported a small reduction in median quantity of paracetamol ingested from 10 to 8 g and a reduction in serum paracetamol concentration at 4–6 h (37–27 mg/l). However, the number of severe poisoning post regulations introduction was reported as little changed (unclear as to the criteria used).
Hawton et al. **(8)**	No difference in mean highest blood paracetamol concentration recorded and only a slight decrease in number of tablets taken.
Sheen et al. **(9)**	Found little difference in number of positive paracetamol assays or assays reporting potentially hepatotoxic poisonings.
Donohoe et al. **(14)**	976 calls for paracetamol poisoning in 1998 compared to 1,044 calls in 1997 ($p>0.1$). No statistical significance in number of cases taking more than 48 tablets.
Laing et al. **(15)**	No decrease in patients taking >8g of paracetamol. Slight increase in number of cases taking >16g
Thomas and Jowett **(16)**	Reduction in severity (based on small number of cases) with proportion taking > 16 tabs falling from 68% (n=30) to 51% (n=18)

Hospital attendance

Five of six studies showed reduction in hospital attendance, ranging from 11–31%. One study indicated that the change occurred prior to the introduction of the regulatory changes.

Mortality

The results on mortality data were conflicting. In a study looking at the data for England and Wales, a 12% decrease (95% CI 5 to 34) in deaths from paracetamol alone was reported **(8)**. For one study based on the mortality dataset from Scotland, no change was found during the study period from 1990–1999 **(11)**. In another study looking at the mortality trend in Scotland, an average of 28 deaths per year (1994–2000) was reported, which decreased to 20 deaths in 1998, but increased to 31 deaths in 2000 **(12)**.

Sales

There were two studies investigating change in sales of paracetamol following the implementation of the new legislation. Both studies analysed the same set of data (OTC sales from manufacturers and wholesalers) using different methods and both reported a reduction in amount of paracetamol sold. **(8, 10)**

Summary of the literature review by Hawkins et al. (17)

In this literature review, the selection criteria was any study in UK from 1998 onwards that assessed changes in at least one aspect of paracetamol poisoning. The search was performed in Medline, EMBASE, CINHAL databases but confined to publications in English only.

Thirteen studies that met the above criteria were found and a further 4 studies were identified from review of the reference lists in the selected studies.

A variety of outcomes of paracetamol poisoning following changes in legislation were examined in the 17 studies: mortality, hepatotoxicity, hospital admissions, sales data and severity of poisoning.

Annex III - Paracetamol Table 3: Outcomes of poisoning following changes in legislation

Study	Period and setting	Parameters assessed
Bateman et al. **(11)**	1990–1999; Scotland	Discharge rates, mortality.
Bateman et al. **(18)**	1995–2004; Scotland	Mortality (1995–2003), discharge rates (1995–2004).
Hawton et al. **(8)**	1996–1999; E&W (mortality), data from 5x liver units (England) and seven general hospitals (England). UK (sales data)	Mortality, liver transplants and referrals to specialist liver units, number of overdoses and tablets taken, blood concentrations of drugs, prothrombin times, sales data.
Hawton et al. **(19)**	1997–2001; E&W (suicides), data from 6x liver units (England and Scotland) and five general hospitals (England). UK (sales data).	Mortality, liver transplants and referrals to specialist liver units, nonfatal self-poisoning, sales data.
Hughes et al. **(13)**	1995–2002;University hospitals and the Queen Elizabeth Hospital liver unit, Birmingham, UK	Hospital admissions for paracetamol overdose, admissions to the specialist liver unit with paracetamol-induced hepatotoxicity.
Inglis **(20)**	1991–2002; Scotland	Deaths and emergency admissions.
Laing et al. **(15)**	1996–2000; Scottish Poisons Information Bureau, Scotland	Telephone enquiries made to a poisons centre involving paracetamol.

Study	Period and setting	Parameters assessed
Langford et al. **(21)**	1998–1999, 2002; West Midlands, UK	Mortality, hospital admissions, severe overdoses, admissions with paracetamol toxicity to a tertiary unit.
Morgan et al. **(22)**	1993–2002; England and Wales	Mortality, hospital admissions.
Newsome et al. **(23)**	1992–2001; Scottish liver transplantation unit, Scotland	Paracetamol-induced acute liver injury, acute liver failure, acute liver failure meeting poor prognostic criteria.
Prince et al. **(5)**	1998–1999; Freeman liver unit, Newcastle-upon-Tyne. UK transplant special support authority (UKTSSA)	Referrals to specialist liver units, transplantation requests, amount of paracetamol ingested, biochemical data, clinical features.
Robinson et al. **(7)**	1998–1999; five general hospitals in the Belfast area, Ireland	Amount of paracetamol ingested, serum paracetamol concentrations, liver enzyme levels, INR, antidote administration.
Sheen et al. **(24)**	1995–2000; Ninewells Hospital, Scotland	Paracetamol assay (serum concentration) requests.
Sheen et al. **(12)**	1994–2000; Scotland	Number and annual incidence of paracetamol-related deaths.
Sheen et al. **(10)**	1998–2000; UK (sales data)	Sales (mass) of aspirin, paracetamol and ibuprofen.
Thomas and Jowett **(16)**	1998–1999; Withybush General Hospital, Wales	Hospital admissions for all paracetamol and non-paracetamol overdoses.
Turvill et al. **(6)**	1995–1999; Royal Free Hospital, London, UK	Number of overdoses and severe overdoses and those where acetylcysteine or methionine was indicated, benzodiazepine overdose (control).

Mortality

Eight of the 17 studies examined mortality as an outcome. Three of the studies **(8, 19, 22)** reported a reduction in mortality following the change in legislation, one **(20)** showed an initial reduction and then increased mortality, one study **(18)** showed an overall increase and three studies **(11, 12, 23)** showed no difference in mortality trends before and after the legislative changes.

Of note, mortality needs to be interpreted with caution, as recording of deaths is not straightforward. For example, if more than one substance were to be implicated, the death certificate would not indicate **(8)** which was the primary substance responsible for death.

Hepatoxicity

There were seven studies that considered liver transplants and/or admissions to specialist liver units associated with paracetamol poisoning as an outcome measure of the effectiveness of paracetamol pack size changes. Five of these **(5, 8, 13, 19, 21)** showed reductions in the rate of specialist liver unit admission as a result of paracetamol poisoning and three **(5, 8, 19)** also found reductions in number of liver transplants or transplant requests. In the remaining two studies, one **(17)** found no significant change

in liver function tests, while the other **(23)** found no change in the rates of paracetamol-induced liver injury, acute liver failure or acute liver failure meeting poor prognostic criteria.

Hospital admissions

Four **(11, 13, 21, 22)** out of seven studies that examined hospital admission data reported a reduction in hospital admissions due to paracetamol poisoning. One study **(18)** found an increase in adult admissions associated with paracetamol overdose, whilst another **(20)** showed an initial decline followed by an eventual increase and the remaining study **(16)** found a decline in paracetamol-related admissions but an increase in admissions for non-paracetamol overdose.

Sales

Sales of paracetamol may not be a sensitive indicator of impact of the legislation on paracetamol poisoning. Two **(8, 19)** studies reported no significant change in number of tablets sold before and after the legislation change, whilst one study **(10)** reported a progressive decline in the drug mass sold in the two years after legislation.

Severity of poisoning

Severity of poisoning was analysed by different measures in the studies, such as the number of tablets ingested and use of antidotes; studies examining the mortality data and transplantation have already been discussed earlier in this example. There were three studies that investigated plasma paracetamol concentration, out of which two studies **(8, 24)** showed no significant difference, while one **(7)** showed a decline (not clinically significant) following the change in legislation. Other studies chose to analyse other indicators of severity.

Discussion

There were nine publications that were included in both sets of literature reviews. Morgan et al. (2005) had included 3 additional studies, while Hawkins et al. (2007) included 8 other studies. The authors of both publications recognised the data limitations for the systematic review. Firstly, there was a variety of outcome measures used in the studies that made it difficult to accurately determine whether the legislation has been a success. There was no single outcome measure common to all studies. Therefore, any quantitative analysis of the data was not possible. In addition, many of the studies were localised or represent only a small number of hospitals.

The majority of the studies included a follow-up period of less than or up to two years after the legislative changes took place. This approach assumes that the new legislation would have led to rapid changes. Moreover, it should be noted that a short follow-up period would not be sufficient to observe any long-term effects of the legislation and also to account for any potential short-term changes that could be affected by a number of other epidemiological factors. Also, the majority of the studies do not differentiate between paracetamol preparations affected by legislation versus those that are unaffected (e.g. those on prescription only). The inclusion of all paracetamol preparations could reduce any apparent effectiveness of the legislation.

Since these reviews were undertaken, a recent article in the BMJ appears to suggest some long-term beneficial effect of legislation in an interrupted time series study in the UK **(25).**

Conclusion

Based on the data presented in the two separate reviews of studies examining the impact of the legislation changes on paracetamol pack size on paracetamol overdose, it is very difficult to draw any firm conclusions as to whether it has had the desired impact. The studies investigated different outcome measures and arrived at various interpretations and conclusions of the impact and success of the legislative changes. In general, there appears to be trends indicative of reduction in hospital admissions and liver transplantations due to paracetamol poisoning following the legislative changes, while the trend for other outcome measures such as mortality, severity of poisoning, sales data (as indicators of success of risk minimisation via pack

size reduction) tended to be more variable. Perhaps this case study serves to illustrate that for certain product risks, while the objectives of the risk minimisation plan may be clearly defined at initiation, there may be some challenges and a lack of consensus on the best outcome or surrogate measure to assess the effectiveness of the risk minimisation activity in meeting its target.

References

1. Hawton K, Ware C, Mistry H, et al. Why patients choose paracetamol for self-poisoning and their knowledge of its dangers. BMJ. 1995, 310(6973): 164.
2. Flanagan R, Rooney C. Recording acute poisoning deaths. Foren Sci Int. 2002, 128: 3–19.
3. Gunnell D, Murray V, Hawton K. Use of paracetamol (acetaminophen) for suicide and nonfatal poisoning: Worldwide patterns of use and misuse. Suicide Life Threat Behav. 2000, 30(4): 313–26.
4. Morgan O, Majeed A. Restricting paracetamol in the United Kingdom to reduce poisoning: a systematic review. J Public Health. 2005, 27: 12–18.
5. Prince M, Thomas S, James O, Hudson M. Reduction in incidence of severe paracetamol poisoning. Lancet. 2000, 355: 2047–2048.
6. Turvill J, Burroughs A, Moore K. Change in occurrence of paracetamol overdose in UK after introduction of blister packs. Lancet 2000, 355: 2048–2049.
7. Robinson D, Smith A, Johnston GD. Severity of overdose after restriction of paracetamol availability; retrospective study. Br Med J 2000, 321: 926–927.
8. Hawton K, Townsend E, Deeks J et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self-poisoning in the United Kingdom; before and after study. BMJ 2001, 322: 1203–1207.
9. Sheen C, Dillon J. The effect on toxicity and healthcare costs on reducing the size of available acetaminophen pack sizes in the Tayside region of Scotland. Gastroenterology. 2001, 120 (Suppl. 1): A-228.
10. Sheen C, Dillon J, Bateman N, Simpson K, Macdonald T. Paracetamol pack size restriction: The impact on paracetamol poisoning and the over-the-counter supply of paracetamol, aspirin and ibuprofen. Pharmacoepidemiol Drug Saf. 2002, 11: 329–331.
11. Bateman N, Bain M, Gorman D, Murphy D. Changes in paracetamol, antidepressant and opioid poisoning in Scotland during the 1990s. Q J Med. 2003, 96: 125–132.
12. Sheen C, Dillon J, Bateman N, Simpson K, Macdonald T. Paracetamol-related deaths in Scotland 1994–2000. Br J Clin Pharmacol. 2002, 54: 430–432.
13. Hughes B, Durran A, Langford N, Mutimer D. Paracetamol poisoning – impact of pack size restrictions. J Clin Pharm Therap. 2003, 28: 307–310.
14. Donohoe E, Tracey J. Restrictions on sale of paracetamol in Ireland had no impact on the number of tablets ingested in acute deliberate overdose. (The official Journal of the EAPCCT is the Journal of Toxicology - Clinical Toxicology.) J Toxicol Clin Toxicol. 2001, 38: 251.
15. Laing W, Gordon L, Lee D, Good A, Bateman D. Have the new pack size regulations impacted on UK paracetamol overdose. J Toxicol Clin Toxicol 2001, 39: 301.
16. Thomas M, Jowett N. Severity of overdose after the restriction of paracetamol availability. Restriction has not reduced admissions with self-poisoning. Br Med J. 2001, 322: 554.
17. Hawkins LC, Edwards JN, Dargan PI. Impact of restricting paracetamol pack sizes on paracetamol poisoning in the United Kingdom. A review of the literature. Drug Safety. 2007, 30(6): 465–479.
18. Bateman DN, Gorman DR, Bain M et al. Legislation restricting paracetamol sales and patterns of self-harm and death from paracetamol-containing preparations in Scotland. Br J Clin Pharmacol. 2006, 62(5): 573–581.
19. Hawton K, Simkin S, Deeks J, et al. UK legislation on analgesic packs: Before and after study of long-term effect on poisonings. BMJ. 2004, 329: 1076.
20. Inglis JHC. Restricting sales of paracetamol tablets: effect on deaths and emergency admissions for poisonings in Scotland 1991–2002. Scot Med J. 2004, 49(4): 142–143.
21. Langford NJ, Aruna RS, Mutimer D, et al. The impact of pack size legislation on paracetamol (acetaminophen) poisoning in the West Midlands, UK. J Toxicol Clin Toxic. 2003, 41(4): 419–420.
22. Morgan O, Griffiths C, Majeed A. Impact of paracetamol pack size restrictions on poisoning from paracetamol in England and Wales: An observational study. J Public Health. 2005, 27(1): 19–24.
23. Newsome PN, Bathgate AJ, Henderson NC et al. Referral patterns and social deprivation in paracetamol-induced liver injury in Scotland. Lancet. 2001, 358: 1612–1613.
24. Sheen CL, Dillon JF, Bateman DN et al. The effect on toxicity on reducing the size of available paracetamol pack sizes. Gut. 2001, 48 Suppl 1: A105.
25. Hawton K, Bergen H, Simkin S, Dodd S, Pocock P, Bernal W et al. Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: Interrupted time series analyses. BMJ. 2013, 346:f403. http://www.bmj.com/content/346/bmj.f403, accessed 1 February 2014.

F. Rosiglitazone (INN), Avandia®

Pharmacology	Thiazolidinedione (TZD) class of drug which works as an insulin sensitizer to receptors in fat and muscle cells, making blood glucose levels decrease.
Indication/Disease treated	Diabetes Type 2
Risks targeted for additional risk minimisation	Congestive heart failure and myocardial infarction.
Risk minimisation tools (beyond routine)	FDA sent warning letter to manufacturer. Patient enrolment programme requested by FDA for restricted access. Restricted distribution from November 2011, only specially certified pharmacies participating.
Effectiveness measurement methods	Not available.
Conclusion	Not available.

Type 2 diabetes drug rosiglitazone is presented as an example to describe how various tools of medicinal product risk minimisation have recently been applied for a new important pharmaceutical product. Furthermore, the example indicates the impact of the tools over the entire lifecycle of a biopharmaceutical product.

Pharmacological profile of rosiglitazone (Avandia®, GSK)

Rosiglitazone belongs to the thiazolidinedione (TZD) class of drugs and works as an insulin sensitizer. It binds to the nuclear peroxisome proliferator activated receptor gamma (PPAR) receptors. These receptors are located especially in adipose (fat) cells but also in muscle cells. As a result the cells are more responsive to insulin and blood glucose levels decrease.

Regulatory approval (1999–2000)

The U.S. FDA approved rosiglitazone in May 1999. The FDA medical review stated that oedema was reported 2–3 times as frequently in diabetes patients on rosiglitazone as in other treatment groups. The reviewer expressed concerns about increase in patients' body weight, undesirable effects on serum lipids and deleterious long-term effects on the heart. The Sponsor was to provide adequate information in the label about changes in weight and lipids. Moreover, a postmarketing study to address these issues was to be a condition of approval **(1)**.

In Europe CHMP issued in October 1999 a negative opinion (based on a majority vote) for granting a Marketing Authorisation due to insufficient safety documentation. In the light of submitted additional data CHMP recommended granting a Marketing Authorisation in July 2000 but required some provisions **(2)**.

Rosiglitazone use was indicated primarily in combination with other diabetes medications.

CHMP was satisfied with the short-term safety of rosiglitazone (some five trials involving 2,900 patients with mostly 26 weeks follow-up) but contraindicated use in patients with congestive heart failure and added a warning to the product information regarding the possible development of fluid retention and congestive heart failure.

According to CHMP the prescribing physician was to have experience in treatment of type 2 diabetes.

Moreover, the MAH committed to perform a double blind study in chronic heart failure NYHA classes HI and a long-term cardiovascular morbidity/mortality study called the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD) **(2)**.

Post-approval experiences and regulatory actions

2001: Health Canada reported on 166 adverse drug reaction cases associated with use of rosiglitazone including 20 patients with cardiovascular problems (congestive heart failure, heart failure and oedema) **(3)**.

2002: The FDA changed the product information (in April) with appropriate statements in the Warnings and Precautions section based on observations in post-approval studies. These related to the possibility of fluid retention which could lead to or exacerbate congestive heart failure. Patients experiencing an unusual rapid increase in weight or oedema or shortness of breath should report symptoms to their physician. Rosiglitazone should not be used in patients with NYHA class III or IV cardiac failure. Discontinuation of rosiglitazone is recommended if cardiac status deteriorated **(4)**. Health Canada changed the product information as FDA above **(5)**.

2003: In Europe CHMP gave positive opinion for extension of indication for rosiglitazone to allow its use as a second-line monotherapy.

2007: The FDA after review of post-authorisation adverse event reports added (in August) a boxed warning emphasizing that glitazones including rosiglitazone may cause or exacerbate congestive heart failure in some patients **(6)**.

The *New England Journal of Medicine published* in June 2007 a meta-analysis of 42 clinical trials with rosiglitazone. Rosiglitazone was associated with a significant increase in risk of myocardial infarction and risk of death from cardiovascular causes that had borderline significance **(7)**.

The FDA (in November) added new information to the existing boxed warning in the product labelling about potential increased risk for heart attacks **(8)**.

The EMA/CHMP undertook a new assessment of rosiglitazone and confirmed (in October) positive benefit-risk balance for rosiglitazone. However, the prescribing information was updated to include a warning that, in patients with ischemic heart disease, rosiglitazone was only to be used after careful evaluation of each patient´s individual risk **(9)**.

2008: Based on a re-assessment of rosiglitazone by EMA/ CHMP a new warning was added to the product information. Use of rosiglitazone was not recommended in patients with ischemic heart disease and/or peripheral arterial disease. Moreover, a new contraindication was introduced stating that rosiglitazone was not to be used in patients with an acute coronary syndrome, such as angina or some types of myocardial infarction **(10)**.

The FDA published in February 2008 a Medication Guide on Avandia for patients describing symptoms of heart failure and other heart problems **(11)**.

The American Diabetes Association (ADA) and the European Association for Study of Diabetes (EASD) issued a consensus statement which recommended greater caution in using glitazones including rosiglitazone, especially in patients at risk of or with congestive heart failure **(12)**. The editorial in the *Lancet* considered these recommendations as guidelines that explicitly advised against the use of rosiglitazone for type-2 diabetes **(13)**.

The FDA inspection found omissions of some data from periodic safety reports to FDA and a warning letter was sent to the company in March 2008 **(14)**. The FDA published in December a revised guidance requesting sponsors to conduct a long-term cardiovascular risk trial on new anti-diabetic therapies.

2009–2010: Results of the RECORD study (follow up of some 4,450 patients up to five to seven years) were published. Rosiglitazone was confirmed to increase the risk of heart failure and of some fractures in people with type 2 diabetes, mainly in women, compared to the active control which received standard glucose-lowering therapy Although the data was inconclusive about any possible effect on myocardial infarction, rosiglitazone did not increase the risk of overall cardiovascular morbidity or mortality compared with standard glucose-lowering drugs **(15)**.

A detailed analysis of heart failure events in the RECORD trial confirmed the increased risk of these events in people treated with rosiglitazone. The editorial comment on the article stated that the rise and fall of

rosiglitazone raised critical scientific and ethical questions about drug development and marketing, with profound consequences, including the recent decision by US regulatory authorities to require cardiovascular outcome studies for all new diabetes drugs **(16, 17)**.

Based on publication of recent studies, European Commission requested EMA to review the safety of rosiglitazone. The EMA completed (in September 2010) the safety review and concluded that the marketing authorisations for all rosiglitazone-containing medicines should be suspended.

The FDA decided in September 2010 that rosiglitazone should remain on the US market but its use was to be restricted and a REMS put in place.

2011: The FDA requested patients to enrol in a special programme to receive the drug. From November 2011 rosiglitazone has not been obtainable in the US from retail pharmacies. Patients enrolled in the Avandia-Rosiglitazone Medicines Access Programme can receive their medicine by mail order through specially certified pharmacies participating in the programme.

References

1. www.accessdata.fda.gov/drugsatfda_docs/NDA/99/21071 Avandia medr.pdf.
2. www.ema.europa.eu/ Search document library: 831385/2010.
3. Canadian Adverse Reaction Newsletter. 2001, 11: 3.
4. www.fda.gov/medwatch. 24 April 2002.
5. Canadian Adverse Reaction Newsletter. 2002,12: 2–3.
6. www.accessdata.fda.gov/drugsatfda docs/label/2007/021071s031lbl.pdf.
7. New England Journal of Medicines. 2007, June 356: 2457.
8. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm109026.htm.
9. www.ema.europa.eu/ Search document library: 484277/2007.
10. www.ema.europa.eu/ Search document library: 42232/2008.
11. Avandia Medication Guide http://www.fda.gov/downloads/Drugs/DrugSafety/ucm085922.pdf.
12. Diabetes Care. 2008, January Vol. 31, No. 1: 173–175.
13. Rosiglitazone no longer recommended. Lancet. 2008, 372: 1520.
14. http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2008/ucm1048360.htm.
15. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M, McMurray JJ .Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. Lancet. 2009, June 373: 2125–2135.
16. Komajda M et al. Heart failure events with rosiglitazone in type 2 diabetes: Data from the RECORD clinical trial. European Heart Journal. 2010, 31(7): 824–831.
17. Nissen SE. The rise and fall of rosiglitazone. European Heart Journal. 2010, 31(7): 773–776.

G. Natalizumab (INN), Tysabri®

Pharmacology	Monoclonal antibody (mAb)
Indication/Disease treated	Multiple sclerosis (MS), relapsing remitting type (and Crohn's Disease in the U.S.).
Risks targeted for additional risk minimisation	Progressive multifocal leukoencephalopathy (PML), an infection of the central nervous system due to the John Cunningham virus (JCV) in the immunocompromised, potentially fatal.
Risk minimisation tools (beyond routine)	REMS in place in the US. Mandatory restricted access programme through enrolment requiring informed consent in Tysabri Outreach Unified Commitment to Health (TOUCH) in the U.S. Elsewhere, education and information tools used along with postmarketing studies and registries as a result of regional differences in legal and health systems. In the EU: Patient Alert Card, recommended use of treatment initiation and continuation forms, some post-approval studies and registries by company or researchers. Risk stratification including a biomarker, JCV serology.
Effectiveness measurement methods	Surveys (HCP, patient organisations).
Conclusion	An effective risk management approach can support benefit-risk so that a product with a serious risk can be maintained or re-introduced to the market with stringent risk minimisation measures. Wide collaboration of stakeholders has occurred and is contributing to the evolution of scientific and regulatory knowledge in a challenging area of public health.

Executive summary

Natalizumab was developed by Biogen Idec and is a monoclonal antibody indicated and used in Multiple Sclerosis (MS) in various countries and additionally indicated for Crohn's Disease (CD) in the US. Following initial accelerated approval in the US based on high levels of efficacy, a rare but very serious risk emerged regarding the occurrence of progressive multifocal leukoencephalopathy (PML), resulting in suspension of marketing. As scientific knowledge accrued on this issue, the product returned to market with wide-ranging risk management strategies in place including a mandatory restricted access programme involving controlled distribution (TOUCH) in the US. Regulatory approval and marketing in other regions outside the US occurred sequentially, with risk management strategies that are different from the US in their emphasis on education and information tools rather than controlled distribution; these are supplemented by postmarketing studies and registries. This divergence has occurred due to regional differences in legal and health systems.

As clinical experience with natalizumab on the market increased, the scientific knowledge base also increased in parallel and it has become clear that risk factors of prior immunosuppression, long duration of treatment and a biomarker (anti-JCV antibody) can be applied in PML risk stratification for patients being treated with natalizumab. In turn this could allow informed benefit-risk decisions being taken by physicians and patients on an individual basis. The risk management approach regarding natalizumab also lead to new ways of interaction between a wide variety of stakeholders as shown by a transatlantic workshop on PML held at the European Medicines Agency (EMA) in July 2011. In this workshop the latest state of

scientific and product knowledge was shared in a transparent way amongst the participants in order to support research and regulatory initiatives to manage drug-related PML risks going forward.

Introduction

Tysabri contains natalizumab which is a humanized monoclonal IgG4 antibody to α4-integrin that is indicated in the treatment of relapsing remitting multiple sclerosis (RRMS). Tysabri is currently marketed in approximately 70 countries for relapsing remitting MS and is also indicated for treatment of CD in the US.

PML

Progressive multifocal leukoencephalopathy (PML) is an infection of the central nervous system due to the JC virus that occurs in situations of immune compromise. Several decades ago, PML was an AIDS-defining diagnosis in the context of HIV-1 infection. More recently and with the advent of highly active anti-retroviral treatments for HIV, PML has become a more rare condition but is now reported in association with immunomodulating drugs in general and some monoclonal antibodies, including natalizumab. Our understanding of the pathophysiology of PML has until recently been quite limited but has gathered speed since the increased reporting of PML with the use of immunomodulating drugs. PML is potentially fatal and therapeutic options not yet identified or developed.

Regulatory background - United States (1)

November 2004: Accelerated approval.

February 2005: Suspended marketing due to three cases of PML (two with fatal outcome, two in MS patients and one in a CD patient) that occurred after around two years of treatment in the confirmatory studies in RRMS. This led to a clinical hold on the studies by the FDA. The reporting of PML cases in these studies in subjects who received a mean of 17.9 doses of Tysabri, represented an incidence of approximately one case per 1,000 patients (95% confidence interval: 0.2 to 2.8).

February 2006: The clinical hold was lifted by FDA.

March 2006: FDA consulted with its Peripheral and Central Nervous System Drugs Advisory Committee.

June 2006: Based on recommendations from the Advisory Committee, FDA approved the resumed marketing of Tysabri (natalizumab) subject to a special restricted distribution programme (TOUCH). A Risk Evaluation and Mitigation Strategy (REMS) is currently in place for Tysabri in the US.

TOUCH (Tysabri Outreach: Unified Commitment to Health) programme

Tysabri (natalizumab) is available only under a special restricted distribution programme called the TOUCH Prescribing Programme. Under this programme, only prescribers, infusion centres, and pharmacies associated with infusion centres registered with the programme are able to prescribe, distribute, or infuse the product. For prescribers and patients, the TOUCH Prescribing Programme has two components: MS TOUCH (for patients with multiple sclerosis) and CD TOUCH (for patients with Crohn's Disease). Natalizumab must be administered only to patients who are enrolled in and meet all the conditions of the MS or CD TOUCH Prescribing Programmes.

To enrol in the TOUCH Prescribing Programme, prescribers and patients are required to understand the risks of treatment with natalizumab, including PML and other opportunistic infections. Prescribers are required to understand the information in the Prescribing Information and to be able to:

- Educate patients on the benefits and risks of treatment with natalizumab, ensure that the patient receives the Medication Guide, instruct them to read it, and encourage them to ask questions when considering natalizumab treatment. Patients may be educated by the enrolled prescriber or a healthcare provider under that prescriber's direction.
- Review the TOUCH Prescriber/Patient Enrolment form for natalizumab with the patient and answer all questions.

- As part of the initial prescription process for natalizumab, obtain the patient's signature and initials on the TOUCH programme enrolment form, sign it, place the original signed form in the patient's medical record, send a copy to Biogen Idec, and give a copy to the patient.
- Report serious opportunistic and atypical infections with natalizumab to Biogen Idec and to the FDA's MedWatch Programme.
- Evaluate the patient three months after the first infusion, six months after the first infusion, and every six months thereafter.
- Determine every six months whether patients should continue on treatment and if so re-authorise treatment every six months.
- Submit to Biogen Idec the Tysabri Patient Status Report and Reauthorisation Questionnaire six months after initiating treatment and every six months thereafter.

There are other special considerations in the TOUCH programme including provision of insurance cover and human resources (including a case manager for the patients) by the company. In addition to collecting data on PML, the TOUCH programme also targets other major immune effects that could emerge during natalizumab treatment. A major advantage is the fact that physicians are required to use the product according to the label and have to sign the appropriate forms to this effect. The patients exposed are all under monitoring so the denominator data are complete which allows accurate risk calculations to be made. Quality of data collection is also reinforced by the fact that FDA has power to inspect the programme and has done so regularly.

Regulatory background - European Union (EU)

Tysabri (natalizumab) was authorised in 2006 via the EU centralised procedure by the EMA with a risk management plan (RMP) agreed at marketing authorisation. This RMP included a risk minimisation plan in the form of educational materials for the physician and patient information including an Alert Card.

All prescribers in the EU receive a risk minimisation pack from the manufacturer that includes the statutory Summary of Product Characteristics (SmPC, the EU 'label'), Package Leaflet for patients, as well as additional risk minimisation materials: Physician Information and Management Guidelines and Patient Alert Card, which the prescribing physician hands to the patient at the initial consultation.

In contrast to the US situation, it is more complex from a legal perspective to apply a controlled distribution programme throughout the whole of the EU. There are however a number of post-approval studies and registries of patients receiving natalizumab in the EU; some are sponsored by the company whilst others are conducted by independent researchers. The main objectives of such registries are collection of safety data including detection of any cases of PML.

The continuing occurrence of PML cases in the postmarketing setting prompted the EMA and CHMP to initiate a benefit-risk review of natalizumab in an Article 20 referral procedure in October 2009. As a result of this review, the natalizumab RMP and EU label (SmPC) were updated to include baseline and annual MRIs, additional signs of PML (e.g. change in a patient's mood), as well as a review of benefit-risk by the physician after two years of treatment, due to an increase in the risk of PML with increased treatment duration. At this time the patient is informed of PML risks before continuing therapy; the patient is also informed of the PML risk at two years before starting therapy. The use of informed consent is not legally enforceable in Europe except in the context of a clinical trial. Consequently, the provision of template treatment initiation and continuation forms to facilitate a discussion between the patient and their physician on benefits and risks was considered the closest alternative to obtaining informed consent in terms of treatment continuation.

Transatlantic PML workshop (2)

This is a novel approach in the case of a safety issue and was held at the EMA in July 2011. Participants included regulatory authorities from the EU, US and other regions, pharmaceutical companies, clinicians, researchers in the area of neurology/PML and patient organisations. There was a free exchange of information

including details of PML cases being reported with several medicinal products. One of the key discussion areas was the use of a new risk stratification algorithm for natalizumab based on duration of treatment, use of previous immunosuppressive therapies and JC virus serology testing. This has subsequently been incorporated into the natalizumab label/SmPC and has been published in the literature **(3)**.

Another novel aspect of the PML Workshop was the formation of the PML Consortium which is in the process of collecting scientific data on PML cases exposed to different monoclonal antibodies, including natalizumab. This consortium is a collaboration of several pharmaceutical companies that share their data in order to advance knowledge on PML occurring as an adverse drug reaction to a variety of pharmaceutical products.

Clinical monitoring and management

This is primarily based on clinical monitoring by the physician supplemented by review of emerging symptoms by the patient and imaging using MRI. Where suspicion of PML arises, cerebrospinal fluid (CSF) is examined for JCV DNA for a diagnosis (or exclusion) of PML.

In case of suspected PML, natalizumab is discontinued and the patient undergoes plasma exchange to actively remove the drug from the system. Some patients develop Immune Reconstitution Syndrome (IRIS) which can be treated with systemic corticosteroids. A more recently identified risk factor for development of PML with natalizumab has been the development of a specific biomarker in the form of anti-JCV antibody testing. A positive serology status appears to confer increased risk of developing PML and this is increased further by two other factors which are: long treatment duration (>2 years) and prior exposure to immunosuppressive therapies. The totality of this risk stratification algorithm is reproduced from the U.S. Prescribing Information USPI **(4)**, in Table 1 below and is also included in the Physician Information and Management Guidelines supplied to all EU prescribers of Tysabri.

Annex III - Tysabri Table 1: Estimated incidence of progressive multifocal leukoencephalopathy

	Anti-JCV Antibody Positive**	
Tysabri Exposure*	No Prior Immunosuppressant Use	Prior Immunosuppressant Use
1 – 24 months	<1/1,000	2/1,000
25 – 48 months	5/1,000	11/1,000

Notes: Based on postmarketing PML data as of 5 September 2012 and Tysabri use data as of 31 August 2012.
**Data beyond four years of treatment are limited.*
***Risk in anti-JCV antibody patients was estimated based on the assumptions that 18% of Tysabri-treated MS patients have a history of prior immunosuppressant treatment and that 55% of Tysabri-treated patients are anti-JCV antibody positive.*

Regional considerations

The key aspects of Tysabri (natalizumab) risk minimisation as applied regionally are summarised in Table 2 focussing on US and Europe.

Annex III - Tysabri Table 2: Risk minimisation comparison of US and EU

	US	EU
Special patient information considerations	Black box warning	None
Informed Consent	Yes (TOUCH)	No: SmPC recommends that patients be informed of the risk of PML prior to starting treatment and again after 2 years.
Risk stratification	Yes: ► Anti-JCV antibody status ► Treatment for >2 years ► Prior immunosuppressant use	Yes ► Anti-JCV antibody status ► Treatment for >2 years ► Prior immunosuppressant use
Clinical monitoring algorithm	Baseline gadolinium enhanced MRI, repeated on clinical suspicion; stop treatment and examine CSF for JCV viral DNA.	Baseline MRI within 3 months; Annual MRI and ad hoc if symptoms emerge (cognitive, psychiatric); stop treatment and examine CSF for JCV viral DNA.
Serology (anti-JCV antibody) testing	Consideration should be given to baseline and 6-monthly testing (if negative at baseline). Once positive always positive.	Testing of anti-JCV antibody status prior to treatment, and re-testing of anti-JCV antibody negative patients every 6 months is recommended. SmPC refers to Physician Information and Management Guidance for quantification of risk.
Educational – HCPs and patients	Via TOUCH REMS Medication Guide	Physician Information and Management Guidelines, Package Leaflet, Patient Alert Card, Treatment Forms.
Restricted distribution	Yes	No
Registries/PASS	TOUCH (complete coverage)	Yes (partial coverage), some independent from sponsor

Conclusions - Key points for consideration

The Tysabri (natalizumab) risk management experience raises a number of important points:

- An effective risk management approach can support benefit-risk so that a product with a serious risk can be maintained or re-introduced to the market with stringent risk minimisation measures.
- Different approaches in intensity of risk minimisation and mitigation strategies have been applied depending on local regulation. However, there is no clear evidence in the public domain that such differences in approach have impacted public health differently on a regional level.
- Scientific knowledge evolved so that a risk stratification mechanism has been identified and is now in the label/SmPC of Tysabri (natalizumab). This risk stratification involves a combination of risk factors and a biomarker (JCV serology) that has the potential to allow physicians and patients to estimate and discuss risk of PML at individual level and make informed treatment decisions.

- Wide collaboration of stakeholders has occurred and is contributing to the evolution of scientific and regulatory knowledge in a challenging area of public health.

References

1. Information on Natalizumab (marketed as Tysabri) http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm107198.htm, accessed 29 January 2014.
2. Transatlantic Workshop on Drug-related Progressive Multifocal Leukoencephalopathy (PML). Workshop Proceedings. EMA/674403/2011. 2011, September Rev. 1. http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/09/WC500111562.pdf, accessed 29 January 2014.
3. Bloomgren G, Richman S. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. New England Journal of Med, 2012, 366(20): 1870–1880.
4. U.S. Prescribing Information (USPI). Tysabri, Highlights of prescribing information, Ref. ID: 3422104, 2013, Table I: 5. http://www.tysabri.com/pdfs/l61061–13_PI.pdf, accessed 8 April 2014.

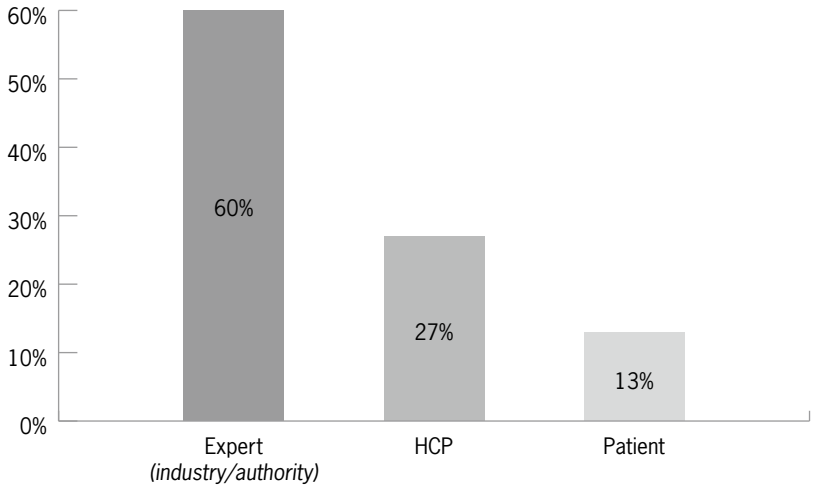
ANNEX IV

BROADER STAKEHOLDER INPUT – SURVEY

This Broader Stakeholder Input Survey was conducted at the Annual EuroMeeting of the Drug Information Association (DIA) in March 2012 in Copenhagen, Denmark, during a session entitled, 'Risk(y) Business! Stakeholder interactive input into risk minimisation planning.'

A real-time study was conducted with the audience that was present, in order to evaluate the utilisation and the content of a harmonised risk management toolkit to minimise the risks associated with medicine usage. In all, 188 participating stakeholders (S/H) were asked to provide input about risk minimisation tool and strategy design and implementation to validate feasibility and effectiveness. At the outset, the audience were requested to answer whether they replied to the questions in their capacity as expert (including pharmaceutical industry or regulatory authority), healthcare provider (HCP), or patient. The outcome of this request is presented as the audience representation in Fig. 1. When providing feedback, respondents were instructed to make a single selection from multiple answers and to adhere to the stakeholder perspective that was chosen throughout the entire survey. A response rate for each inquiry in the questionnaire is calculated in Table 1.

Annex IV - Stakeholder survey Fig. 1: Representation.



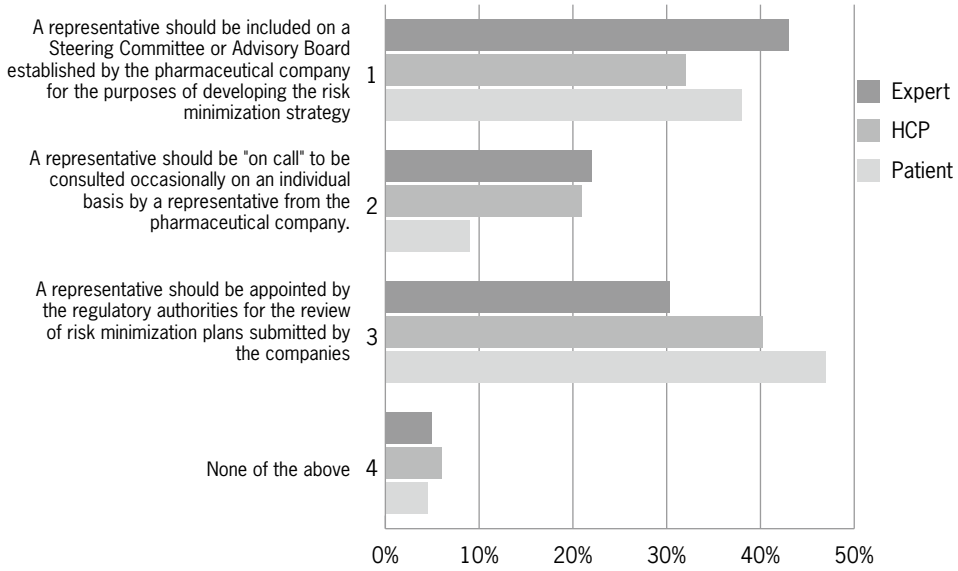
Annex IV - Stakeholder survey Table 1: Respondent participation categorised.

Question	Valid Answers	Blank or Invalid Answers	Respondent Adherence
1. What category do you consider yourself to represent?	184	4	98%
2. How should stakeholders' (i.e. doctor, pharmacist, patient) representatives be involved in the design of risk minimisation activities?	174	14	93%
3. How should stakeholders' (i.e. doctor, pharmacist, patient) representatives be selected, trained and compensated for providing input on the risk minimisation program?	176	12	94%
3a. When (or at what time point) should a representative from the stakeholder group physicians have input into the design of the risk minimisation strategy?	166	22	88%
3b. When (or at what time point) should a representative from the stakeholder group pharmacists have input into the design of the risk minimisation strategy?	182	6	97%
3c. When (or at what time point) should a representative from the stakeholder group patients have input into the design of the risk minimisation strategy?	188	0	100%
4. How should patient stakeholder (i.e. doctor, pharmacist, patient) representatives be selected geographically?	184	4	98%

Stakeholder survey outcome

Q: Stakeholders' (i.e. doctor, pharmacist, patient) representative involvement in the design of risk minimisation activities.

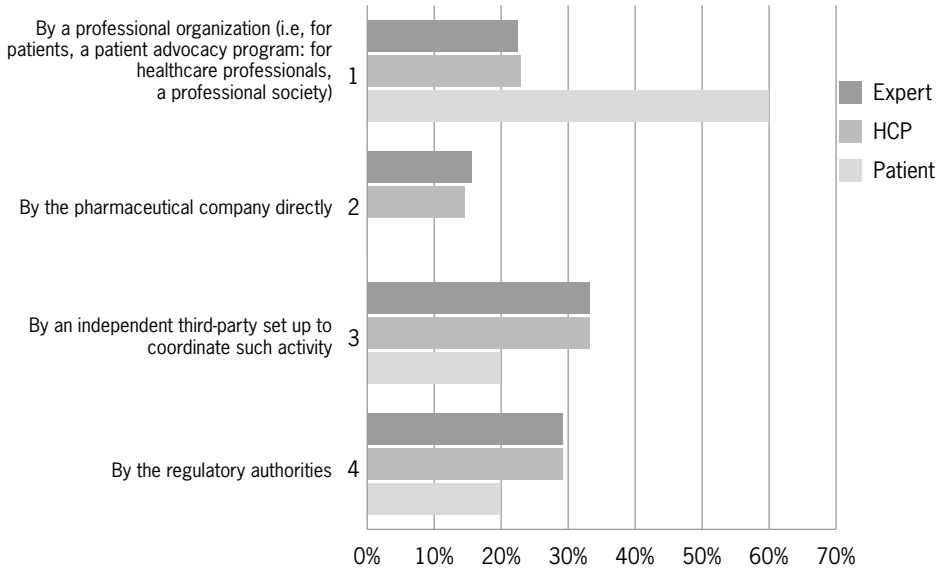
Annex IV - Stakeholder survey Fig. 2: S/H involvement in design



Outcome: All three stakeholder categories (i.e. experts, HCPs and patients) had a preference for two options with respect to RMP development – participation in a pharmaceutical company or marketing authority holder's (MAH's) Steering Committee or Advisory Board or appointment by the regulatory authorities (patients favoured the latter option slightly more). 'On call' availability for intermittent consultation received fewer votes (approximately 20% for experts & HCPs and 10% for patients). About 5% of all stakeholders considered a different opportunity for engagement as an alternative.

Q: Stakeholder (i.e. doctor, pharmacist, patient) selection, training and compensation for providing input on the risk minimisation programme.

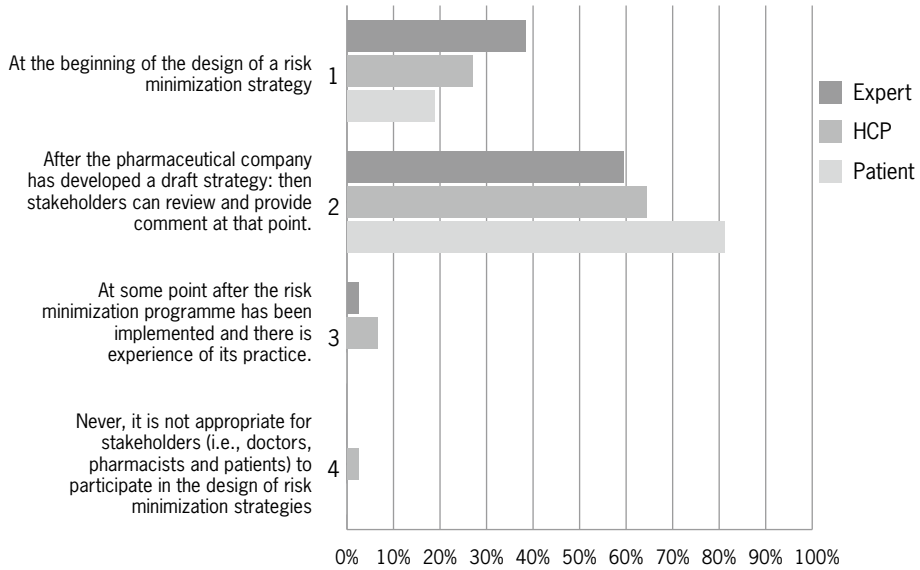
Annex IV - Stakeholder survey Fig. 3: S/H selection, training and compensation



Outcome: Nearly 60% of the present patients preferred a professional organisation to be in charge of these activities, while none wished to see the direct involvement of a pharmaceutical company or marketing authority holder (MAH). The rest of the stakeholders, experts and HCPs, were almost equally split for engaging professional organisations, MAHs, independent third-party organisations or regulatory authorities. The involvement of a third-party organisation was rated marginally higher than the rest of the options.

Q: Timing of physician input into the design of the risk minimisation strategy.

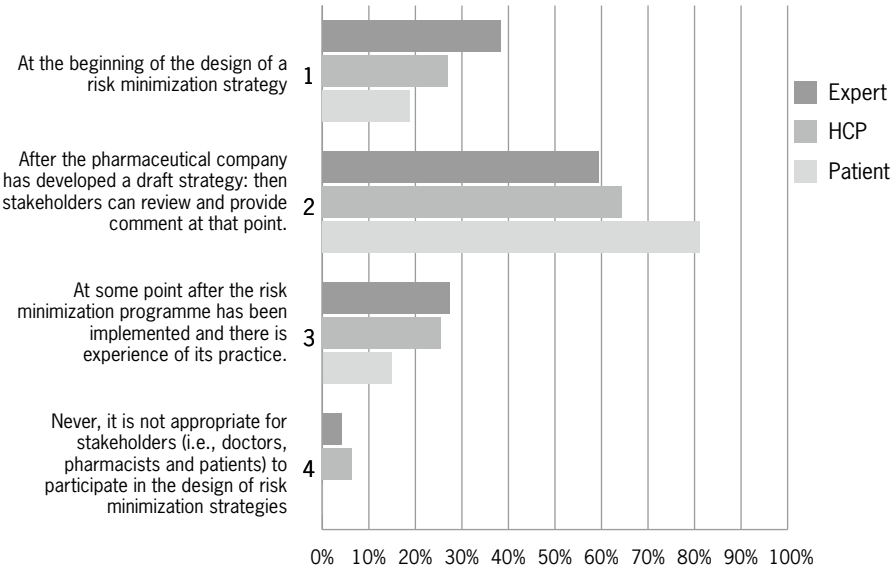
Annex IV - Stakeholder survey Fig. 4: Timing of physician input.



Outcome: The majority of experts (approximately 60%), HCPs (~ 65%) and patients (~ 81%) thought that physician input should have occurred after the MAH had developed a draft strategy. A smaller portion of the experts, HCPs and patients (approximately 18–28%) called for physician input at the beginning of the design of a risk minimisation strategy. Very few votes were received for physician involvement after the implementation of the risk minimisation programme and almost no votes were registered to eliminate physician participation in the design of risk minimisation strategies.

Q: Timing of pharmacist input into the design of the risk minimisation strategy.

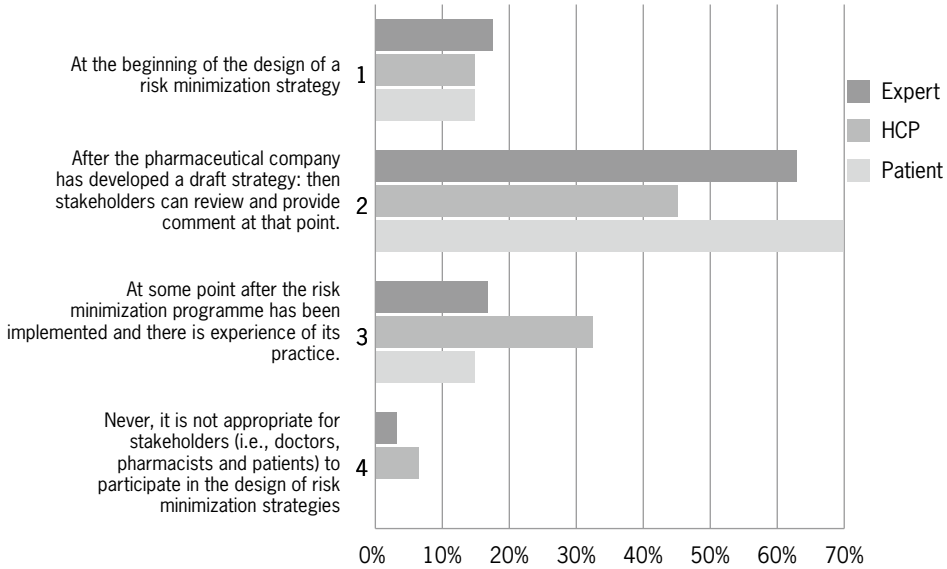
Annex IV - Stakeholder survey Fig. 5: Timing of pharmacist input.



Outcome: Similarly to the results from Fig. 3a, the majority of the audience (approximately 48% of the experts, ~53% of the HCPs and ~74% of the patients) considered pharmacist involvement after MAH's draft strategy. Conversely, almost identical split of expert, HCP and patient opinion was observed for pharmacist engagement at the beginning and at some point after the implementation of the risk minimisation strategy. The least popular option was to ignore pharmacist involvement in the design of risk minimisation strategies.

Q: Timing of patient input into the design of the risk minimisation strategy

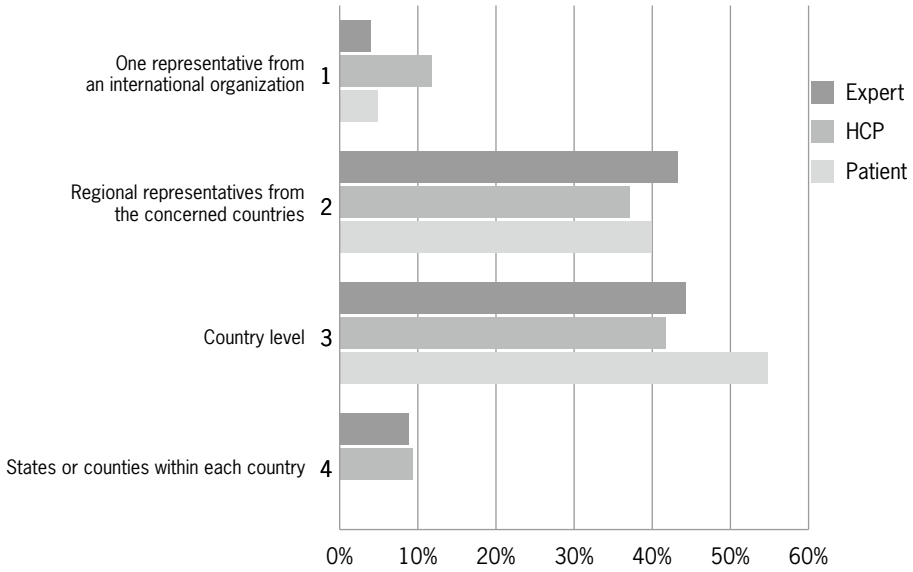
Annex IV - Stakeholder survey Fig. 6: Timing of patient input.



Outcome: Again, the overwhelming majority of experts (approximately 63%), HCPs (~45%) and patients (~70%) preferred patients to be involved after the creation of the MAH's draft strategy. Somewhat equal number of votes was received for patient engagement at the beginning of the design of the risk minimisation strategy and at some point after the implementation of the RMP. A few experts (~3%) and HCPs (~6%) were against patient engagement in risk minimisation strategy design.

Q: Geographic selection of stakeholder representatives (i.e. doctors, pharmacists, patients).

Annex IV - Stakeholder survey Fig. 7: Geographic selection of S/Hs



Outcome: Geographic selection of stakeholder representatives (i.e. doctors, pharmacists, patients). Among the present audience, the majority of the experts, HCPs and patients (collectively greater than 90%) selected two options for a feasible geographic stakeholder representation – at regional and at national level. The rest of the respondents suggested one representative from an international organisation or representatives from states or counties within each country as an appropriate geographic assignment of stakeholder representatives.

ANNEX V

CHECKLIST TO EVALUATE THE EFFECTIVENESS OF A RISK MINIMISATION PROGRAMME

As described in Chapter V of this report, the proposed checklist summarises the most important points to consider in the study protocol that will serve to evaluate the effectiveness of a risk minimisation programme.

Points to consider at the level of the study protocol

- **Have the applicable regulatory requirements for this study been considered?**

Points to consider at the level of a risk minimisation programme

- **Does the study protocol sufficiently specify the risk to be minimised in line with the relevant regulatory document (e.g. RMP, REMS)?**
  E.g. 'hepatotoxicity' is a rather vague medical description while 'hepatic failure' is a clear diagnosis. The two terms have a different impact in terms of the sample size that will be required to evaluate the effectiveness of a possible risk minimisation programme.
- **Is the goal of the risk minimisation programme clearly stated?**
  Can the goal be achieved through a change in behaviour?
- **Are study endpoints clearly specified?**
  Has the sponsor specified clearly the endpoints of the study? And are these endpoints in line with the aims of the risk minimisation programme? What is the rationale for the chosen safety-related outcome(s) of interest (or endpoint(s))? Can a morbidity or mortality endpoint reflect a change in behaviour and demonstrate effectiveness? Can the choice of a composite or a surrogate safety endpoint (e.g. level of co-prescription, biomarker) as a secondary option be justified?
- **Is the proposed threshold for success (i.e. measure of performance) clinically relevant and achievable given the overall benefit-risk of the medicine under consideration?**
- **Will a comparison be performed to demonstrate effectiveness?**
- **Has the sponsor obtained input from regulatory authorities on the study design and/or statistical analysis plan?**
  Has input been incorporated as much as possible taking into account regulatory authority suggestions which may vary regionally (early interactions with such authorities is recommended)? In addition to feedback on study design and SAP, the data to be reported from any interim analyses (see below) and timing of such reporting to regulators should be clarified.
- **Are time points for (interim) analyses considered?**
  How will interim analyses demonstrate with reasonable confidence the desired effectiveness of the risk minimisation programme given the endpoint(s) selected and the sample size at each time point?

- **Will success be evaluated at a global, regional (provide regions) or national (provide countries) level?**
  Are countries involved comparable in terms of healthcare system? Is there a justification for clustering countries in the analyses? Will a hierarchical (e.g. national to global) approach be considered for the (interim) analyses?
- **Does the risk minimisation programme involve one or several risk minimisation interventions?**
  Has the potential for success of each proposed risk minimisation intervention been considered in the context of its burden on patients and the healthcare system? Are all interventions appropriately described? Are the interventions user-friendly (e.g. easier from a user perspective)?

Points to consider at the level of each intervention

- **Are the stakeholders involved in each intervention and the recipients ('risk minimisation targets') of each intervention well defined?**
  Please specify the key stakeholders targeted by the intervention: these may be patients and/or HCPs (e.g. pharmacists, physicians [general practitioners or specialists], nurses) and/or others.
- **Has the content (e.g. educational material) and/or the tool planned to be used in an intervention (e.g. web-based tool on a personal computer, a touchpad or a smartphone) been tested/piloted by appropriate stakeholders/users?**
  Will the intervention provide the correct education or encourage the appropriate behaviour? To what extent did the information, or knowledge delivered in the intervention, match the specified content and purpose of the intervention? Were language translations accurate and complete? Were proposals made by stakeholders to improve content or tool considered? Are the proposed tools sufficient to encourage utilisation (e.g. are they user-friendly)?
- **Are process indicators evaluating the fidelity of implementation being considered?**
  How will the components and content of the risk minimisation activities be optimised?

  Are the following parameters appropriately explored?

  - **Exposure:** Has the intervention reached the right audience and in the right amount? Have the stakeholders been sent and have they received the intervention? Were any subgroups under- or over-represented? Did the stakeholders read and remember the content of the intervention? Is their role in the intervention well understood?
  - **Adoption (utilisation):** To what extent did the stakeholders who agreed to deliver an intervention deliver it? Which parts of the tool are routinely used in the 'real world?'
  - **Frequency:** Was the intervention consistently delivered in the specified frequency to target recipients as originally intended?
  - **Maintenance/duration:** Was the intervention delivered consistently for the specified time period? Is the contribution of each stakeholder in an intervention sustained over time? Are paper or electronic reminders needed?
- **Is the study protocol version-controlled?**

ANNEX VI

RISK MINIMISATION FOR VACCINES

The CIOMS/WHO Working Group on Vaccine Pharmacovigilance published a report on *Definition and Application of Terms for Vaccine Pharmacovigilance* (2012), which included general definitions of vaccine pharmacovigilance and adverse events following immunisation (AEFIs). Points to consider regarding pharmacovigilance for vaccines are addressed in this report. This Annex VI addresses points to consider which are specific to risk minimisation for vaccines, based on the terminology and concepts from the report of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance and focusing on differences in risk minimisation for vaccines compared to other medicinal products.

The benefit-risk balance for vaccines fundamentally differs from the benefit-risk for other medicinal products because vaccines are usually administered to healthy people to prevent rather than to treat an existing condition; are often administered universally to populations under public programmes; and may even be required by governmental organisations. In addition, vaccines are associated with specific risks, different from those of other medicinal products, in terms of identified and potential risks as well as missing information which needs to be collected from large populations or special population groups. Vaccines more than other medicinal products are subject to concerns arising in the general public/communities, concerns of healthcare professionals working in the community, or concerns emerging for individuals belonging to a vaccine target population, individual vaccinees, or their families/carers. Therefore, comprehensive risk assessments addressing all safety concerns including those emerging from others than those entrusted with the assessment are essential. Risk communication forms the core of risk minimisation for vaccines, to address evidence and uncertainty, as well as emotions.

Vaccines are complex biological products, which may include multiple antigens, live organisms, adjuvants, and other excipients (e.g. preservatives, stabilising and anti-aggregatory agents). Each component may have unique safety implications. Variability and (even small) changes in the manufacturing process may have impact on quality, protective effect, and safety. Batch information is of crucial importance.

The Annex is structured by differences in risk minimisation for vaccines compared to other medicinal products based on types of risk:

- risks related to vaccine composition (Section A);
- risks related to the impact of the vaccine on natural disease (Section B); and
- risks related to vaccine use (Section C).

Examples of each type of risk and possible risk management/risk minimisation tools that can be used to address that risk are provided. The examples are not exhaustive; the tables include examples that were considered sufficiently vaccine-specific and most instructive for the particular risk under discussion. The Annex concludes with a general discussion of communication relevant to risk minimisation for vaccines (Section D).

A. Risks related to vaccine composition

Vaccines are derived from biological sources and can contain live active substances, either intentionally to produce immune response and protection, or unintentionally during vaccine production. In addition, vaccines can contain adjuvants to improve the immune response, as well as preservatives and stabilisers.

• Live vaccines

Live vaccines induce cell-mediated as well as humoral immunity, leading to long-term protection, and can produce herd immunity. These benefits must be balanced against the risk of disease due to the vaccine strain, in either the vaccinee or contacts, whether immunocompromised or immunocompetent. Disease can occur depending upon the degree of attenuation and potential virulence of the vaccine strain, as well as host immune status. Possible scenarios are discussed below.

Scenario: Administration of the vaccine to an immunocompromised vaccinee

Examples
► Measles pneumonitis after administration of MMR vaccine **(1)**.
► Progressive vaccinia after administration of smallpox vaccine **(2)**.
► Disseminated BCG after administration of BCG vaccine **(3)**.
► Vaccine Associated Paralytic Polio (VAPP) after administration of oral poliovirus vaccine (OPV) **(4)**.
► Viscerotropic or neurological disease after yellow fever vaccine **(5)**.
Potential Risk Management/Risk Minimisation Tools
► Contraindicating these vaccines for patients known to be immunocompromised.
► Use of alternative, non-live vaccines (e.g. inactivated poliovirus vaccine [IPV] instead of OPV) in these patients.

Scenario: Administration of the vaccine to an immunocompetent vaccinee

Examples
► Aseptic meningitis following Urabe mumps vaccine **(6)**.
► Intussusception following rhesus rotavirus vaccine (mechanism unknown) **(7)**.
Potential Risk Management/Risk Minimisation Tools
► Withdrawal from the market or selective use (depending upon benefit-risk balance and availability of an alternative vaccine).
► Use of an alternative, non-live vaccine in the population (if available).
► Substitution of further attenuated strains that are available or developed through application of new technology (e.g. reverse genetics) in the development of new vaccines.

Scenario: Transmission of vaccine strain from a vaccinee to an immunocompromised contact

Examples
► VAPP after administration of OPV **(4)**. ► Vaccinia in an immunocompromised patient who is in contact with the local site of smallpox vaccine administration **(8)**.
Potential Risk Management/Risk Minimisation Tools
► Contraindicating the vaccine if the potential recipient will be in close contact with an immunocompromised patient, and use of inactivated vaccine if available. ► Avoiding contact with immunocompromised patients for a period of time after immunisation consistent with the known duration of infectivity related to vaccine viral shedding. ► Avoiding contact with immunocompromised patients if rash develops in a vaccinee (e.g. following varicella vaccine).

Scenario: Transmission of vaccine strain from a vaccinee to an immunocompetent contact

Examples
► VAPP after administration of OPV. Reversion of vaccine strain to a more virulent strain can occur, as has been demonstrated for OPV **(4)**. ► Secondary and tertiary transmission of vaccinia virus to immunocompetent patients has been reported; the disease is generally self-limiting **(9)**.
Potential Risk Management/Risk Minimisation Tools
► Improved immunisation rates (to decrease number of susceptible patients in the population). ► Use of an alternative, non-live vaccine, if available (e.g. IPV). ► Improved vaccine technology in the development of new vaccines.

• Adventitious agents

An adventitious agent has been defined as "a microorganism (including bacteria, fungi, mycoplasma/spiroplasma, mycobacteria, rickettsia, viruses, protozoa, parasites, Transmissible Spongiform Encephalopathy (TSE) agent) that is inadvertently introduced into the production of a biological product" **(10)**. Recent methods for adventitious agent detection can detect very low quantities of virus and viral DNA. Current methods rely on the use of multiple overlapping strategies; nevertheless, because detection tools are not required or applied for every possible agent, absence of an adventitious agent cannot be absolutely assured.

The potential impact of adventitious agents is infection, with or without resultant disease, including cancer.

Examples
► Simian Virus 40 (SV40) in IPV **(11)**. ► Non-infectious, defective particles of Endogenous Avian Retrovirus (EAV) in egg-produced vaccines **(12)**. ► Porcine Circovirus (PCV) from porcine trypsin in rotavirus vaccines **(12, 13)**. ► TSE (theoretical risk due to animal-derived materials in vaccines).
Potential risk management/Risk minimisation tools
Pre-approval Approaches used to test **(10, 14)**, evaluate, and eliminate potential risks of adventitious agents during manufacture must be included in the marketing authorisation application for a new vaccine **(15)**. *Post-approval* If an adventitious agent is detected with additional testing post-approval, the risk minimisation strategy is determined on a case-by-case basis, depending upon the likelihood of an infectious risk to humans **(16)**. Additional risk assessment might be necessary, including long-term observational studies. Additional risk minimisation strategies might include: ► Temporary or permanent withdrawal of the vaccine, depending upon benefit-risk balance, e.g. availability of alternative products, assessment of severity of risk. ► Altering the manufacturing process. ► No release of additional lots until vaccine is available that is free of adventitious agent (strategy used when IPV was found to contain SV40 **(11)**). ► Sourcing of raw materials from low-risk countries (e.g. bovine-derived materials from low Bovine Spongiform Encephalopathy [BSE]-risk countries).

• New adjuvants

A vaccine adjuvant is any substance that enhances, re-directs, and/or sustains the immune response to a co-administered antigen. Adjuvants exert their activities by presenting, uptaking, distributing and protecting antigens for immune modulation and potentiation **(17)**.

The initial development of adjuvants for vaccines dates from the 1920s to the 1940s; the broadened use of oils and aluminium adjuvants from the 1940s to the 1970s; the development of synthetic adjuvants and second-generation delivery–depot systems from the 1970s to the 1990s; and the development of rational receptor-associated adjuvants that activate the innate immune system from the 1990s to the present **(18)**.

New technologies in the fields of analytical biochemistry, macromolecular purification, recombinant technology, and a better understanding of immunological mechanisms and disease pathogenesis have helped to improve the technical basis for adjuvant development and application **(18)**.

Adjuvants may induce local and systemic adverse events. New safety concerns, e.g. auto-immune diseases, rare adverse events, delayed onset of adverse events, may emerge with the use of new adjuvants, in addition to synergistic reactions of adjuvant and active antigen.

Example
Reactogenicity of new adjuvants **(19)**
Potential risk management/Risk minimisation tools
Pre-Approval Identification, analysis and assessment of preclinical and clinical studies for anaphylaxis/hypersensitivity, carcinogenicity, local tolerance, pyrogenicity, and acute/repeated dose, foetal, reproductive and systemic toxicity, where applicable, to control, and avoid, minimise, or eliminate unacceptable risks. *Post-Approval* Information on rare adverse events, acute or chronic toxicity, drug interactions, and use in special groups or in patients with comorbidities, is often incomplete or unavailable due to the characteristics of clinical studies. Pharmacovigilance planning is necessary, therefore, to supplement this data, including the identification of adverse events and unknown interactions, change in the frequency, risk factors, and possible mechanisms, and to disseminate information necessary for the improvement of regulation and promoting rational drug use. Determination of population background rates of events that could emerge in the vaccine target group provides data needed for the expected number of events without a vaccine programme. While it is challenging in the post-approval setting to design studies to distinguish adverse effects due to adjuvant rather than antigen, risk assessment strategies might include: ► Routine pharmacovigilance (e.g. use of targeted follow-up questionnaires). ► Additional pharmacovigilance: Active monitoring in collaboration with national groups/agencies). ► Post-authorisation safety studies: — Designs for safety evaluation of repeated and concurrent exposure to adjuvanted vaccines and longer-term safety data. — Search for early biomarkers of adjuvant activity/toxicity to aid in clinical study evaluation and postmarketing surveillance studies. — Novel clinical trial designs to more efficiently answer questions of safety, immunogenicity, and effectiveness. Studies on duration of immunogenicity and cross-protection, including clinical effectiveness studies to confirm these properties. — Reassessment as to whether adjuvanted vaccines would allow for a compressed vaccination dose schedule. — Identification of correlates of protection for vaccine targets to aid in optimal design and testing of adjuvanted vaccine candidates.

B. Risks related to impact of vaccine on natural disease

Widespread use of vaccines in a population has the potential to change the epidemiology of the target disease. In fact, one of the goals of universal vaccination may be to modify or eliminate the disease from a population or from a segment of the population. Disease elimination is clearly a desirable outcome; however, there is also the potential for vaccination to perturb disease epidemiology with the possibility of resulting undesirable outcomes. Some ways in which vaccination can affect the epidemiology of disease include: 1) disease eradication (overall or regionally), 2) disease reduction with a relative increase in disease caused by non-vaccine organisms (type replacement), 3) herd immunity, which describes a situation in which a sufficient proportion of a population is vaccinated against a disease and person-to-person spread wanes. In this way, unvaccinated individuals derive some protection because the disease has little opportunity to spread within the community (e.g. widespread use of pneumococcal conjugate vaccine in infants resulted in decreasing vaccine-type pneumococcal disease in the elderly, who were not vaccinated **(20)**). The beneficial effect that widespread vaccination may have in changing the epidemiology of the target disease may in itself alter the benefit-risk balance of the vaccine. The complex interplay of disease and vaccination should be considered as part of a comprehensive risk minimisation strategy for vaccine products.

• Disease incidence reduction/eradication

Successful vaccination programmes can lead to significant reductions or partial elimination of the targeted natural disease. There may come a time when the natural occurrence of the disease (either in general, or in a segment of the population) is so low that the risk of vaccination, even if low, outweighs the risk of the disease.

Example
► As polio incidence dropped due to the success of live virus vaccine, the risks of polio vaccination, especially vaccine-associated paralytic polio, although very rare, were more common than the natural disease **(21)**.
Potential Risk Management/Risk Minimisation Tools
► Epidemiologic studies of disease incidence. ► Public health monitoring of disease incidence. ► Revise immunisation recommendations based on ongoing benefit-risk evaluations (e.g. switch to an inactivated vaccine with no risk of VAPP, to restore or maintain a positive benefit-risk profile).

Additionally, when disease incidence is reduced due to vaccination, natural boosting, which happens when the targeted disease is still in circulation within the community, may be reduced. Diminished natural boosting may influence the duration of vaccine effect (see **Effect related to the immune response** below).

• Type replacement

When vaccination targets a subset of organism types (e.g. bacterial serotypes, viral types), there may be concern that type replacement may diminish the overall effectiveness of the vaccine. This issue arises when vaccination against the subset of organism types is successful, but the non-targeted types then increase in prevalence and cause disease. Type replacement in this context refers to a true increase in the disease caused by non-vaccine types and not merely a proportional increase due to a decrease in vaccine-type disease.

Example
► Pneumococcal type replacement after widespread use of a seven-valent conjugated pneumococcal vaccine **(22)**.
Potential Risk Management/Risk Minimisation Tools
► Epidemiologic studies of the prevalence of type-specific disease ► Studies of long-term effectiveness ► Laboratory or microbiology surveys ► Development of vaccines with a broader representation of types

• Effect related to the immune response

At the time of first marketing authorisation of a vaccine, the duration of effect is rarely known. For the benefit of public health, it may not be prudent to withhold the approval of the vaccine until long duration trials are completed. For diseases where life-long immunity is optimal, booster or repeated doses will likely be required. Vaccine effectiveness may be longer in a setting where natural boosting occurs, that is, when the targeted disease is still in circulation within the community. As the natural disease incidence wanes, the duration of vaccine effectiveness may be shorter. Additionally, waning protection against natural disease due to the decrease of antibody levels over time might affect the clinical expression of the disease with potentially more severe infection. Therefore, information will be required to inform on the duration of effect and on the ability of the vaccine product to produce a booster response. Booster dose should be administered at the appropriate time and at the appropriate dosage. If given too soon after the previous dose or at a higher dose, it might result in increased local reactogenicity, as has been shown with diphtheria-containing vaccines **(23)**.

Example
► Efficacy for mumps vaccine was initially found to be durable at least to 12 years; as natural boosting waned, the effectiveness appeared less durable **(24)**.
Potential Risk Management/Risk Minimisation Tools
► Studies to follow long-term effectiveness and immunogenicity in a cohort of subjects to determine a time point for significant waning. Clinical trial subjects can be followed so as to inform recommendations on duration earlier than data might be available from the vaccinated population as a whole. ► Studies to test the ability of the vaccine product to boost immunity or to 'restore' waned immunity. ► Monitor the epidemiology of the targeted disease before and after a vaccine programme ► As information becomes available, the booster or a repeat dose recommendation should be assessed. ► Update the indication section of the Product Information for prescribers with the timelines for booster dose as soon as the first results of the effectiveness studies are available. ► Communicate the results of these studies to Healthcare Professionals and plan a media campaign for the public on the need for booster.

Example
► Increased reactogenicity of 4th and 5th booster doses of acellular pertussis-tetanus-diphtheria vaccines **(24)**.
Potential Risk Management/Risk Minimisation Tools
► Reduce antigen content of booster dose formulations. ► Changes to immunisation schedule.

Example
► Risk of worsening viral infection (e.g. dengue in individuals with incomplete or waning protection against one or more dengue virus serotypes compared to naive subjects; this could result in severe dengue infection **(25)**).
Potential Risk Management/Risk Minimisation Tools
► Studies of long-term efficacy with specific surveillance of severe cases in vaccinees, such as case control studies based on cases of dengue infection requiring hospitalisation. ► Initial introduction in countries with effective surveillance system. ► Mathematical modelling at population level, integrating diverse data sources like movement of dengue virus, vector circulation, and climate changes to better anticipate the need for booster **(26)**.

C. Risks related to vaccine use

Vaccines are used in the framework of recommended vaccination schedules or ad hoc, for example in the case of pandemics or for travelling to endemic areas.

Recommended vaccination schedules form a key part of public health programmes that aim to control a number of infectious diseases. In addition, a public health programme taking the shape of a vaccine mass campaign against a specific disease may be necessary to combat an outbreak or pandemic situation, or as a part of an eradication programme such as polio eradication. Where large populations are targeted with vaccination, and that is usually the case in both these public health scenarios, this may lead to increases in the frequency of AEFI reports which may be sufficient to be considered a signal requiring a root-cause investigation if there is a real risk related to vaccination. A campaign in particular involves a large number of doses given over a short time period and may substantially increase reporting of AEFIs during that period. In such settings, coincidental events could appear as a cluster but actually represent the normal background incidence of that event in the population **(27)**.

Depending on the purpose of vaccination and the framework for its delivery, vaccines may be used in various settings, i.e. not only healthcare settings, but also in schools and other non-healthcare institutions involved in the public health programme. This may impact on storage conditions and the availability of equipment to treat AEFIs should they occur. Also, vaccinators may differ in their expertise to vaccinate and capacity to manage AEFIs in individuals, especially if they experience an anxiety-related reaction. For example, the need to immunise large populations in a condensed time period during an outbreak or pandemic strains human resources and raises the potential for a true increase in immunisation errors due to lack of trained vaccinators. When adolescents are targeted by a vaccine, there may be an increase in anxiety-related reactions.

Vaccine product-related issues have already been discussed under Sections 1 and 2. Immunisation errors, particularly those more commonly seen with vaccines as compared to other medicinal products, and anxiety-related reactions are discussed below.

• Immunisation errors

Immunisation errors include inappropriate vaccine handling, prescribing or administration and thus by their nature can be preventable. "Inappropriate" refers to usage (handling, prescribing and administration) other than what is authorised and recommended in a given jurisdiction based on scientific evidence or expert recommendations. These errors may cause adverse events following immunisation, so called 'immunisation-error related reactions', including infectious, toxic or traumatic injury.

Vaccination by an improperly trained vaccinator can lead to a cluster of events. Improper immunisation practice may result in abscess or other blood-borne infections.

Example
▶ Incorrect sterile technique or inappropriate procedure with a multidose vial (e.g. toxic shock syndrome due to improper handling of vaccine vials after use/reconstitution; a number of patients immunised from the same vial may develop local infections or even die within a short time of injection).
Potential Risk Management/Risk Minimisation Tools
▶ Training about the procedure of vaccine preparation may be needed. ▶ Use of single dose vaccine presentation. ▶ Use of preservative in multi-dose vials. ▶ Auto-disable syringes to prevent repeated use of the same syringe. ▶ Pre-filled vaccination device. ▶ Vial temperature indicators.

Example
▶ Failure to adhere to a contraindication (e.g. disseminated infection with an attenuated live vaccine agent following administration to an individual with a known immunodeficiency that should have contraindicated use of any live vaccines).
Potential Risk Management/Risk Minimisation Tools
▶ Identification of any immunodeficiency condition before immunisation. ▶ Training for the vaccinator for immunodeficiency detection before immunisation.

Example
▶ Use of an incorrect diluent to reconstitute lyophilized vaccine. ▶ Injection of a product other than the intended vaccine.
Potential Risk Management/Risk Minimisation Tools
▶ Dedicated vaccine refrigerators. ▶ When possible ship and store vaccine and diluents together. ▶ Clear labelling and packaging. ▶ 2-dimensional bar coding to avoid product confusion **(28)**.

• Anxiety-related reactions

AEFI may occur as a result of anxiety about the immunisation before, during or after the actual administration of vaccine. Such reactions may be mediated by vasovagal response or hyperventilation usually in close association (15–20 minutes) with immunisation. There is minimal risk associated with anxiety-related AEFI in terms of the initial manifestations including syncope, dizziness or paresthesiae. All are short-lived and resolve with minimal intervention such as lying down to restore blood flow to the brain during a vasovagal reaction or calming an individual during a panic attack. The associated risks relate more to injuries incurred if fainting occurs in an unsafe environment or if unnecessary treatment or contraindications to future vaccines result because the reaction has been mistaken as anaphylaxis or respiratory compromise.

Another type of anxiety reaction is termed 'mass sociogenic illness', which is a type of stress-related psychiatric disorder ('mass hysteria') which has been associated on occasion with vaccine campaigns involving older children and adolescents in school settings **(29)**. The onset may be hours to days after the immunisation event, making diagnosis difficult. The major impact of such an event is a sudden demand on the healthcare system and potential media focus.

Example
► Vasovagal reaction mistaken as anaphylaxis, resulting in treatment for anaphylaxis and possibly a false contraindication for future doses of vaccine. ► Syncope with tonic-clonic movements could be mistaken as a seizure and could result in low public acceptance of the implicated vaccine (e.g. Human papillomavirus HPV vaccine). ► Head injury or other injury incurred as a result of fainting. ► Mass psychogenic illness.
Potential Risk Management/Risk Minimisation Tools
► Ensure that immunisation is done in a safe setting with vaccinees kept seated or lying down during immunisation and kept under observation for 15 minutes after immunisation. ► Train immunisation clinic staff in recognition and minimisation of anxiety-related reactions, in particular vasovagal and hyperventilation syndromes, including how to differentiate these from true emergencies such as anaphylaxis. ► In school-based and other mass campaign settings involving adolescents and adults, ensure staff are aware of the possibility for frequent occurrence of anxiety-related AEFI or more rarely mass psychogenic illness. ► Identify settings and individuals at risk for anxiety-related AEFI and ensure they understand the need to limit unsafe activities for 15–20 minutes post-immunisation (such as going up or down stairs, driving a car).

D. Communication relevant to risk minimisation for vaccines

The three previous sections of this Annex have alluded to communication challenges in relation to vaccines. For example, manufacturing technology such as reverse genetics, the potential risk of cancer due to adventitious agents, safety concerns over autoimmune diseases or uncertainty around causality of adverse events following immunisation are not trivial issues to understand, elucidate and handle, neither for vaccine specialists nor for those using vaccines. Users of vaccines, i.e. individuals, their carers, healthcare professionals and those responsible for public health may have special concerns, which would need to be addressed by specialists

through assessment and communication. This also applies to concerns over potential risks which may be considered highly unlikely or implausible to assessors, which therefore do not easily find their way into the assessment. Issues and uncertainties which have not been included in initial assessments of evidence may result in a communication vacuum and require reactive assessment and communication efforts.

Any concerns need to be put in the context of the expected benefits for individuals and the community, for risk assessment, risk minimisation and risk communication.

Looking at benefit at individual as well as population level is special for vaccines and one source of potential mistrust by the public, which may fear that interests of public health or political agendas overtake protection of individuals vulnerable to risks of vaccines. There are also people who do not believe in the benefits of vaccines. Hence, comprehensive assessment of identified risks, potential risks and any other concerns and implementing risk minimisation measures where necessary are crucial for successful risk minimisation of vaccines. In addition, engaging in a dialogue between all stakeholders on the risks and benefits of vaccines and wider communication strategies are paramount in supporting safe and effective use both from an individual and a public health perspective.

Communication between those assessing and managing vaccine risks, vaccine manufacturers, users of vaccines and the general public has to be based on scientific evidence on the benefits and risks and be conducted in a trustworthy manner.

Inadequate communication including unmet information needs in relation to vaccines is a risk to individual and public health itself, as this may result in population attitudes rejecting vaccines and in vaccination coverage insufficient for disease control. Benefit-risk communication for vaccines has not only to address the benefits and risks of a vaccine as such, but also to describe the impact of the uncontrolled disease.

For the individual, information will often be needed regarding risk susceptibility of specific populations like pregnant women, persons with autoimmune diseases or immunocompromised persons. The information provided should take into account common knowledge, and for example explain why it is recommended to vaccinate pregnant women with a particular vaccine, while normally one should avoid taking medicines during pregnancy. Concerns to be addressed may also relate to excipients or manufacturing process residues, such as adjuvants, preservatives and proteins. It is important to reassure the public regarding absence of or low level of risk, wherever data allow such a conclusion, or else to explain what is known and what is uncertain.

Risk minimisation activities for vaccines, therefore, would need to include training of vaccinators/healthcare professionals on how to communicate the benefits and risks of vaccines in this wider sense, and how to deal with vaccine anxiety and non-acceptance as well as vaccine anxiety-related reactions. The latter, if not managed adequately, may cause community scares and wider public outrage. These may easily be amplified by cultural, including religious and political, concerns. Some anti-vaccination activist groups draw their motivations from such concerns.

The benefit-risk perceptions vary between regions and change over time, as a function of the epidemiology of disease and vaccination success and impact of cultural aspects.

Methods for identifying and understanding perceptions of medicines, so far especially for vaccines, have been developed by the social sciences, with support from psychology, and include surveys as well as media coverage analyses and rumour investigations, both in relation to the traditional as well as web-based media. Changes in perceptions detected by these methods may also be useful for the evaluation and future improvement of effectiveness of communication interventions.

In summary, effective communication of activities aimed at minimising risks intrinsic to the vaccine product and the vaccination process is necessary in order to address public concerns. There should be a close interaction and dialogue between all stakeholders for the preparation of risk minimisation activities in relation to vaccines. The key aim of these strategies is to allow for informed choice in relation to individual vaccination and to achieve vaccination rates which protect public health at the population level **(30–38)**.

It is recommended that the reader of this CIOMS Annex refers also to the *GVP product- or population-specific considerations on Vaccines* used in the prophylaxis of infectious diseases published in December 2013 by the EMA. **(39)**

E. References

1. Angel JB, Udem SA, Snydman DR et al. Measles pneumonitis following Measles-Mumps-Rubella vaccination of a patient with HIV infection, 1993. MMWR. 1996, 45(28): 603–606.
2. Bray M, Wright ME. Progressive vaccinia. Clin Infect Dis. 2003, 36: 766–774.
3. Talbot EA, Perkins MD, Silva SFM, Frothingham R. Disseminated Bacille Calmette-Guérin disease after vaccination: Case report and review. Clin Infect Dis. 1997, 24: 1139–1146.
4. Minor P. Vaccine-derived poliovirus (VDPV): Impact on poliomyelitis eradication. Vaccine. 2009, 27: 2649–2652.
5. Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. Expert Rev Vaccines. 2012, 11(4): 427–448.
6. Balraj V, Miller E. Complications of mumps vaccines. Rev Med Virol. 1995, 5: 219–227.
7. Lynch M, Shieh WJ, Bresee JS, Tatti KM, Gentsch JR, Jones T et al. Intussusception after administration of the rhesus tetravalent rotavirus vaccine (Rotashield): the search for a pathogenic mechanism. Pediatrics. 2006, 117: e827-e832.
8. Neff JM, Lane JM, Fulginiti VA, Henderson DA. Contact vaccinia - transmission of vaccinia from smallpox vaccination. JAMA. 2002, 288(15): 1901–1905.
9. Young GE, Hidalgo CM, Sullivan-Frohm A, Schulte C, Davis S, Kelly-Cirino C et al. Secondary and tertiary transmission of vaccinia virus from US military service member. Emerging Infect Dis. 2011, 17(4): 718–721.
10. U.S. FDA Guidance for Industry: Characterization and qualification of cell substrates and other biological materials used in the production of viral vaccines for infectious disease indications. 2010, February. http://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/guidances/vaccines/ucm202439.pdf, accessed 30 April 2014.
11. Engels EA. Cancer risk associated with receipt of vaccines contaminated with simian virus 40: Epidemiologic research. Expert Rev Vaccines. 2005, 4(2): 197–206.
12. Krause PR. CBER assessment of porcine circovirus in vaccines. FDA VRBP Advisory Committee Meeting, May 7, 2010.
13. EMA. Questions and answers on the detection of unexpected viral DNA in live attenuated vaccines: Outcome of a procedure under Article 5(3) of Regulation (EC) 726/2004. November 18, 2010.
14. ICH Harmonised tripartite guideline on viral safety evaluation of biotechnology products derived from cell lines of human or animal origin Q5A(R1), Step 4, dated 23 September 1999.
15. ICH Harmonised tripartite guideline on the common technical document for the registration of pharmaceuticals for human use: Quality - M4Q(R1), Step 4, dated 12 September 2002.
16. Petricciani J, Sheets R. An overview of animal cell substrates for biological products. Biologicals. 2008, 36: 359–362.
17. EMA. Guideline on adjuvants in vaccines for human use. EMEA/CHMP/VEG/134716/2004. January 2005.
18. Singh M, Editor. Vaccine adjuvants and delivery systems, Hoboken, New Jersey: John Wiley & Sons, Inc. 2007, 1: 1–2.
19. Petrovsky N, Heinzel S, Honda Y, Lyons A. New age vaccine adjuvants: Friend or foe? BioPharm Intern Guide. 2007: 24–33.
20. Lexau CA, Lynfield R, Danila R et al. Changing epidemiology of invasive pneumococcal disease among older adults in the area of pediatric pneumococcal conjugate vaccine. JAMA. 2005, 294: 2043–2051.
21. Prevots DR, Burr RK, Sutter RW, Murphy TV. Poliomyelitis prevention in the United States. Updated recommendation of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep. 2000, 49 (RR-5): 1–22.
22. Hicks LA, Harrison LH, Flannery B et al. Incidence of pneumococcal disease due to non-pneumococcal conjugate vaccine (PCV7) serotypes in the United States during the era of widespread PCV7 vaccination, 1998–2004. J Infect Dis. 2007, 196: 1346–54.
23. Rennels MB, Deloria MA, Pichichero ME et al. Extensive swelling after booster doses of acellular pertussis-tetanus-diphtheria vaccines. Pediatrics. 2000, 105: e12
24. Date AA, Kyaw MH, Rue AM et al. Long-term persistence of mumps antibody after receipt of 2 Measles-Mumps-Rubella (MMR) vaccination and antibody response after a third MMR vaccination among a university population. J Infect Dis. 2008, 197: 1662–1668.
25. Whitehorn J, Simmons CP. The pathogenesis of dengue. Vaccine. 2011, 29: 7221–7228.
26. Lam SK, Burke D, Capeding MR et al. Preparing for introduction of a dengue vaccine: Recommendations from the 1st Dengue v2V Asia-Pacific meeting. Vaccine. 2011, 29: 9417–9422.
27. Black S et al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines. Lancet. 2009, 374: 2115–2122.
28. www.cdc.gov/vaccines/pubs/vis/vis-barcodes.htm.
29. Kharabsheh S, Al-Otoum H, Clements J et al. Mass psychogenic illness following tetanus-diphtheria toxoid vaccination in Jordan. Bull WHO. 2001, 79: 764–770.
30. Ball LK, Evans G, Bostrom A. Risky business: Challenges in vaccine risk communication. Pediatrics. 1998, 101: 453–458.
31. Bouder FE. A comparative analysis of risk perception related to human health issues. In: Richter IK, Berking S, Müller-Schmid, eds. Risk society and the culture of precaution. Houndmills, New York, N.Y.: Palgrave Macmillan. 2006.
32. Burgess DC, Burgess MA, Leask J. The MMR vaccination and autism controversy in United Kingdom 1998–2005: Inevitable community outrage or a failure of risk communication? Vaccine. 2006, 24: 3921–3928.
33. Dittmann S. Vaccine safety: Risk communication – A global perspective. Vaccine. 2001, 2446–2456.
34. Larson HJ, Cooper LZ, Eskola J, Katz SL, Ratzan S. Addressing the vaccine confidence gap. Lancet. 2011, 378: 526–535.
35. Leach M, Fairhead J. Vaccine anxieties: Global science, child health and society. London: Earthscan. 2007.
36. May T. Public communication, risk perception, and the viability of preventive vaccination against communicable diseases. Bioethics. 2005, 19: 407–420.

37. Offit PA, Jew RK. Addressing parents' concerns: Do vaccines contain harmful preservatives, adjuvants, additives, or residuals? Pediatrics. 2003, 112: 1394–1397.
38. Paterson P, Larson HJ. The role of publics in the introduction of new vaccines. Health Policy Plan. 2012, 27 Suppl 2: ii77–79.
39. GVP product- or population-specific considerations on vaccines used in the prophylaxis of infectious diseases. EMA, 2013, December. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/12/WC500157839.pdf, accessed 20 January 2014.

ANNEX VII

FAILURE MODE AND EFFECT ANALYSIS (FMEA)

A. Background

Failure Mode and Effect Analysis (FMEA) is a risk assessment technique for systematically identifying potential failures in a system or a process. The term 'failure mode' refers to a way in which something might fail. Failures are any safety risks, errors or defects, especially those that affect the customer (or, in this context, the patient), and can be potential or actual. 'Effects analysis' refers to studying the consequences of those failures.

FMEA is one in a collection of risk assessment techniques and methodologies that offer a systematic, structured approach to identifying, evaluating, characterising, and quantifying the type and degree of risk(s) to be managed **(1, 2)**. As such, it is directly applicable to the development of a risk minimisation strategy for a new drug product. In addition, because the FMEA framework can be used iteratively, it can also be used to evaluate the impact of risk minimisation strategies.

Other alternative research methods to FMEA include:

Six Sigma

- Project management
- Decision analysis
- Design and implementation of public health interventions
- Behavioural psychology
- Social science methodologies
- Educational design specialists
- Research methods (quantitative and qualitative)
- Survey design
- Communication experts

The following example provides an illustration of how one might conduct a FMEA for a hypothetical new product, Drug X. In this instance, the FMEA is being conducted as a precursor to developing a risk minimisation strategy. It could also be used at other points in the lifecycle of a product, such as when one or more new safety concerns have been identified.

B. The FMEA approach: An example

A cross-functional, multi-disciplinary team was established to conduct an FMEA to define the highest priority risks associated with Drug X. In this example, Drug X is an immunosuppressant, hence screening for active or latent tuberculosis was indicated prior to drug initiation.

FMEA team members were subject experts on different aspects of Drug X and consisted of representatives from the following functional areas: Manufacturing, Quality Assurance, Clinical Development, Risk Management, Pharmacovigilance, Regulatory, and Human Factors.

An FMEA involves a multi-step process. Each step is described below. In addition, the results of the FMEA are summarised in Table 1.

Step #1: Identify the 'ideal' treatment pathway for patients using Drug X. In order to do so, the team referred to the proposed product information (SmPC and Package Insert for prescribers). Based on this labelling information, the team identified the steps that a prescriber, patient, pharmacist and other key actors in the treatment pathway should follow when prescribing, dispensing and using Drug X appropriately.

Step #2: For each step in the treatment pathway, the team then identified real or potential 'hazards' or risks that could affect the patient if there were deviations from the appropriate treatment pathway. Risks were identified based on a diverse array of information gained from clinical trial results to date for Drug X, product manufacturing, epidemiological and human factors data on the target patient population, learning gained from the postmarketing experience of similar drug products, and knowledge of the healthcare systems in which Drug X would be launched.

Step #3: After listing all of the potential risks that could occur for each step in the treatment pathway, failure modes contributing to each risk were identified. Similar to the risk identification process, identification of failure modes was made based on the team's collective knowledge and experience with Drug X and similar products in the same therapeutic class. Failure modes included those involving the prescriber (e.g. failure to screen the patient for a pre-existing health condition prior to prescribing Drug X), patient (e.g. failure to communicate pertinent details of his or her medical history), the pharmacist (e.g. failure to dispense with a Patient Leaflet), and other key actors (e.g. informal caregivers).

Step #4: Next, a probability of occurrence (P) was estimated for each of the identified risks. This probability estimate was based on the team's collective 'best' guess based on postmarketing experience accrued from similar compounds. A variety of scales can be employed to assign a probability; in this example, a numerical severity rating scale ranging from 1 (Low) to 5 (High) was used.

Step #5: In the following step, a severity rating (S) was assigned to each of the identified risks. This severity rating was derived from clinical judgement as to the potential impact of a given failure mode on a patient. A variety of scales can be employed; in this example, a numerical severity rating scale ranging from 1 (Low) to 5 (High) was used.

Step #6: Each severity rating was then multiplied by the occurrence probability (P X S) to provide a means of prioritising risks and mitigation efforts. The possible score range was from 1 to 25. Based on the computations, each risk was classified as being High [Score range of 13–25], Medium [Score range 9–12)] or Low [Score range </= 8)]. In this particular instance, both 'high' risks requiring immediate action and 'medium' level risks (i.e. those requiring evaluation of the need for further action to either reduce their severity or lower their frequency of occurrence) were identified. It is up to the individual FMEA team to determine whether it will focus exclusively on mitigating all high as well as medium risks identified. This decision involves multiple considerations, including for example, degree of resource constraints, current regulatory environment and internal company standards for product quality. In this example, the team elected to focus on risks with a 'high' rating.

Step #7: For each of the failure modes with an associated 'high risk' rating, the team then identified specific risk mitigation activities to put in place to reduce the likelihood of the risk occurring. Selection of each risk mitigation activity was guided by data from the literature and/or prior company or industry experience attesting to the effectiveness of that control.

The completed FMEA can be re-visited periodically and refined once the product is launched. Using postmarketing data, this analytic exercise can be repeated at periodic intervals to evaluate the effectiveness of the risk mitigation strategy as a whole.

Other risk assessment tools can also be used to complement the FMEA process. These include, for example, such approaches as Fault Tree Analysis, and Fishbone Diagram. The Fault Tree Analysis (FTA) is another risk analysis tool used for identifying use-related hazards. It differs from the FMEA in that the FTA uses a top-down, deductive approach to identifying potential risks associated with a drug product as opposed to the bottom-up approach used by an FMEA. An FTA shows the logical combination of events that lead to undesired outcomes. It captures interactions between failure modes and therefore permits a systematic analysis of more complex scenarios than does the FMEA. A Fishbone Diagram is an exercise which builds on the results of prior risk analyses and provides a way to categorise and graphically depict the core set of root causes which are driving a risk or set of risks.

Annex VII - Table 1: Failure mode and effect analysis (FMEA) for drug X

STEP	TREATMENT PATHWAY	RISK	FAILURE MODE	PROBA-BILITY (P)	SEVERITY (S)	RISK LEVEL (P X S)	MITIGATION TOOL(S) TO ADDRESS RISK LEVEL	ANTICIPATED EFFECTIVENESS
1	Physician determines if patient is appropriate for Drug X per labelled indication.	Patient may experience adverse effects.	Physician fails to assess if patient is appropriate to take Drug X per labelled indication.	1	2	2	**Product information (label); Physician checklist** specifies how to determine if patient is appropriate.	Proposed action plan anti-cipated to lower risk to "low".
2	Physician screens for active and latent TB.	Patient who has latent TB experiences TB reactivation.	Physician does not screen for TB and Drug X administered.	2	4	8	**Product information (label)** specifies need to screen for active and latent TB. **Physician checklist** specifies that patient screening be conducted.	Same as above.
3	Physician takes patient history of TB and initiates prophylaxis in patient with past TB history for whom adequate course of therapy cannot be confirmed.	Patient who has latent TB has TB reactivated.	Physician does not take patient history for TB and anti-TB prophylaxis is not initiated (latent TB).	2	4	8	**Product information (label);** **Physician checklist** to ensure patient history is assessed.	Same as above.

STEP	TREATMENT PATHWAY	RISK	FAILURE MODE	PROBABILITY (P)	SEVERITY (S)	RISK LEVEL (P X S)	MITIGATION TOOL(S) TO ADDRESS RISK LEVEL	ANTICIPATED EFFECTIVENESS
4	Physician takes patient history of TB and initiates prophylaxis in patient with past TB history for whom adequate course of therapy cannot be confirmed.	Patient with latent TB has TB reactivated.	Patient does not inform physician of past history of TB; hence physician does not initiate prophylaxis for TB.	4	4	16	**Patient leaflet** emphasises patient should inform physician of history of TB.	Same as above.
5	Physician screens for presence of other active infections.	Patient's infection worsens.	Physician fails to assess for active infections.	2	4	8	**Product information (label);** **Physician checklist.**	Same as above.
6	Pharmacist dispenses Drug X with Patient Leaflet.	Patient goes untreated for serious infection.	Pharmacist fails to dispense Drug X with Patient leaflet; as a result, patient does not know to inform physician of new signs/ symptoms of a new serious infection.	3	5	15	**Dear pharmacist letter** sent to all dispensing pharmacists informing them of importance of providing and explaining Patient leaflet to patients receiving Drug X.	Same as above.

C. References

1. Fetterman JE, Pines WL, Nickel WK, Slatko GH. A Framework for pharmaceutical risk management. Food and Law Institute Press: Washington, DC. 2003.
2. Stamatis D.H. Failure Mode and Effect Analysis: FMEA from theory to execution, 2nd Ed. Milwaukee, WI: ASQ Quality Press. 2003.

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