What are risk minimisation measures and why are they imposed

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Medicines Evaluation Board
• What is risk management

• What are risk minimisation measures

• Type of risk minimisation measures

• How to select/how do regulators decide
Binary thinking

Hazard is part of any effective medical intervention

LIFECYCLE APPROACH
What we know at the end of the clinical trial programme
Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma

Hans-Georg Eichler, Francesco Pignatti, Bruno Flamion, Hubert Leufkens and Alasdair Breckenridge

**PERSPECTIVES**

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<tr>
<th>Industry</th>
<th>Payers/prescribers/HTA organizations</th>
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<td>Require favourable conditions for innovation</td>
<td>Request comparative efficacy/effectiveness data</td>
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<th>Patient groups</th>
<th>Media/scientific community</th>
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<td>Demand early access to potentially life-saving drugs (for example, Abigail Alliance)</td>
<td>Demand stricter safety assessment after series of market withdrawals</td>
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<th>Unmet medical need</th>
<th>Excess medicalization</th>
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<td>For example, epidemiology of obesity, diabetes</td>
<td>For example, obesity, metabolic syndrome, mood disorders</td>
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**Time to marketing authorization**

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<th>Shorter timelines</th>
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<td>Higher level of uncertainty</td>
<td>Delayed market access</td>
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Figure 1 | The regulator’s dilemma. Regulators are confronted with a growing number of external needs, stakeholders, and their interests and concerns. All of these factors influence, or seek to influence, the timing of marketing authorization, which determines the time at which patients gain access to new drugs. The conundrum results from the fact that some of these external forces, although often legitimate in their own right, are pointed in different directions and become irreconcilable. HTA, health technology assessment.
What is risk management

1. Risk identification and characterisation (known and unknown)
2. Planning of pharmacovigilance activities
3. Planning of risk minimisation measures

During the life cycle of a drug
risk minimisation measures

- **GVPs of specific relevance**
  - GVP V Risk Management Plan
  - GVP VIII Post authorisation safety studies
  - GVP XV Safety communication

- **GVP XVI** Risk minimisation measures: selection of tools and effectiveness indicators
Basic Components of a Risk Management Plan

Risk Management Plan

Safety Specification
Summary of important identified risks, important potential risks and missing information (ICH E2E)

Pharmacovigilance Plan
Based on safety specification; Routine PV practices and action plan to investigate specific safety concerns (ICH E2E)

Risk Minimization
Activities to be taken to minimize the impact of specific safety concerns on the benefit-risk balance

Guideline on good pharmacovigilance practices: Module V – Risk management systems

(English only) adopted 25/06/2012

02/07/2012
Guideline on good pharmacovigilance practices (GVP)
Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators

Draft finalised by the Agency in collaboration with Member States and submitted to ERMS FG | 21 March 2013
Draft agreed by ERMS FG | 27 March 2013
Draft adopted by Executive Director | 6 June 2013
Released for consultation | 7 June 2013
End of consultation (deadline for comments) | 5 August 2013
Revised draft finalised by the Agency in collaboration with Member States | 15 January 2014
Revised draft agreed by ERMS FG | 29 January 2014
Revised draft adopted by Executive Director as final | 21 February 2014
Date for coming into effect | 1 March 2014
Risk minimisation measures

• Strategies to prevent or reduce the occurrence or severity of an adverse drug reaction when a drug is used in daily practice

• The measures can aim to
  – Selection of patients to be treated
  – Drug initiation, prescription, dispensing, administration
  – Patient monitoring
  – Use by patient
  – Early recognition of adverse drug reactions

“The right medicine, at the right dose, at the right time, to the right patient” (GVP, Module XVI)
V.B.11.1. RMP part V section “Routine risk minimisation”

Routine risk minimisation activities are those which apply to every medicinal product. These relate to:

- the summary of product characteristics;
- the labelling;
- the package leaflet;
- the pack size(s);
- the legal status of the product.

V.B.11.2. RMP part V section “Additional risk minimisation activities”

Additional risk minimisation activities are those risk minimisation measures which are not the routine risk minimisation activities listed above. Additional risk minimisation activities should only be suggested when essential for the safe and effective use of the medicinal product and these should be science based, and developed and provided by suitably qualified people. If additional risk minimisation activities are proposed, these should be detailed and a justification of why they are needed provided.

Many additional risk minimisation tools are based on communication which aims to augment the information in the summary of product characteristics (SmPC) and the package leaflet. Any communication material should be clearly focused on the risk minimisation goals, and should not be confused or combined with promotional material for marketing campaigns. Further description and guidance on the use of additional risk minimisation activities is provided in Module XVI.
Routine risk minimisation measures

Required for all drugs

- Summary of product characteristics (SmPC)
- Package leaflet (PIL)
- Labeling
- Pack size
- Legal status (i.e. OTC, prescription)
SmPC advice

Examples:

• NSAIDs and risk of GI bleedings
• Dose reduction advice in elderly
• Contraindication for use in patients with a history of MI
• Regular monitoring blood levels
• Prescription vs non-prescription status
• Limited pack size of paracetamol

What is already known on this topic

Paracetamol poisoning, which occurs mainly through intentional overdose, is an important worldwide cause of deaths and reason for liver transplantation due to hepatotoxicity

UK legislation implemented in 1998 to restrict pack sizes of paracetamol sold over the counter has shown initial benefits, in terms of non-fatal overdoses and liver unit activity in England and Wales

The long term effect of the legislation has yet to be evaluated

What this study adds

The legislation appears to have had long term benefits in terms of fewer deaths due to paracetamol poisoning, after controlling for changes in overall rates of death by self poisoning and suicide

Less robust evidence suggested a reduction in liver unit registrations and transplantation owing to paracetamol induced hepatotoxicity

Nevertheless, substantial numbers of deaths due to paracetamol poisoning still occur annually, and further preventive measures might be warranted
Long term effect of reduced pack sizes of paracetamol on poisoning deaths and liver transplant activity in England and Wales: interrupted time series analyses

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Regulatory actions/ Tools

Fig. 1. Levels of regulatory actions. In many cases regulatory responses to safety issues result in additional information requests or risk mitigation activities that do not result in changes to the terms of marketing authorization. Some safety issues warrant changes to the SPC, which in urgent cases are accompanied by a DHPC. In case of severe safety issues, which changes the benefit-risk balance, regulators may decide to suspend the marketing authorization or even revoke it. **DHPC** = Direct Healthcare Professional Communication; **SPC** = Summary of Product Characteristics.
XVI.B.2. Risk minimisation measures

XVI.B.2.1. Educational programme

XVI.B.2.1.1. Educational tools

XVI.B.2.1.1.1 Educational tools targeting healthcare professionals

XVI.B.2.1.1.2. Educational tools targeting patients and/or carers

XVI.B.2.2. Controlled access programme

XVI.B.2.3. Other risk minimisation measures

XVI.B.2.3.1. Controlled distribution systems

XVI.B.2.3.2. Pregnancy prevention programme

XVI.B.2.3.3. Direct health care professional communication (DHPC)
Additional risk minimisation measures (aRMMs)

- Only for some risks routine risk minimisation activities are not sufficient and additional risk minimisation activities are necessary
  - E.g., very serious adverse drug reaction, new complicated method of administration, potential for misuse/overdose

- aRMMs should not be suggested by default since they can add burden to the health systems

- aRMMs should be adequately justified and have a clear objective
**Additional risk minimisation measures (aRMMs)**

Measures beyond those routinely required e.g.:

- Educational tools for HCPs or patients
- Controlled access programme
  - requirements need to be fulfilled before the product is prescribed and/or dispensed
- Other risk minimisation measures
  - Pregnancy prevention programmes (PPP)
  - Controlled distribution system
  - Direct healthcare professional communication (DHPC)

\(^1\) GVP Module XVI – risk minimisation measures
Educational tools

• Lots of possibilities and can be suggested for variety of drugs and risks

• Aimed at different target groups:
  – for prescribers, pharmacists or other HCPs
  – Patients, caregivers

• Can be different formats
  – Brochure, checklist, website, interactive programme or in-person training, patient alert card

• Tool to communicate and remind
  – knowledge on risks
  – Recommended actions (what to do, what not to do)
Patient alert card

- To ensure that special information regarding the patient’s current therapy and its important risks (e.g. potential life-threatening interactions with other therapies)

- Patient always carry this card with him and reaches the relevant healthcare professional as appropriate

- Ability to carry this easily (e.g. can be fitted in a wallet) should be a key feature of this tool
Controlled access programmes

• Requirements need to be fulfilled before the product is prescribed and/or dispensed e.g.,
  – drug prescription /dispensing only by certified HCPs
  – specific testing / examination
  – inclusion in a registry
  – informed consent

• Implementation can be challenging
Other risk minimisation measures

• Pregnancy prevention programmes (PPP)
  – For teratogenic drugs
  – Education, exclude pregnancy before and during therapy, use contraceptives etc.

• Controlled distribution system
  – For drugs with potential for misuse and abuse
  – Facilitate traceability of the product. Track the stages of the distribution chain of a medicinal product until the prescription and/or pharmacy dispensing the product

• Direct healthcare professional communication (DHPC)
  – Letter sent to HCPs. To communicate at one point in time NEW safety information and NEW recommendations for use/prescribing/dispensing
Drugs with aRMMs

• A cross-sectional analysis in 2010 showed that

  – 58/391 active substances in the EU had aRMMs
  – +/- 25-30% of the newly authorised drugs per year

  – Concerned mainly drugs prescribed/used in hospitals

  – Heterogeneity in type of drugs and safety concerns addressed with aRMM

  • Teratogenicity >>> PPP
  • Hepatotoxicity >>> patient monitoring

1 Zomerdijk et al. Risk minimization measures in the EU – a descriptive study. Drug saf 2012; doi: 10.2165
Number of drugs with aRMM is increasing

Figure 1: Active substances with and without additional RMAs per year of marketing authorisation.

- Without additional RMAs
- With additional RMAs

Introduction EU-RMP

Year of marketing authorisation
Drugs with aRMMs – type of aRMM

- In the analysis of the 58 drugs with aRMM in 2010

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<thead>
<tr>
<th>Type of aRMM</th>
<th>Drugs with this aRMM</th>
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<tr>
<td>Instructions for HCPs</td>
<td>58 (100%)</td>
</tr>
<tr>
<td>Material for patients</td>
<td>31 (53%)</td>
</tr>
<tr>
<td>Controlled distribution system</td>
<td>10 (17%)</td>
</tr>
<tr>
<td>Pregnancy prevention programme</td>
<td>5 (9%)</td>
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Additional risk minimisation measures (aRMMs)

- When to request/suggest aRMMs?
- What form of aRMM to use?
- Are the measures effective?
Selection of (best) tools

• Risk minimisation measures are drug specific, so there is no best tool

• Case-by-case assessment >> possibilities

• Points to consider
  – Objective of the risk minimisation strategy
  – Likely treatment pathways and target group
  – Drug characteristics e.g. duration of use, frequency of use, the risks
  – Therapeutic area/patient population treated
  – Anticipate the feasibility in real clinical practice

• Selection of the best tool remains difficult because information on effectiveness is not available up front
Conclusion

• Risk management it is important to
  – Characterise the important safety concerns and uncertainties
  – Is there a need to further investigate a certain uncertainty (potential risk)
  – How can the risks be minimised, routine or additional RMM

• There are no golden standards

• The best tool depends on many factors

• Need for knowledge on effectiveness and best practices to facilitate selection of (best) tools
Risk minimisation

Actions taken

Effectiveness: to which extent an intervention fulfills its objective

Is there an optimum?
• Definitions of success/failure:
  – What do we want to achieve, how should we measure eg PPP

• Quality of the aRMM
  – A RMM should have a clearly defined objective

• Distinguishing between evaluation of goals and tools is important
  – achievement of goals and performance of tools may not be linked

• Distinguishing between process and outcome is important
  – a need for different remedies

• Is more always better?
  – Eg iPledge, is there an optimum?
The impact of the iPLEDGE program on isotretinoin fetal exposure in an integrated health care system

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Elizabeth Kass, MD, d Monica A. Yoshinaga, PharmD, e Mike Sorel, MPH, e Jeffrey S. McCombs, PhD, c
and Stephen Sidney, MD, MPH e

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Conclusion

In conclusion, this study found no evidence that the iPLEDGE program significantly decreased the rate of fetal exposures to isotretinoin in FCBP. There is lack of evidence that the iPLEDGE program and all previous RMPs over the past 28 years have been effective. Before changes are made to the current iPLEDGE program, which already increases the workload burden and cost associated with prescribing isotretinoin, the criteria used to measure the success of the RMP and a method to measure those criteria should first be clearly established. Further examina-
Concomitant use of isotretinoin and contraceptives before and after iPledge in the United States†

KEY POINTS
- A small increase in concomitant use of contraception among patients prescribed isotretinoin coincident with the time of iPledge implementation was observed, particularly among younger women.
- No differences in concomitancy trend over time were observed between the periods preceding and following iPledge implementation.

A study conducted in The Netherlands, where a less stringent risk management program has been in place, suggested higher, albeit still insufficient, concomitant contraception use with isotretinoin prescriptions. In the Dutch study, the proportion of women with total monthly overlap of isotretinoin and contraceptives ranged 38%–41% for systemic contra-
Avoiding risks is impossible,
.....managing them is critical to sustained success
Risk minimisation is aimed at improving the B/R balance
Burden should be taken into account
Results fast
Need for cooperation
Navigating the regulatory landscape amid the growing complexities requires collaboration between agencies, manufacturers, insurance, HCPs and patients
Transaction refused you have enough shoes

CINDERELLA IS LIVING PROOF THAT
ONE NEW PAIR OF SHOES CAN CHANGE YOUR LIFE!