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Towards optimising risk minimisation measures

Report on EMA's workshop on risk minimisation measures

Introduction

All medicines have risks as well as benefits. While completely avoiding risks is impossible, it is critical to manage them to ensure that medicines made available to patients are as safe as possible. Critical steps for managing risks include: promoting safe use of medicines by proposing risk minimisation measures; putting these measures into practice; measuring the effect of the measures; and, finally, using the knowledge gathered to refine risk minimisation measures and improve their effectiveness.

Currently, medicines regulators draw on various tools to minimise the risks of medicines in everyday use. In addition to the product information (i.e. summary of product characteristics and package leaflet), which remains the primary means, other tools include practical guides ('educational material') for patients and healthcare professionals on specific aspects of use of the medicine, extra controls on the availability of medicines ('restricted access') and procedures for ensuring that medicines harmful to an unborn baby are not used in pregnancy ('pregnancy prevention programmes'). However, risk management is an evolving field, with new tools likely to be developed in the future as new technologies become available. The challenge lies not only in developing novel tools but on being able to evaluate how the introduction of risk minimisation measures translates into safer use of medicines. In this context, it is recognised that the evaluation of the effectiveness of risk minimisation measures is an evolving area of medical sciences with a need for further development of methods and harmonised approaches.

On 16 September 2015 EMA organised a workshop at its headquarters in London to look into current practices regarding the implementation and evaluation of risk minimisation measures, and discuss the way forward. The workshop brought together patients and healthcare professionals' representatives, academics, members of EMA's scientific committees and EMA staff. The contribution from healthcare professionals and patients is of paramount importance to ensure that risk minimisation measures are adequate, balanced, and feasible, and do not create an undue burden to the healthcare system.

Current approaches for minimising risks with medicines

Risk management involves both pharmacovigilance activities to collect and evaluate information on the safety of medicines and the implementation of risk minimisation measures.



A risk minimisation measure is a strategy to prevent or reduce the occurrence or severity of an adverse drug reaction when a medicine is used in daily practice. There are two types of risk minimisation measures. 'Routine' measures apply to every medicine and cover:

- the summary of product characteristics (SmPC) and package leaflet: these include specific information on a risk for example as warnings, precautions and advice on correct use;
- the medicine's labelling: its design should help prevent medication errors. Advice on correct use can also be included on the medicine's labelling;
- the pack size: the amount of medicine (e.g. the number of tablets) in a pack is chosen to support that the medicine is used correctly;
- the legal status: the level of control on the supply of a medicine to the public (e.g. with or without prescription) can help minimise its risks.

Routine measures can be very effective, as demonstrated by the decrease in the number of deaths and liver transplantations after the pack size of paracetamol medicines was reduced (Hawton, Bergen et al. 2013). However, for some risks, a routine approach is not sufficient, and in these exceptional cases 'additional' measures are warranted. These additional measures can come in several forms:

- educational materials for healthcare professionals and patients, such as brochures, checklists and patient alert cards. They provide information on a specific risk together with recommended actions to manage the risk (supplementing the advice already available in the SmPC and package leaflet);
- controlled access programmes: these restrict how the medicine can be prescribed or dispensed; for example, a medicine may be used only by healthcare professionals with specific expertise or in certain settings only, or patients may be required to acknowledge that they have been informed of a specific risk before receiving a medicine;
- pregnancy prevention programmes: procedures set up for medicines likely to cause serious harm to an unborn baby to ensure that women are not pregnant when starting treatment or do not become pregnant during treatment. The programme usually combines controlled access (the medicine is supplied only after tests have ruled out pregnancy) with educational materials (spelling out precautions for avoiding pregnancy);
- controlled distribution system: special control over supply chains to facilitate traceability of medicines such as those with potential for misuse and abuse;
- direct healthcare professional communications (DHPC): these are letters sent directly to healthcare professionals who are likely to use the medicine, to warn them of a new safety concern and to inform them of the actions needed to mitigate the new risk.

According to an analysis of medicines approved from 1995 to 2010, the number of medicines with additional risk minimisation measures is increasing (Zomerdijk, Sayed-Tabatabaei et al. 2012). But does the increasing number of risk minimisation measures mean better protection for the patient? So what measures should regulators request and when?

When selecting risk minimisation measures, regulators understand that there isn't such a thing as the perfect tool and each medicine needs to be assessed individually. It is essential that the use of additional risk minimisation measures is adequately justified, that their objectives are clear and that they are feasible and proportionate in terms of the burden they place on the healthcare system. It is also important to measure the effectiveness of the measures on protecting patients from risks, although this is probably the most challenging task.

Patients as end-users of medicines are uniquely placed to contribute to monitoring the safety of medicines. Patients often provide earlier and more detailed information on the side effects they experience, their severity and impact on their lives. From patients' perspective, risk minimisation tools need to be both effective and sustainable. Patients can help regulators understand which tools work best and how to improve them. The workshop highlighted that many patients have difficulty understanding the package leaflet, and many find the design of the packaging and the medicine's name confusing. Regulators need to be aware of the different levels of health literacy when considering the likelihood of uptake of risk minimisation measures (WHO 2013).

When developing tools for minimising risks and assessing their feasibility it is also important that regulators engage with healthcare professionals, who have deep insight into everyday clinical practice and how healthcare systems work. In the workshop healthcare professionals shared examples of effective measures implemented locally that led to improved patients' safety. Such success stories help us learn from best practice.

Introducing adequate risk minimisation measures through regulatory procedures might not be sufficient to manage risks if these measures are not communicated effectively to patients and healthcare professionals. Communication is key to risk minimisation and EMA, together with national authorities, has a central role in ensuring that reliable, timely and consistent messages on the risks of medicines are readily available to patients and health professionals. EMA's safety communications and summaries of risk management plans are examples of tools EMA uses to communicate key information on risk minimisation measures. When developing communication material, EMA works closely with patients' and healthcare professionals' representatives, who provide invaluable input to ensure that messages are clear and meet patients' information needs.

EMA closely collaborates with the national authorities to ensure that safety information reaches individual patients and healthcare professionals. The work done in Croatia in this respect was illustrated at the workshop. The Croatian medicines regulatory agency publishes on its website all DHPCs and educational material that are distributed. Furthermore, DHPCs are linked to the general practitioners' systems for generating electronic prescriptions ('E-prescription system'), making these important documents easily accessible when prescribing. The Croatian agency also works closely with patients' organisations and is exploring new ways of communicating risks to patients using educational theatre for raising awareness on the correct use of medicines and the importance of reporting adverse reactions.

How to implement and evaluate risk minimisation measures

Successful mitigation of medicines' risks needs that risk minimisation measures are adhered to, but implementing these measures into clinical practice may not always be straightforward and may require active participation of several parties.

At the workshop, the example of the antiepileptic medicines containing valproate illustrated how risk minimisation measures issued by EMA were implemented in clinical practice (Tomson, Marson et al. 2015). An expert task force with involvement of specialised clinicians was set up to translate the measures into daily practice. This case study showed the importance to consider the wider context, including the full therapeutic armamentarium that remains available when restricting the use of a specific medicine.

Once a risk minimisation measure is implemented into clinical practice, it is essential to measure its effectiveness, and ideally, how it results in a safer use of medicines. Studies to measure the impact of risk minimisation measures, either routine or additional, can be requested throughout the lifecycle of a

medicine, and information prior to the implementation of the measure should be collected where possible to be used as comparator. Several evaluation models exist based on a sequential approach in which every level provides more information on the usefulness of the risk minimisation measure (Prieto, Spooner et al. 2012, Smith, Banerjee et al. 2013).

The first levels of evaluation measure *coverage* (e.g. how often an alert is downloaded from the web), *awareness* (e.g. how many healthcare professionals are aware of a new concern) and *risk knowledge comprehension* (e.g. using surveys or focus groups). The next levels assess the impact on *behaviour* (e.g. change in prescribing pattern) followed by what should be the ultimate goal of every evaluation: the *safety outcome* (e.g. changes in incidence of an adverse event after implementing a risk minimisation measure).

Numerous hurdles exist in the evaluation methods, including how to collect reliable data, how to measure meaningful outcomes and how to define what constitutes successful risk minimisation (e.g. should regulators be satisfied if 80% of healthcare professionals who receive a DHPC act on it?).

Several initiatives are underway to tackle such challenges, in particular to provide better data sources. One such initiative from the [European Multiple Sclerosis Platform](#) presented at the workshop involved merging different registries of multiple sclerosis patients across several countries in order to contribute to the monitoring of safety outcomes. Such approaches provide a sharper picture while simultaneously using resources more efficiently. However, challenges include participating countries agreeing on what data should be recorded, taking into account differences in national data protection legislation and ethical conventions.

An example of how to measure uptake of risk minimisation measures is provided by the UK medicines regulatory agency (MHRA). The MHRA regularly monitors viewing figures for 'drug safety updates', an online publication for communicating safety information to healthcare professionals in the UK. Viewing figures increased in 2014 after format changes were introduced to improve the publication's accessibility. But viewing figures do not reveal who reads the publication or whether reading translates into the desired action. The MHRA therefore performed two surveys (in 2011 and 2014) to ask about the usefulness of drug safety updates. The overall feedback was positive but the results need to be interpreted with caution because of the relatively low response rate. The MHRA went on to determine if the introduction of restrictions in the use of certain medicines led to changes in prescribing patterns (Thomson, Meeraus et al. 2015). In some cases, it was also possible to study not only prescribing changes but clinical outcome (Hawton, Bergen et al. 2009).

Challenges and opportunities

When looking at the barriers and critical success factors to managing risks, it is important to have a deeper understanding of the social context, and social sciences can help us assess the impact of science and regulatory action on society.

Sociological research shows that regulators, healthcare professionals and patients deal with uncertainties in different ways. Risk management is only one way of dealing with uncertainties; other key contributors are trust and hope. Medicines users may find risk knowledge rather abstract and not connected with their daily life. It has been suggested that patients in their vulnerability and their need to cope with their illness may perceive risk differently and make decisions influenced by hope and trust. The probabilistic information on risks used to determine the likelihood of an outcome is very useful to regulators to decide on different interventions, but this information may not always be used by medicines users, and in everyday life risk perception may be more simplistic (e.g. a patient may regard a 90% risk as certainty or a 5% risk as no risk). It is also important to be aware that health

benefit is one, but not the only, goal for people who might have other priorities than those health-related. So, attitude towards risks will be shaped by the broader social context of each individual.

Trust and confidence in the doctor and the healthcare system can critically shape practices towards risks. In turn, healthcare professionals' trust in regulators will guide how well they follow regulators' guidance. Healthcare professionals play a vital role in the management of risks since they profoundly influence the way a patient will think about these risks. It is important to provide adequate information to healthcare professionals so that they can better inform patients, taking into account that individuals deal with risks in different ways and whilst some patients are more comfortable being told what to do, others may prefer active participation in decision-making.

While it is crucial to ensure that knowledge flows from regulators to healthcare professionals and then to patients, it is also important to ensure that knowledge flows in the opposite direction so regulators learn from the patients' experience of medicines, both in terms of benefits and risks. To promote the reporting of side effects by medicines' users, there is a need to increase awareness of side effects of medicines. However, this may draw more attention to the downside of medicines and, in turn, discourage use of potentially lifesaving treatments. The challenge is therefore to increase risk awareness without undermining trust in medicines and regulators (Eichler, Abadie et al. 2009).

Regulators are introducing many initiatives in the area of risk minimisation. Regarding the planning of risk minimisation activities, EMA is working to increase involvement of patients in its activities particularly at the level of the CHMP, as well as on the involvement of PRAC members in scientific advice, which would allow early input from those experts on safety when the medicine is still being developed. In addition, the good pharmacovigilance practice (GVP) module V on risk management is being revised, with a focus on important risks to ensure that risk minimisation measures are in proportion to the importance of the risk.

Regarding the collection of data for risk minimisation activities, work is under way to increase the utility of registries (EMA 2015), to improve use of data from post-authorisation safety and efficacy studies (PASS and PAES), and to collect data on risks using mobile apps and social media. Additionally, an initiative from the Head of Medicines Agencies (a network of the Heads of the National Competent Authorities) tackles how to address [medication errors](#).

Regarding the detection of safety issues, there is a plan to give further public access to EudraVigilance data, which include information on suspected adverse effects. Data from the [PROTECT study](#) is also being analysed to find new ways of detecting safety issues.

Regarding the evaluation of safety data, EMA is working to implement more structured benefit-risk methods in medicines' evaluations that take also into account patients' values and their willingness to accept risks. In order to support risk management activities, there is a need to improve the product information, and the European Commission is reviewing this. EMA is also developing the EU medicines web-portal, which will allow patients to find information on all medicines authorised in Europe using a single interface.

Further work needs to focus on making regulatory output more accessible so that it can be used by prescribing and dispensing systems. Smart phones and social media are being explored in projects such as [WEB-RADR](#) not only as tools to disseminate safety information on medicines but also as useful means for reporting side effects.

Conclusions and way forward

The workshop aimed at reviewing what is working well with the development, implementation and evaluation of risk minimisation measures as well as identifying what can be improved. This was achieved by bringing together the voices of different players involved in these processes. The goal of risk minimisation measures, as recognised during the workshop, is to reduce harm from use of a medicine as evidence is gathered in clinical use, reducing the uncertainties that exist at time of authorisation. To ensure that this goal is achieved, the following proposals emerged from the workshop:

- *Make optimal use of current regulatory tools.* In this respect, as primary means to deliver risk minimisation measures, the SmPC and package leaflet should be optimised and adapted to the needs of their audience (and their health literacy) and by better describing benefits and risks. It is recognised that patient organisations have a key role in addressing the issue of varying health literacy.
- *Collaboration with healthcare professionals and patients is key to developing risk minimisation measures.* These groups should be involved early in the design, as their input can be invaluable to optimising existing measures, as well as to developing new ones. Much can be learnt from best practice and the real-life experience of those closely involved in the implementation of risk minimisation measures, such as nurses and pharmacists. Engagement can take place through the existing frameworks of EMA's working parties as well as through new interactions with other organisations and individuals.
- *Good understanding of the factors that affect adherence to risk minimisation measures by patients and health professionals.* Regulators need to ensure that risk minimisation measures are well balanced and feasible to avoid undue burden on healthcare systems. Consideration should also be given to unintended consequences of a measure (e.g. lack of safer alternatives when restricting access to a critical medicine). Some of these factors go beyond medicines regulation, such as: varying levels of health literacy; how social factors and trust in the system affect risk perception; and how healthcare professionals' continued learning and professional development can make a difference. Adequate training and education programmes need to be in place, as well as a strong network and communication channels that allow healthcare professionals to engage with patients and regulators. Regarding trust, regulators need to engage further with stakeholders and more is to be done to create an atmosphere of risk awareness without undermining trust. In particular, there is a need to cultivate a more 'critical trust' amongst medicines users, as opposed to seeing a choice between blind trust on the one hand and no trust on the other.
- *Effective communication.* An excellent risk minimisation tool is of limited value without appropriate communication channels for the message to be heard and understood. Thus the workshop emphasised the need of maximising existing communication tools and exploring new technologies. With the advent of new tools that allow instant access to online information and media, there is a need to move beyond paper-based communications (such as the DHPC) and consider other channels for exchanging information, such as web-based or social media, making sure that the correct communication tool is chosen in each situation and the message adapted to each audience.
- *A more systematic approach to measuring the effectiveness of risk minimisation measures at different levels.* Measuring the impact of risk minimisation measures is now embedded in the product life-cycle, but there is a need to develop criteria for when (and how deeply) to assess effectiveness, considering public health importance and feasibility and to define what constitutes success in risk minimisation. Much can be learnt from case studies in order to understand possible

success factors. Engaging patients', consumers' and healthcare professionals' associations on the impact of risk minimisation will help guide process improvements. Finally, there is a huge potential for maximising the utility of patient registries to detect risks and to monitor effectiveness of risk minimisation measures.

Participants agreed that designing the future of risk management needs to start now, but research is required to inform the way forward and all players need to actively collaborate. The Healthcare Professionals Working Party – Topic Group on risk minimisation measures – will take forward the workshop's outcome in terms of engagement with healthcare professionals when designing risk minimisation measures and measuring their impact; other proposals from the workshop will be addressed through different work plans and research activities, as stated above.

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