10 April 2014
EMA/141854/2014
Stakeholders and Communication Division

Regulatory and methodological standards to improve benefit-risk evaluation of medicines

Workshop report

Introduction

For a medicine to be approved for marketing, its benefits must be shown to outweigh its risks. Capturing and quantifying a medicine's benefits and risks in a way that allows one to be offset against the other is one of the most difficult areas of the approval process. Several on-going international initiatives seek to develop and improve methods to support a more structured benefit-risk decision-making process and facilitate benefit-risk communication to the general public.

The EMA is actively engaging in and supporting research in this area. On 26 February 2014, in conjunction with the joint meeting of the EMA's patients and consumers organisations working party and healthcare professionals' working party, the Agency held a workshop at its headquarters in London, which brought together representatives of patients, consumers and healthcare professionals with members of the EMA's scientific committees, EMA staff and academics. The main objective was to provide an overview of current initiatives as well as recent EMA/CHMP benefit-risk projects. Participants had also an opportunity to discuss, through practical examples, how benefit-risk models in general could support individual treatment decisions.

Where are we today in the benefit-risk debate?

How are benefit-risk decisions made in the EU?

The way the EMA's Committee for Medicinal Products for Human Use (CHMP) evaluates the benefits and risks of a new medicine is standardised and begins with evidence of efficacy and safety provided by the company developing the medicine. This is mainly based on results from pivotal studies comparing the medicine with placebo or an active comparator, and data on any risks identified during the preclinical and clinical development.

The main measures of efficacy ('efficacy endpoints') should be objective and measurable parameters that do not depend on the individual's perception in order to be considered acceptable. Regarding safety, risks are also classified in an objective way, to ensure that they are comparable. All side effects reported by patients or healthcare professionals are identified with their frequency and then ranked as

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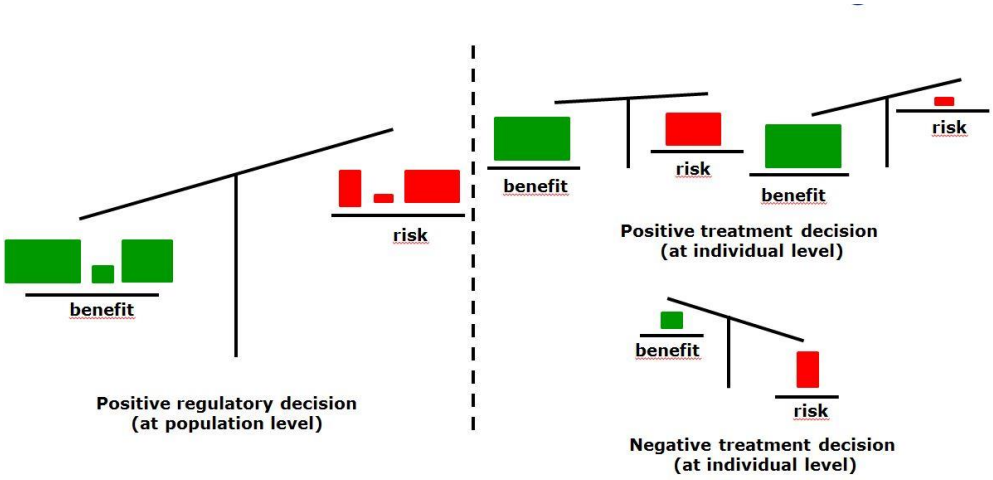
mild, moderate, severe, life-threatening or leading to death. On the basis of the data submitted, the first major task of the CHMP is to provide an impartial description of benefits and risks, also taking into account any uncertainties.

The next and maybe most challenging task is to judge the benefits against the risks and come to a benefit-risk decision. This is first done by considering the value of each favourable and unfavourable effect, then assessing the positive effects balanced against the risks. The outcome is a regulatory decision that the benefit-risk balance is either positive or negative in a clearly defined patient population. However, the regulatory decision taken at population level is distinct from the treatment decision taken for the individual patient, and a positive regulatory decision based on objective findings does not exclude a negative benefit-risk balance for an individual (see Figure below). In addition, personal preferences of individual patients may mean that benefits and risks are perceived and weighed differently.



While the regulatory decision represents the first impartial assessment of the benefit-risk balance of a medicine, it is only one of the milestones that must be passed in order to bring a medicine from bench to bedside. Once a medicine is authorised, pricing and reimbursement decisions will need to be taken at national level, followed by the final treatment decision at the patient/physician level. A clear rationale must be given for the regulatory decision so that it is comprehensible and useful for non-regulators, and allowing room for value judgements from social communities, such as health technology assessment bodies and institutions that pay for health services, as well as individual patients and healthcare professionals. The common goal is to benefit the individual patient.

Overview of current international benefit-risk initiatives

The challenging task of any decision maker is to make transparent, reproducible and defensible decisions. To date, there is no standard methodology that is used to aid regulatory decisions on the benefits and risks of medicines, but several initiatives are ongoing worldwide to explore how methods can help medicines regulators make more structured and transparent benefit-risk decisions. Some of the methods being investigated are based on a mainly qualitative approach while others use a more quantitative approach, which involves the assignment of weights to benefit and risk considerations. In the US, for example, the FDA has adopted a structured qualitative approach that is designed to support the identification and communication of the key considerations in the FDA's benefit-risk assessment and how that information led to the regulatory decision.[1] In Europe, the EMA started in 2009 a benefit-risk methodology project[2] aimed at identifying decision-making models that can be used to make the assessment of the benefits and risks of medicines more consistent, more transparent

and easier to audit (for more information, see 'Outcomes of recent EMA/CHMP benefit-risk project' below). The EMA is also coordinator of a collaborative European IMI project called PROTECT[3] (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium) which has a number of workstreams, one of which (PROTECT Work Package 5) aims to develop quantitative methods for use in benefit-risk assessment, with a particular focus on the graphical presentation of benefit and risk data.

Other examples include the Unified Methodologies for Benefit-Risk Assessment (UMBRA)[4] established by the Centre for Innovation in Regulatory Science (CIRS) in 2012 to provide a platform for the coordinated development of benefit-risk methodologies that can be used internationally during medicines' development and regulatory review. Swissmedic (Switzerland), TGA (Australia), HSA (Singapore) and Health Canada have been working together in an initiative called Consortium on Benefit-Risk Assessment (COBRA)[5], with the aim of piloting a standardised approach to benefit-risk assessments.

Although commonalities are starting to emerge between the different benefit-risk methodologies, further harmonisation is desirable. In particular, it would be beneficial to develop standard data exchange models that will streamline data transfer between different stakeholders and with eHealth initiatives.

1. FDA, Draft PDUFA V Implementation Plan - February 2013.

2. EMA benefit-risk methodology project: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580665b63

3. The PROTECT project: http://www.imi-protect.eu/

4. CIRS, UMBRA initiative (background): http://213.120.141.158/content/background

5. CIRS, Regional initiatives: http://cirsci.org/content/regional-initiatives

How to capture patients' values and preferences – an example

MACBETH[1] (Measuring Attractiveness by a Categorical Based Evaluation Technique) is a quantitative method to help decision makers quantify the relative attractiveness of different outcomes. It was used in the 'VALUE' study, which involved a productive collaboration with the UK Multiple Sclerosis Society, to elicit patient preferences for different outcomes in the treatment of multiple sclerosis, and assign weightings that could be used to quantify the relative attractiveness of those outcomes. The study was able to identify factors that influenced patient preferences and willingness to risk adverse effects (notably severity of disease and ability to walk), and showed how input from patients could be used to build decision models for actual treatments.

At the workshop on 26 February 2014, participants had the opportunity to try out the MACBETH software using two examples of cancer medicines. Patients and healthcare professionals were asked to express their preferences for different positive and negative treatment outcomes (such as an increase in overall survival or an increase in the risk of having side effects such as diarrhoea), and to rank the various outcomes in order of importance. The software then translated these data into weightings for the different outcomes to conclude on a positive or negative benefit-risk balance. The exercise gave the opportunity for the participants to gain a better understanding of what type of value judgments need to be taken when making benefit-risk decisions. Both patients and healthcare professionals found it challenging to assign independent values to the different treatment outcomes and also noted that

different patients may have different preferences depending on their particular circumstances. Although further research is needed to understand how this or similar quantitative approaches could be integrated in the benefit-risk assessment, research so far indicates that they could potentially be of help to patients, healthcare professionals, regulators and health technology assessors in identifying the relative importance of the criteria that affect their decisions.

1. MACBETH, http://www.m-macbeth.com

How to explain benefit-risk decisions to stakeholders

Translating benefit-risk information into product information

The product information, which includes the summary of product characteristics (SmPC) and the package leaflet, is an important tool to communicate key information on the benefits and risks of medicines to healthcare professionals and patients. Package leaflets are lay language documents written primarily for the patient taking the medicine. They are based on the SmPC, a more technical document which is aimed at healthcare professionals.

In the SmPC, information should be presented in line with the principles set out in the European Commission's guideline on SmPC. Information on the medicine's benefits is included under section 5.1 ('Pharmacodynamic properties'), which contains a brief description of the mechanism of action and a summary of the main studies carried out in support of the licensing. The study results should be presented both qualitatively and quantitatively and in a concise, clear and balanced way. This would include information on the patient populations studied. Regarding the risks, the SmPC includes under section 4.8 ('Undesirable effects') all side effects for which a causal relationship with the medicine has been established and their frequency category. It also gives detailed information on specific adverse events, and clinically relevant differences in special populations. The SmPC first addresses recommendations that apply to the general patient population, however when relevant information is available it also provides dedicated information for certain subgroups, such as children and older people or patients with co-morbidities, to aid treatment decisions for the individual patient.

Since 2011, more information on treatment benefits has also been included in the package leaflet. This is in line with the expectations of patients, who have advocated developing the package leaflet from 'basic instructions' on how to use a medicine safely into a more comprehensive 'information tool'. Regarding safety, the package leaflet lists all the side effects reported with the medicine under section 4 (Possible side effects), but the most serious reactions are mentioned prominently first, with clear guidance on what actions to take should such effects occur.

The EMA strives to improve the information on medicines in both the SmPC and package leaflet, and to meet the main challenges of providing concise but also comprehensive information, being transparent but not causing undue alarm through inappropriate emphasis on side effects. In 2010, the SmPC Advisory Group was established to provide advice on how to prepare high quality SmPCs and promote consistency between products. In parallel to this work, the EMA is also considering how healthcare professionals might be further involved in the review of SmPCs, also taking into account the experience with the patients' review of package leaflets. Future discussion should also focus on how to establish linkages with eHealth initiatives.

Outcomes of recent EMA/CHMP benefit-risk project (EPAR)

In 2008, a reflection paper on benefit-risk assessment methods was published by the CHMP, which concluded with two main recommendations. The first was to revise the benefit-risk balance section of

the CHMP assessment report to include a more structured description of benefits and risks and their importance in the specific therapeutic indication, and to describe any sources of uncertainty and variability and their impact on the benefit-risk balance. The second was to research methodologies of benefit-risk assessment, in order to improve consistency, transparency and communication of benefits and risks, switching from an implicit to a more explicit decision-making process. As a result of the first recommendation, an updated template for the CHMP assessment report has been used since 2009. To follow up on the second recommendation, in 2009 the EMA started a project to identify decision-making models that could be used when assessing the benefit-risk balance of medicines.[1] After having reviewed and tested different approaches for balancing benefits and risks in decision making, the working group proposed to take forward a qualitative model called PrOACT-URL[2] (Problem formulation, Objectives, Alternatives, Consequences, Trade-Offs, Uncertainties, Risk Attitude and Linked Decisions). This eight-stage model could provide a useful guide to the steps in determining the benefit-risk balance of a medicine. One of the steps of this model suggests the creation of an 'effect table' to display in a compact and consistent way all the favourable and unfavourable effects as well as any uncertainties that are considered as influencing the benefit-risk balance. The effect table is simple to build, and would allow focusing the discussion on relevant issues, improve consistency and the way benefit-risk decisions are communicated. The table will be piloted in CHMP assessment reports in the coming months and is expected to be presented for endorsement by CHMP in the third quarter of 2014. Once endorsed, the effect table will appear in the public assessment report published within the EPAR.

While the PrOACT-URL qualitative model may be sufficient for the more obvious benefit-risk assessments, the working group also suggested that a quantitative tool could be useful for difficult or contentious cases, when for example the benefit-risk balance is marginal and could tip either way depending on judgements of the clinical relevance of the favourable or unfavourable effects. In these cases, a quantitative MCDA (decision analysis modelling)-based model could be developed but it would require more resources/effort to build and further research is needed before implementation.

1. EMA benefit-risk methodology project: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000314.jsp&mid=WC0b01ac0580665b63

2. Hammond, J.S., R.L. Keeney, and H. Raiffa, Smart Choices: A Practical Guide to Making Better Decisions. 1999, Boston, MA: Harvard University Press.

Benefit-risk assessment throughout the medicine's lifecycle: future challenges

In recent years, regulatory agencies have been criticised on the one hand for being overly tolerant of risks and on the other for being excessively risk-averse. This apparent contradiction reflects the difficulty in balancing the expected benefits of a medicine against the harm it might cause once allowed onto the market. At the workshop, three challenges were highlighted that regulators will need to tackle in the near future. The first concerns the availability of evidence on the benefits and risks of a medicine. In the past, the main sources of data assessed by regulators were randomised controlled trials, uncontrolled clinical trials and spontaneous adverse event reports. However, much more information is nowadays generated from other sources, such as registries, observational studies and media reports, which sometimes question regulatory decisions. Regulators are increasingly asked to promptly assess any new data, and be able to revise decisions when new information comes in. New methods able to address data heterogeneity could be explored to assist the assessment process of regulators in such situations.

The second challenge is how to best align acceptance of risks and uncertainty by regulators with the interests of public health. An excessive focus on avoiding risks and uncertainties concerning new medicines might be against the interest of patients, delaying or reducing access to potentially life-saving treatments. Traditionally, regulators have made assumptions about what patients think and prefer. However, recent initiatives taken by regulatory agencies are investigating how patients' values and their willingness to accept risks could be incorporated into licensing decisions.

The last issue discussed was how regulators could help to optimise use of medicines and improve adherence to treatment. For example, modern technologies like text messaging or apps could be used to improve clinicians' communication to patients, and dosing reminders and dosing aids may help with compliance.

Conclusions

There is increasing demand for transparency about how licensing decisions are made – not only in respect to the interpretation of benefit-risk data but also how benefits and risks are valued and balanced off against each other. Several international initiatives are currently exploring methods to help medicines regulators make more structured and transparent benefit-risk decisions. Some of the methods being investigated are based on a mainly qualitative approach while others use a more quantitative approach. The EMA is taking active part in furthering this agenda.

The regulatory decision is only one of the steps to bring a medicine to the patient. It is essential that regulators make clear the factors that influenced their decision, and how each factor was valued in the benefit-risk assessment, since this will help subsequent decision makers, such as health technology assessment bodies and institutions that pay for health services, as well as individual patients and healthcare professionals, make their own decisions.

Recognising that patients are the end users, the EMA will continue to seek their effective involvement in benefit-risk discussions in order to consider their values and preferences appropriately when making regulatory decisions. The input of patients and healthcare professionals is expected to play an increasing role in improving the way benefits and risks are communicated in the product information. In addition, medicines are licensed on the basis of findings from clinical studies, and pre-licensing studies can only provide estimates of benefits and risks. It is therefore important to bring in the real-life experience of the post-marketing phase. To this end, the EMA is working on further developing collaboration with healthcare professionals and in particular general practitioners in order to learn about any differences in benefits and risks in clinical practice and narrow the gap between efficacy and effectiveness.