EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

30 March 2010
EMA/213482/2010
Human Medicines Development and Evaluation

European Medicines Agency Benefit-Risk methodology project

Description of the current practice of benefit-risk assessment for centralised procedure products in the EU regulatory network

Summary of the original report

Introduction

During the March 2008 plenary meeting, the Committee for Human Medicinal Products (CHMP) adopted the Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use (EMEA/CHMP/15404/2007). One of the main recommendations for the CHMP was to explore further methodologies for benefit-risk analysis, including a wide range of quantitative and semi-quantitative tools, and involving assessors and experts. A consequence of this was the initiation of the Benefit-Risk Methodology Project in which the five National Competent Authorities of France, The Netherlands, Spain, Sweden and UK volunteered to participate. A project team was formed involving experts in the field of decision theory. The main objective of this project is to further explore methodologies that can improve the current practice of benefit-risk assessment for medicinal products, with an aim to increase the consistency and transparency of the regulatory process.

This project is planned to be concluded in five subsequent work packages (WPs) and is expected to be completed by the end of 2011. The five WPs are as follows.

1. Current practice of benefit-risk assessment for centralised procedures in the EU regulatory network
2. Applicability of currently available tools and processes for regulatory benefit-risk assessment
3. Adaptation and field testing of recognized tools and processes (from WP 2)
4. Development of a benefit-risk tool/method that can add value in the regulatory process
5. Development of a training package on the new tool/method for regulatory assessors

This current document represents a summary of the report that was produced upon completion of the first WP. The main objective was to describe the current decision making process of benefit-risk assessment for centralised procedures. Two secondary objectives were to suggest actions for improving the current process for assessing the benefit-risk balance and to compose a list of criteria for appraising tools and processes in WP 2.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
An agency of the European Union

Methods and procedure

Between June and September 2009, the project team was invited to visit the five participating agencies (France, The Netherlands, Spain, Sweden and UK). At a later point, Paul-Ehrlich-Institut volunteered to participate in the project and was included in the visits in February 2010.

In order to explore each agency's practice of evaluating and balancing benefits and risks, and to obtain a better understanding of each agency's decision making process, a number of key people (assessors, statisticians, CHMP members, chairmen and directors) were interviewed. The team was also invited to attend a number of internal meetings and discussions. Interviews followed a predefined protocol, developed by the team, which consisted of a list of questions under eight summary headings (table below). The purpose of the visits was observational, with an aim to extract an overall view of how benefit-risk assessment is made Europe-wide, and did not interfere with the agencies' procedures.

Interview protocol
1) Agency's history and purpose 2) Agency's relationships with governmental and non-governmental organisations 3) Agency's organisational structure 4) Information flow 5) Meaning of "benefits" and "risks" 6) Benefit-risk assessment process 7) Consistency 8) Existence of models

Results

Between June and September 2009, the project team was invited to visit the five participating agencies (France, The Netherlands, Spain, Sweden and UK). At a later point, Paul-Ehrlich-Institut volunteered to participate in the project and was included in the visits in February 2010. In total, 55 people, involved in the benefit-risk decision making, were interviewed within the six agencies.

At present, there are no common definitions on the concepts of benefits and risks and no formal guidance on the process of their balancing. As a result, interviewees, between agencies and within the same agency, expressed divergent views on the meaning of benefits and risks, and on their weighing. Especially with regard to risks, there was a great variance of responses. Most notably, the uncertainty of realising a benefit from the use of a pharmaceutical product was frequently mentioned as a risk.

In practice, formulating a benefit-risk balance for a medicinal product is an intuitive and implicit process based on expert judgement. In all the six agencies there was no mention of the use of a validated and structured process for assessing benefits and risks. In contrast, most of the interviewees acknowledged the need for a more systematic approach and the value it can add. A few assessors mentioned the use of a self-constructed and simplistic method for balancing benefits and risks.

The benefit-risk balance is generally considered as the most difficult part of the assessment process, even for experienced assessors. It was mentioned that the most challenging situations are those in which there is substantial uncertainty about the benefits and the risks of a product, the products belong to a new class of drugs, or the products belong to the therapeutic area of oncology.

Discussion/Conclusions

Based on the experience gained from this first phase of the project, the team suggested three actions for improving the current process for evaluating the benefit-risk balance. These suggestions are qualitative and do not aim at the process of weighing benefits and risks; instead they focus on the elements pertaining to the process.

1. To establish commonly agreed definitions for benefits and risks. This may help assessors to structure their assessment and facilitate communication in the different levels of the regulatory process. As a result, the transparency of the regulatory decisions may be increased.

2. To introduce a clear separation between the type of effects that derive from the use of a pharmaceutical product, and the uncertainty surrounding these effects. This can be facilitated by the qualitative model developed by the project team, presented as a table below. Each element of the benefit-risk analysis should have a unique and universal classification based on this model. Prior to forming a benefit-risk balance, the elements pertaining to it should be accordingly separated to each cell.

Four-fold qualitative model	
Favourable effects	Uncertainty of favourable effects
Unfavourable effects	Uncertainty of unfavourable effects

3. Based on the development of the above model, the project team assisted the revision of the benefit-risk section of the CHMP Assessment Report template-guidance, in order for the four-fold model to be incorporated. The new templates were implemented in September 2009.

Next steps

In the next steps (WP 2), the project team will focus on tools and processes that are suitable for regulators, neither overly complex nor too simple, that can add value without disrupting the current workflow.

From the first phase of the project, a list of criteria was composed that is outlined below.

1. Logical soundness
2. Comprehensiveness
3. Acceptability of results
4. Practicality
5. Generativeness

Existing tools and processes that have appeared in the literature, and can potentially aid the regulatory benefit-risk assessment, will be evaluated based on this list of criteria in the second work package.