Benefit-Risk Methodology Project

Project full title

Development and testing of tools and processes for balancing multiple benefits and risks as an aid to informed regulatory decisions about medicinal products

EMEA – CHMP Team:

CHMP Members:
Eric Abadie (Chair)
Gonzalo Calvo Rojas
Pierre Demolis
Pieter De Graeff
Bruno Flamion
Ian Hudson
Tomas Salmonson

EMEA Staff:
Xavier Luria (Sponsor)
Hans-Georg Eichler
Francesco Pignatti
Falk Ehmann
Nikolaos Zafiropoulos
Xavier Kurz
Laurent Brassart

Collaborative Groups

London School of Economics
University of Groningen

INDEX

1. Concept & Objective

1.1 Concept

Pharmaceutical products have become the mainstay of prevention, treatment, and diagnosis of disease. However, modern medicines, while being biologically effective, also have the potential for harm. Balancing the desirable effects (benefits) and undesirable effects (risks) of drugs is the core task of drug regulatory agencies (benefit-risk assessment).

Balancing benefits with risks is complex, as it involves
- uncertainty (difficult to estimate probability of desirable and undesirable effects, effect size, etc. due to limited and sometimes conflicting data),
- multiple objectives (maximising benefits, minimising risks),
- differences in perspectives (patient, societal, regulatory perspectives),
- ill-defined preferences and utilities of outcomes,
- the difficulty of trading off effects of differential importance,
- lack of agreement on what valuation criteria to use, and
- heterogeneity of effects across patient populations.

Faced with the multi-dimensionality of benefit-risk, regulators judgmentally evaluate and synthesize available evidence based on qualitative assessments provided by experts. However, evidence from research in behavioural decision making shows that while expert judgement is good at valuing individual items of evidence, it is less good at synthesizing multiple valuations (Edwards, 1968; Edwards, Phillips, Hays, & Goodman, 1968). In addition, the deliberative reasoning that is required relies on various heuristic methods for simplifying complex problems, often leading to biases in judgments (Kahneman, 2002; Mellers & Locke, 2007).

Furthermore, because of the complexity and the difficulty of synthesizing information, the basis and process of the regulatory decisions is mostly implicit. This in turn creates a problem of communicating the reasons and rationale for regulatory decisions. Yet, transparency, consistency, auditability, and public accountability of regulatory decisions are under increasing scrutiny.

Structured processes that can accommodate data, informed judgement of experts, differences of opinion, and the concerns of stakeholders, are increasingly being used for public policy decisions (Renn, 1999). Research shows that a structured decision approach can lead to better-informed decisions and help legitimize policy decisions (Arvai, McDaniels, & Gregory, 2002).

An EMEA-CHMP working group was set up in 2006 to provide recommendations on ways to improve the methodology and the transparency, consistency and communication of the benefit-risk assessment by the CHMP by making it more explicit as to how the data are used in the benefit-risk assessment.

The group reviewed some well-known methods of benefit-risk assessment, and considered their practical applicability to the CHMP benefit-risk assessment and in March 2008 issued the "Reflection Paper On Benefit-Risk Assessment Methods In The Context Of The Evaluation Of Marketing Authorisation Applications Of Medicinal Products For Human Use" (Annex 1). It contains two main recommendations:

a) To revise the current benefit-risk assessment section of the CHMP assessment report templates, incorporating a structured list of benefit and risk criteria and guidance.

b) To explore further development in methodologies for benefit/risk analysis, including a wide range of quantitative and semi-quantitative tools, e.g. by organising workshops with all stakeholders and specialists of decision-making theory and setting up specific research projects.

The core hypothesis of this research project is that new, structured processes developed specifically for regulatory decision making about medicinal products, could see improvements in the balancing of benefits against risks, thereby benefiting human health.

1.2 Objective

This project is carrying on the second of the above mentioned recommendations in order to adapt or develop tools and processes that could be used to conceptualize and make explicit benefit-risk trade-offs, thereby providing an aid to regulatory decision-making, an aid for training of assessors and an aid for communicating benefit-risk decisions to stakeholders.

2. Overall strategy of the work plan

The basic idea of the work plan is to engage in action research (Argyris, 1993), which requires iterative, collaborative and reflective work among the researchers and participants, leading to useful scientific knowledge about regulatory decision making for medicinal products. The hallmark of action research is to work on a real, live problem facing an organisation. This approach enables researchers to learn what matters and what doesn't, and they are able to determine better what interventions might be useful.

The approach of this project is to work with five European regulatory agencies, exploring the effectiveness of different tools and processes they use while the agency continues, in parallel, to carry out its regular work in its regular way with regard to centralised procedure medicinal products evaluation.

Five specific strategies will accomplish the objectives of this proposal:

- Describe the current practice of benefit-risk assessment for centralised procedure in the EU regulatory network.
- Assess the applicability of current tools and processes for regulatory benefit-risk assessment.
- For one or more domains, develop and field test tools and processes in order to demonstrate their usefulness.
- Using information from the field test, synthesize a benefit-risk tool and process that can add value in other domains.
- Development of a training programme for regulatory assessors.

Considering these strategies, 5 working packages have been defined (see item 3).

3. Detailed work description by work packages (WPs)

3.1 Work Package 1

Work package title: Current practice

Objective
Describe the current practice of benefit-risk assessment for centralised procedures in the EU regulatory network.

Description of work
Through facilitated work groups in each contributing regulatory agency, we will engage participants in making explicit the qualitative processes and quantitative tools that they use in order to make the benefit-risk trade-off and arrive at recommendations. This will be done with a real life issue in the context of centralised procedure for which a particular agency is the (co)Rapporteur.

When selecting contributing regulatory agencies, care will be taken to take into account the heterogeneity of the working models. Given that the contributing Regulatory Agencies were selected to represent the various organisational models present in the EU, it is anticipated that this description of current work practices will also adequately display the heterogeneity present among the regulatory agencies.

The primary task of this work package will be to discover how different agencies take the complex benefit-risk assessment process apart into its constituent parts, how they then deal with evidence on each of the parts and finally how they reassemble the parts.

Secondary tasks will be
- to elicit from assessors opportunities for improvements of the benefit-risk processes
- establish a list of criteria against which the various tools and processes can be appraised. The following criteria, suggested in a conference paper by Larry Lind (2006), will be used as a starting point and will be refined and revisited based on discussions with regulatory agencies:
  - Universal : all interventions and health states
  - Inclusive: multiple benefits and multiple harms
  - Comprehensive: objective and subjective harms and benefits
  - Patient-sensitive: stratified risk analysis
  - Easily interpreted: by all potential stakeholders/perspective
  - Explicit preferences: for both harms and benefits
  - Threshold: inherently defined Harm-Benefit threshold
  - Incorporates uncertainty: quality and source of data, and in the final metric
  - Flexible/Adaptable: rapid, efficient, incorporate new knowledge

Deliverables
Report on the current decision-making processes and models. Included in the report will be a list of perceived opportunities for improvements and a revised list of criteria for appraising the tools and processes with an indication of which ones, either singly or in combination, will be most useful to be tested in WP2.

3.2 Work Package 2

Work package title: Applicability of current tools and processes

Objective
Assessment of the applicability of current tools and processes for regulatory benefit-risk assessment

Description of work
First, we will review the literature on benefit-risk assessment outside the field of pharmaceuticals, e.g. oil & gas explorations, nuclear power & nuclear waste disposal, environmental risk assessment, decision and risk analysis. The elements that will be extracted are methods for:

i) dealing with uncertainty
ii) accommodating multiple benefits and risks, and trade-offs among them
iii) resolving differences in perspectives
iv) managing complexity.

Examples of methods that may be reviewed are:
- Number Needed to Treat (NNT), Number Needed to Harm (NNH)
- Incremental Net Health Benefits (INB)
- Health Outcomes Modeling with Quality-Adjusted Life-Years (QALYs)
- Stated Preference Risk-Benefit Trade-Offs
- Multi-Criteria Decision Analysis
- Semi-Quantitative Structured Framework for Benefit-Risk Assessment.

Second, the applicability of the tools and processes will be assessed against criteria that are relevant to benefit-risk assessment in the regulatory context (i.e. as assessed through our interviews with the contributing regulatory agencies). Potential areas of improvements and the list of criteria identified in WP1 will be used to identify methods or a combination of methods relevant to be considered in further steps.

Third, we will consider the stage at which the benefit/risk discussion could benefit from new tools and processes. It is possible that the new approaches could be useful in pre-approval discussions between regulatory authorities and pharmaceutical companies, particularly as the latter are beginning to use more structured approaches for their own decision making. We will certainly look at the final approval process, but it may also be helpful to see how any new approaches might also be useful in post-marketing surveillance issues brought to the attention of regulatory authorities.

Deliverables
- A report that lists available tools and processes and that provides a matrix of available methods against the criteria identified in Work plan 1.
- A road map for the field tests.

3.3 Work Package 3

Work package title: Field tests

Objective
For one or more domains, develop and field test tools and processes in order to demonstrate their usefulness.

Description of work
With contributing regulatory authorities, domains will be identified in which the tools and processes will be developed and tested. Such domains will be chosen so that they represent relevant and different benefit-risk situations. We will work with experienced regulators in the collaborating agencies to develop processes to supplement and enhance existing processes.

This will be achieved by working in parallel with normal procedures. Participants will be conducting their assessments as usual. Information collected from normal procedures will include the benefits and risks associated with a given issue, how the available evidence bears on those benefits and risks, how the differential importance of those benefits and risks were considered, and how trade-offs were made in arriving at the final benefit-risk conclusions. This information will be used in developing tools and processes applicable to this issue.

It is important to recognise that this action research programme differs from experimental research in which control groups, randomisation and blind trials are used to test statistical and scientific hypotheses. Action research proceeds differently: the investigators work with rather than on the people engaged in the processes that are the subject of the study. An iterative, collaborative approach is taken in which the researchers work with people in the organisation being studied, helping to develop new approaches to problem-solving, observing results, but also reflecting with the participants to evaluate the results, learn from them, and continue to develop improved processes and tools (Reason & Bradbury, 2001). Theorising, data collection and systematic enquiry by the researchers and participants becomes a continuous process throughout the investigation. The study typically ends with the formulation of working hypotheses that can then be further tested for their generality and usefulness in new situations.

Deliverables
For each of the field tests, a report summarising the exercise and identifying those processes, tools and organisational structures that were considered to add value to the process of benefit-risk assessment by regulatory authorities.

3.4 Work Package 4

Work package title: Development of benefit-risk tool and process

Objective
Synthesize information from the field test and develop a benefit-risk tool and process that can add value in other domains. Alternatively, if research establishes, for example, that different levels of complexity in balancing benefits against risks require different approaches, then this work package will outline how the tools and processes are contingent on the level of complexity.

Description of work

The information from the field tests will be integrated to develop a new method that may be used as a decision-aid for benefit-risk assessment by regulators.

The added value of the new method will be appraised by answering the following questions:
- Will this method help regulators make use of all the available relevant information?
- Does it help to aggregate multiple sources of evidence?
- Does it help regulators to provide structure to the discussion of benefit-risk assessment?
- Does it help regulators deal with uncertainty?
- Does it help regulators make their assumptions, values and trade-offs explicit?
- Does it help refine the regulatory opinions (e.g. indications, restrictions, dosages, etc.)
- Does it help regulators anticipate possible consequences of deviations from recommended conditions of use?
- Does it help to resolve differences of opinion between assessors?
- Does it enhance consistency of benefit-risk assessment?
- Does it aid in writing up the assessment report?
- Does it facilitate the communication of the benefit-risk assessment to external stakeholders?
- Does it enable the different perspectives of stakeholders to be tested for their impact on the results?

The experienced regulators participating in the study will answer these questions using Likert rating scales (Likert, 1932), which will provide a comparison with the new method. Average scores for each of the above 12 questions will provide an overall indication of the extent that value is added by each method, and discriminant statistical analyses will be conducted to determine the most salient features of the new method. This will enable the decision aid to be focussed on its most important contributions to aiding the benefit-risk assessment process. We would then be able to provide guidance about the circumstance under which each decision aid would provide added value. For relatively straight-forward approvals, we might find that no aid at all could add value.

Deliverables
- An operational decision-aid, which is sufficiently flexible that it can be tailored to the needs and requirements of individual regulatory agencies for select cases.

- A consultative workshop will be held to inform and engage interested stakeholders in order to explore the acceptability and the potential implementation of the tools and processes.

3.5 Work Package 5

Work package title: Training package

Objective
Development of a training package for regulatory assessors.

Description of work
The experience gathered with the development of the decision-aid in collaboration with regulatory agencies will be translated into a training module for junior assessors in European regulatory agencies. The purpose of this training will be to enhance the capabilities of users to bring structured judgement to the process of assessing benefit-risk. As such, the training would concentrate on those issues that are generic to most drug approvals. But we would also show how the new approaches can be extended to enable criteria and other context-relevant considerations that are unique to each individual situation could be brought to bear on the benefit/risk discussion, if extending the analysis were thought to be worth the effort.

Deliverables
Training materials containing the following:
- Printed hand-outs
- Real life case-studies based on published data
- Set of PowerPoint presentations
- Supporting computer software enabling the testing of different assumptions, carrying out sensitivity analyses and exploring alternative scenarios.

These training materials will be available in electronic format and will be sufficient for a dedicated benefit-risk assessment module.

These training materials will be made available to regulators, academics and the pharmaceutical industry.

4. Timing of the project

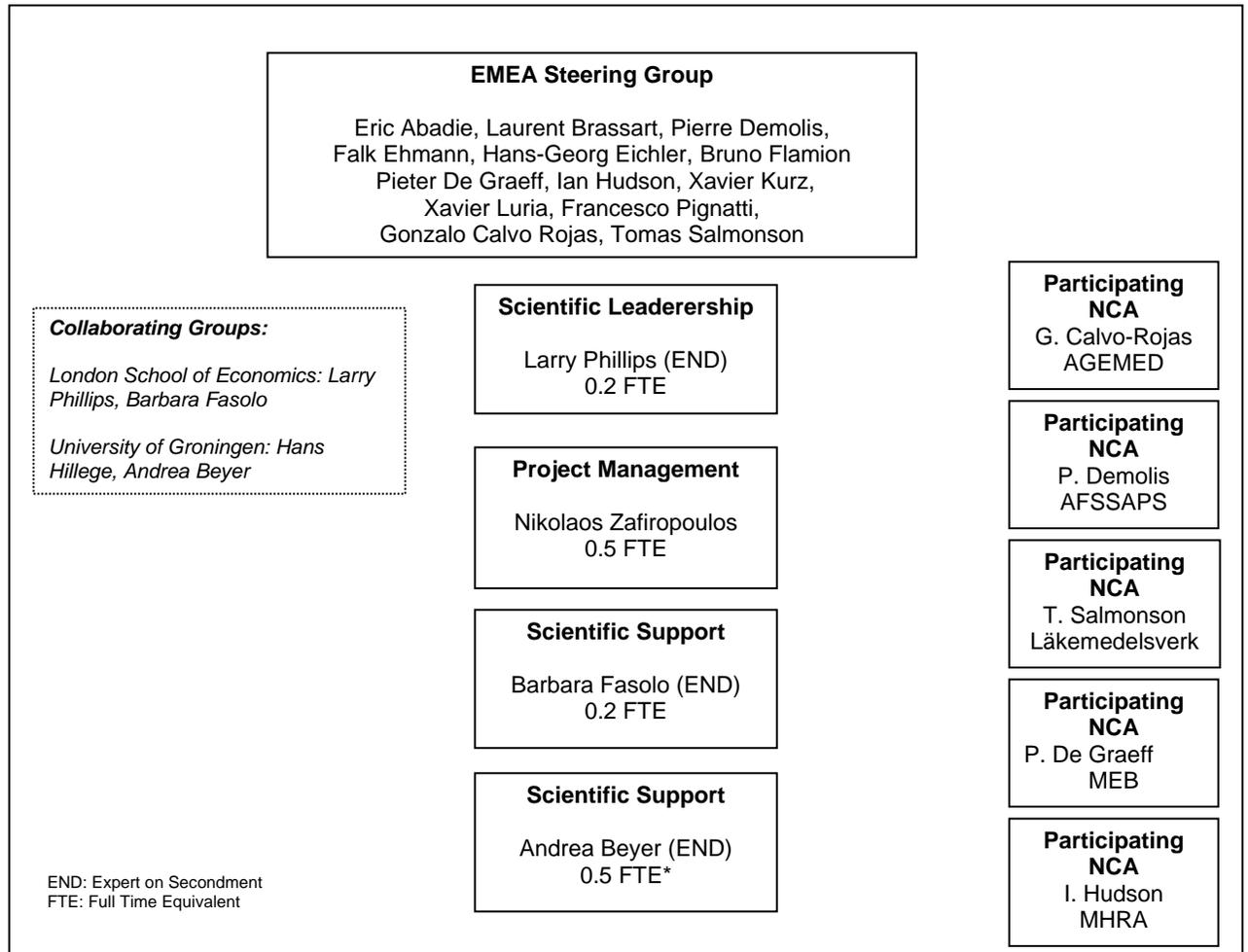| 1/2009 – 12/2009	• Report on the current practise of benefit-risk assessment in the EU regulatory network (WP1) • Report on the applicability of available tools and processes for regulatory benefit-risk assessment (WP2)
1/2010- 12/2010	• Development and field test of proposed tools and processes (WP3) • Adaptation of the tested tools and processes (WP4) • Consultative workshop with interested stakeholders (WP4)
1/2011-12/2011	• Development of a training programme for regulatory assessors (WP5)

5. Management structure and procedures

5.1 Management

The project is a EMEA-CHMP initiative, integrated as well in the CHMP Work Plan 2008-2010, and therefore a Steering Group is created. This Group will be chaired by the CHMP Chair and will be in charge to review and monitor the progress of the project. The Group will decide when a report from a Work Package requires to be addressed to the CHMP and to EMEA Management. It will meet or have a teleconference at least one every quarter.

Human Pre Unit/ S&E Sector is the responsible of implementation and operations of the project and it will work in conjunction with the Senior Medical Officer of the EMEA. Scientific Leader, Project Manager/s, Scientific Support, etc will be located in this Sector and they will produce a monthly progress report to be emailed to all Steering Group members. Additionally a specific report will be issued at the conclusion of each Work Package and at the end of the project.

Larry Philips, from the LSE, will act as Scientific Leadership.

5.2 Project structure

EMEA Steering Group

Eric Abadie, Laurent Brassart, Pierre Demolis,
Falk Ehmann, Hans-Georg Eichler, Bruno Flamion
Pieter De Graeff, Ian Hudson, Xavier Kurz,
Xavier Luria, Francesco Pignatti,
Gonzalo Calvo Rojas, Tomas Salmonson

Collaborating Groups:

London School of Economics: Larry Phillips, Barbara Fasolo

University of Groningen: Hans Hillege, Andrea Beyer

Scientific Leaderership

Larry Phillips (END)
0.2 FTE

Project Management

Nikolaos Zafiropoulos
0.5 FTE

Scientific Support

Barbara Fasolo (END)
0.2 FTE

Scientific Support

Andrea Beyer (END)
0.5 FTE*

END: Expert on Secondment
FTE: Full Time Equivalent

Participating NCA
G. Calvo-Rojas
AGEMED

Participating NCA
P. Demolis
AFSSAPS

Participating NCA
T. Salmonson
Läkemedelsverk

Participating NCA
P. De Graeff
MEB

Participating NCA
I. Hudson
MHRA

6. Contribution of the project

6.1 Expected impacts

- Improve the quality of regulatory benefit risk assessments
- Improve transparency of benefit risk communication with stakeholders
- Increase public confidence in regulatory decision
- Make benefit-risk assessments more predictable, making drug development more efficient, thereby fostering innovation in the pharmaceutical field
- Facilitating submission of Marketing Authorisation Application
- Contribute to harmonisation of benefit risk assessment across the European regulatory network

6.2 Spreading excellence, disseminating knowledge

Publication of results of the research in refereed journals is anticipated, and the training programme will make the results widely available. It is not sufficient for new tools and processes simply to be published. Action research programmes have shown that for lasting organisation change to be effected, it is necessary to show organisations how to use the tools and processes, for they will inevitably have to be adapted to the culture and context of each regulatory authority.

References

Argyris, C. (1993). *Knowledge for Action: A Guide to Overcoming Barriers to Organizational Change*. San Francisco: Jossey-Bass.

Arvai, J. L., McDaniels, T., & Gregory, R. (2002). Exploring a structured decision approach as a means of fostering participatory space policy making at NASA. *Space policy, 18*(3), 221-231.

CIOMS_IV. (1999). *Benefit-Risk Balance for Marketed Drugs. Evaluating Safety Signals*. Geneva: Council for International Organizations of Medical Sciences.

Edwards, W. (1968). Conservatism in human information processing. In B. Kleinmuntz (Ed.), *Formal representations of human judgment* (pp. 17-52). New York: Wiley.

Edwards, W., Phillips, L. D., Hays, W. L., & Goodman, B. (1968). Probabilistic information processing systems: Design and evaluation. *IEEE Transactions on Systems Science and Cybernetics, SSR-4*, 248-265.

Kahneman, D. (2002). *Maps of bounded rationality: A perspective on intuitive judgment and choice*. The Nobel Foundation. Retrieved December 8, 2002, 2002, from the World Wide Web:

Likert, R. (1932). A technique for the measurement of attitudes. *Archives of Psychology, 140*(55), 44-53.

Lind, L. (2006). Methods in quantiative benefit-risk assessment, *ISPE 22nd Conference on Pharmacoepidemiology & Therapeutic Risk Management*. Lisbon.

Mellers, B., & Locke, C. (2007). What have we learned from out mistakes? In W. Edwards & R. F. Miles Jr. & D. von Winterfeldt (Eds.), *Advances in Decision Analysis: From Foundations to Applications* (pp. 351-374). Cambridge: Cambridge University Press.

Renn, O. (1999). A model for an Analytic-Deliberative Process in Risk Management. *Environmental Science and Technology, 33*(18), 3049-3055.

Annex 1: Reflection Paper on Benefit-Risk

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**REFLECTION PAPER ON BENEFIT-RISK ASSESSMENT METHODS IN THE
CONTEXT OF THE EVALUATION OF MARKETING AUTHORISATION
APPLICATIONS OF MEDICINAL PRODUCTS FOR HUMAN USE**

DISCUSSION OF FINAL REPORT BY CHMP	*22 JANUARY 2007*
DEADLINE FOR COMMENTS	*13 FEBRUARY 2007*
ADOPTION FOR RELEASE FOR PUBLIC CONSULTATION	*19 FEBRUARY 2007*
DEADLINE FOR COMMENTS	*29 MAY 2007*
DISCUSSION OF REVISED REPORT BY CHMP	*FEBRUARY 2008*
ADOPTION BY CHMP	*19 MARCH 2008*

REPORT OF THE CHMP WORKING GROUP ON
BENEFIT-RISK ASSESSMENT METHODS

EXECUTIVE SUMMARY

The assessment of the benefits and risks in the context of a new drug application is a complex process that requires evaluation of a large amount of data.

A CHMP working group was set up to **provide recommendations on ways to improve a) the methodology, and b) the consistency, transparency, and communication** of the benefit-risk assessment by the CHMP.

The group reviewed some well-known methods of benefit-risk assessment, and considered their practical applicability to the CHMP benefit-risk assessment.

Expert judgment is expected to remain the cornerstone of benefit-risk evaluation for the authorisation of medicinal products. Quantitative benefit-risk assessment is not expected to replace qualitative evaluation. Nevertheless, several features of the benefit-risk analysis methods are of interest, such as:

- The most important benefits and medically serious risks that drive the assessment can be identified more clearly.

- Explicit weights are assigned to individual benefits and risks depending on their importance.

- The strengths of evidence and uncertainty are identified and quantified.

Following this analysis, the working group recommends that the CHMP works in two steps:

1) **To revise the current benefit-risk assessment section of the CHMP assessment report templates, incorporating a structured list of benefit and risk criteria and guidance.**

1.1 A proposal for modification is provided **(Annex 1)**. The main features are:

- To use a structured and mainly qualitative approach.

- To be explicit about the importance of benefits and risks in the specific therapeutic context.

- To describe sources of uncertainty and variability and their impact on the benefit-risk assessment.

1.2 The proposal has been revised based on comments received during the public consultation

1.3 The new templates should be pre-tested on a few completed applications for which an assessment is available using the old template. Following this phase, model templates will be produced for testing using a few new applications, at different stages of the procedure. Following this phase, the CHMP shall consider the need to seek input of other stakeholders as necessary for further revision.

1.4 Implementation phase: The roll-out of the new templates will be preceded by training of assessors, to be continued on a regular basis, and monitoring.

2) **To further research the methodology of benefit risk assessment, involving further experts and assessors.**

- To explore further development in methodologies for benefit/risk analysis, including a wide range of quantitative and semi-quantitative tools, e.g. by organising workshops with all

- The CHMP should continue to interact with relevant stakeholders on international and European initiatives related to the benefit-risk assessment methods

1. Background and problem statement

The assessment of the benefits and risks **in the context of a new drug application** is a central element of the scientific evaluation of a marketing authorisation application and related variations. The assessment must reach, as objectively as possible, a sufficient level of confidence that a set level of quality, efficacy and safety of the new medicinal product has been demonstrated. This requires evaluation of all relevant data as well as the use of judgement and arguments. Article 26 of Directive 2001/83 as amended states that the marketing authorisation shall be refused "if the benefit-risk balance is not considered to be favourable or if therapeutic efficacy is insufficiently substantiated". The CHMP is endowed with the task of assessing the benefit-risk balance of new medicinal products. Questions have been raised regarding a) the optimal methodology to establish the benefit-risk balance of new medicinal products, and b) the consistency and transparency of the methods used by the CHMP to reach conclusions on benefit-risk.

In 1998, the Council for International Organizations of Medical Sciences (CIOMS) stated that "it is a frustrating aspect of benefit risk evaluation that there is no defined and tested algorithm or summary metric that combines benefit and risk data and that might permit straightforward quantitative comparisons of different treatment options, which in turn might aid in decision making" (CIOMS, 1998). Of note, none of the main regulatory authorities (EU, US, Japan) has issued a list of benefit and risk criteria, and detailed CHMP guidance on the principles and methodology for benefit risk assessment is currently lacking. The CHMP assessment report template entails summaries of the main evidence from the different parts of the dossier and sets out the main aspects of the actual benefit risk assessment. However there is no agreed approach on the methodology to estimate the overall benefit risk balance or on how to describe the way the evidence is weighed and balanced.

Following the CHMP audit in November 2004 and in relation with OFI No A04010-02 (benefit-risk analysis), the need to improve the methodology for benefit risk analysis has been recognised. The CHMP set up a working group to deal with this matter, aiming to improve the consistency, transparency, and communication of the benefit risk assessment in CHMP assessment reports.

2. EVALUATION OF THE CURRENT SITUATION AND Examples of Methods of Benefit/Risk Assessment

The working group first reviewed the way CHMP conducts benefit-risk evaluations for the authorisation of medicinal products. Real examples of marketing authorisation processes and CHMP assessment report templates were examined thoroughly. Indisputably, expert judgement has been the cornerstone of the benefit-risk evaluations for the authorisation of medicinal products.

The working group also recognized that a number of quantitative and semi-quantitative methods have been proposed to aid the scientific review of drug applications. These methods are designed to weigh all the relevant efficacy and safety data and to incorporate value judgements as objectively and explicitly as possible into a single construct, reflecting the intellectual process of assessing the empirical evidence and uncertainties, accommodating risks and balancing risks and benefits. The working group thus decided to review some well-known methods of benefit-risk assessment described in the literature. The aim of this review was to assess the need for conducting a more comprehensive examination of available methods for benefit-risk assessment, and the need to explore further development in tailored methodologies for benefit-risk analysis.

There is a wide range of quantitative and semi-quantitative methods that can be considered for benefit-risk analysis. A non-exhaustive list of examples is referenced at the end of this document. Some of the simpler methods are intended to be used for individual clinical trials, such as for

example the Number Needed to Treat/Number Needed to Harm (NNT/NNH) method. More general methods, such as for example the "Principle of three" and the TURBO methods have been developed for the reassessment of marketed medicines in case of new safety issues as described in the report of the CIOMS Working Group IV entitled: "Benefit risk balance for marketed drugs: evaluating safety signals" (CIOMS, 1998). Another method with applications in medicine is multi criteria decision analysis (MCDA), which is also widely used in business and government decision-making. The working group decided to consider this method in more detail (see below). Several methods have also used quality-adjusted life years (QALYs), which is a way of measuring both the quality and the quantity of life lived, as a means of quantifying the benefit of a medical intervention. Finally, besides the few examples mentioned here, there is a large body of research developed by pharmaco-epidemiologists or derived from pharmaco-economics on quantitative and semi-quantitative methods developed for benefit-risk assessment. Some of them have been used essentially in the pharmacovigilance field or for purposes of reimbursement. Most of these methods are still in the research domain and their validity and usefulness remain to be tested in various contexts.

The different methods differ in terms of a number of important characteristics in the context of the scientific review of a drug application, such as simplicity of use and the ability to explore different situations and assumptions. Simple methods such as the NNT and NNH as opposed to complex mathematical methods are often preferred by clinicians and reimbursement bodies because they are based on few criteria and are easy to use and to interpret.

More complex methods such as the MCDA, or methods that deal with multiple benefits and risks such as those described by Holden et al. (2003), are able to combine judgements and data numerically by assigning weights to the scores given for each of the benefit and risk criteria in a transparent way. Interestingly, MCDA strategies do not simply provide a single score. They provide the degree to which every sub-score and input contributes to that score and can incorporate an element of uncertainty. Many MCDA software tools allow visual and numeric comparison of sub-scores and input contributions for different activities/projects being scored. Similar static and interactive visualizations provide insight into the qualitative nature of the quantitative differences. MCDA strategies are used to inform decision-makers of areas worthy of scrutiny and focus and are not intended for a critical use of the score *per se*. These strategies are also used to gain understanding and articulate the divergence between relevant stakeholders. They can thus lead to a more transparent decision-making process.

Inherently to the practice of epidemiology, many methods can incorporate uncertainties in a formal way. Indeed, the more sophisticated methods incorporate uncertainty about the estimation of certain statistics derived from the data and include the variability derived from the different subjective perceptions between assessors of the importance of different variables and results. For instance, utility functions can be replaced with expected utility functions, which incorporate risk tolerance [Kirkwood, 1997]. Alternatively, the inputs can be characterized with confidence intervals or probability distributions and the uncertainties carried through to the method output. The effect is to provide a probability density function for the method score rather than a single value. Decisions can be based on summary metrics computed from this probability density function, for example the probability that the score exceeds a threshold or lies between two thresholds.

One potential issue with MCDA strategies is the lack of a dependence structure among the different variables (which are often treated as statistically independent). For methods that treat all values and weights as independent of each other without an appropriate dependence structure, the results of sensitivity analyses might be of limited value. This issue can partly be addressed by redefining or combining inputs so they are more preferentially independent than when initially created [Keeney, 1992].

3. Discussion

Expert judgement has been the cornerstone of CHMP benefit-risk evaluation for the authorisation of medicinal products. Although this is not expected to change in the near future, a number of quantitative and semi-quantitative methods designed to weigh all the relevant efficacy and safety data together with value judgements have been proposed. These methods can be useful because:

a) they may stimulate a structured discussion between reviewers on the importance of different data;

b) they could highlight divergences between different stakeholders and lead to a more focussed dialogue;

c) they could help visualise the strength of assumptions and sensitivity to different weights, highlighting and contrasting the qualitative differences.

General principles of benefit-risk assessment

Under Community law (Regulation 726/2004), in the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations such as "cost-effectiveness".

The assessment of the benefit-risk balance should be based on the available tests and trials, which are designed to determine the efficacy and safety of the product under normal conditions of use (Directive 2001/83), and which are generally performed under ideal conditions.

It is important to be explicit about the perspectives of different stakeholders that are taken into account in the assessment of the benefit-risk balance, in particular the perspectives of patients and treating physicians.

Considerations about how the treatment is expected to perform under real conditions of use are relevant in the context of pharmacovigilance activities, for example, to take into account any available information on misuse and abuse of medicinal products which may have an impact on the evaluation of their benefits and risks (Directive 2001/83).

Benefit-risk analysis methods may improve interactions between different assessors and stakeholders

Benefit-risk analysis methods and tools should be regarded as tools to help assessors make benefit-risk decisions. These methods can help to describe and incorporate the uncertainties and variability in perceptions by different assessors and stakeholders. However, these methods should not be used to shift the focus of benefit-risk assessment to overall numerical summaries at the expense of information on the qualitative differences. Each method should be understood as having a margin of error, and users of these methods should have this uncertainty in mind. In the benefit-risk context, excessive reliance on the overall score obtained might amount to making the final decision in one way or another if the score is above or below a predefined threshold. When comparing scores, thresholds can again serve to partition a score difference into ranges with different actions for each range. However, these actions should generally not be decisions on whether to approve a drug or not, but suggestions for the type of assessment activity experts should perform to complete a decision.

The scientific review of a drug application by the CHMP occurs in successive steps as the dossier is updated and issues are resolved during the review. This involves a large number of reviewers and stakeholders. Thus, simplicity of use would be an obvious advantage of any method for benefit-risk analysis. Simple methods do not require time-consuming specification of a complex method structure for every situation, therapeutic area, or even product or indication. However,

their simplicity can be a disadvantage in the context of a complex benefit-risk assessment where multiple benefits and risks variables, from binary to continuous, each with different weights and dimensions, need to be incorporated into the method. The danger of methods that are too simple is that of reducing complex issues to over-simplified abstract numerical quantities.

Benefit-risk analysis methods can focus the discussion by highlighting the divergences between assessors and stakeholders concerning choice for weights. The benefit of such analysis methods is that the degree and nature of these divergences can be assessed, even in advance of any compound's review. The same method might be used with the weights (e.g., of different stakeholders) and make both the differences and the consequences of those differences more explicit. If the analyses agree, decision-makers can be more comfortable with a decision. If the analyses disagree, exact sources of the differences in view will be identified, and this will help to focus the discussion on those topics.

Benefit-risk analysis methods can increase the transparency of decisions

An important area for improvement would be to make more explicit the criteria on which a benefit-risk evaluation is being made. Although the systematic use of sophisticated numerical methods may not be necessary, especially when the benefits clearly outweigh the risks (or *vice versa*), they might be useful in less clear situations. Such methods could allow different assessors and stakeholders to be explicit about the importance given to different data. This could lead to increased transparency and better communication about the benefit-risk assessment process. All these aspects could be reflected into CHMP guidance and templates for the benefit-risk assessment.

The revision of the benefit-risk section of the templates should undergo adequate testing before implementation.

In a first phase of pre-testing, different assessors (not involved in the revision phase), should use the revised template for a few completed applications for which an assessment is available using the old template. This should be followed by structured discussion with the assessors, seeking to identify completeness and relevance of the items in proposed in the new template. Other assessors could be called to compare the former templates with the new ones. Depending on the findings of the pre-testing phase, it may be necessary to adapt the templates.

Following the pre-testing phase, model templates should be produced for testing. The model templates for the benefit-risk section should be tested on a few new applications for the rapporteurs and CHMP assessment reports. Complete assessment reports should still be produced using the current templates. Along with the current templates, the test model templates for the benefit-risk section should be produced simultaneously by both rapporteurs and collected separately. The test model templates should not be circulated to the CHMP or the applicant and should not be considered as part of the assessment report. The collected test model templates should be reviewed at the end of the testing phase by a group of assessors and CHMP members, who should make recommendations for further changes, if necessary. Following the testing phase, the CHMP should consider the appropriateness of any changes to the model templates and, if appropriate, timing for implementation. The CHMP should consider the need to seek input of other stakeholders as necessary for further revision.

The roll-out and implementation of the new templates should be preceded by training of assessors, to be continued on a regular basis, and monitoring.

Benefit-risk analysis methods may be useful beyond initial drug marketing authorisation

It is important that the same benefit-risk principles are consistently applied in the pre- and post-authorisation phases. Quantitative approaches to benefit-risk might also be useful for the

continuous evaluation of products post-approval. The current report is heavily weighted to the initial benefit/risk assessment related to the decision to approve or not approve a new medicine. It is recommended that this work be expanded to include a further examination of the question of how to incorporate post-approval safety/effectiveness data into the risk/benefit analysis (lifetime approach). More generally, benefit-risk assessment is a key component of a number of EMEA activities, and adequate involvement of relevant working parties and committees should be sought (e.g., Pharmaco Vigilance Working Party) as well as sharing of information with other committees (e.g., Committee for Medicinal Products for Veterinary Use, Committee on Herbal Medicinal Products).

Conclusion on benefit-risk analysis methods

Even if no single method is suitable in practice for conducting benefit-risk assessment in the context of the CHMP scientific review of drug applications, there may be a number of theoretical and practical aspects of decision-making theory that can be useful to refine the CHMP assessment, stimulate further work and suggest different approaches. Interest for this field of research should continue and exchange with experts could be sought on a regular basis, in the form of workshops or research projects. Proper validation of any useful methods in the context of CHMP review will be essential. Furthermore, given the knowledge and experience within the EMEA and CHMP, it will be possible to explore further development in tailored methodologies for benefit/risk analysis.

4. Recommendations to the CHMP

The recommendation of the working group to the CHMP is to work in two steps:

1) **To revise the current benefit-risk assessment section of the CHMP assessment report templates, incorporating a structured list of benefit and risk criteria and guidance (Annex 1).**

1.1 A proposal for modification is provided. The main features are:

- To use a structured and mainly qualitative approach.

- To be explicit about the importance of benefits and risks in the specific therapeutic context.

- To describe sources of uncertainty and variability and their impact on the benefit-risk assessment.

1.2 The proposal has been revised based on comments received during the public consultation

1.3 The new templates should be pre-tested on a few completed applications for which an assessment is available using the old template. Following this phase, model templates will be produced for testing using a few new applications, at different stages of the procedure. Following this phase, the CHMP shall consider the need to seek input of other stakeholders as necessary for further revision.

1.4 Implementation phase: The roll-out of the new templates will be preceded by training of assessors, to be continued on a regular basis, and monitoring.

2) **To further research the methodology of benefit risk assessment, involving further experts and assessors.**

To explore further development in methodologies for benefit-risk analysis, including a wide range of quantitative and semi-quantitative tools, e.g. by organising workshops with all stakeholders and specialists of decision-making theory and setting up specific research projects.

- The CHMP should continue to interact with relevant stakeholders on international and European initiatives related to the benefit-risk assessment methods

REFERENCES

- **Laupacis A, Sackett DL, Roberts RS. An assessment of clinically useful measures of the consequences of treatment. *N Engl J Med* 1988; 318(26):1728-33.**

- **CIOMS Working group IV. Benefit risk balance for marketed drugs: evaluating safety signals. CIOMS, Geneva, 1998.**

- **Holden WL. Benefit-risk analysis: a brief review and proposed quantitative approaches. *Drug Saf* 2003; 26(12):853-62.**

- **Heeley E, Waller P, Moseley J. Testing and implementing signal impact analysis in a regulatory setting: results of a pilot study. *Drug Saf* 2005; 28(10):901-6.**

- **Mancini GBJ, Schulzer M. Reporting risks and benefits of therapy by use of the concepts of unqualified success and unmitigated failure: applications to highly cited trials in cardiovascular medicine. *Circulation* 1999; 99(3):377-83.**

- **Mussen F. The evaluation of methods for benefit risk assessment of medicines and the development of a new model using multi criteria decision analysis. Doctoral Thesis, University of Wales, 2005.**

- Holden WL, Juhaeri J, Dai W. Benefit-risk analysis: a proposal using quantitative methods. *Pharmacoepidemiol Drug Saf* 2003; 2:611-6.

- Beckmann J. Basic aspects of risk-benefit analysis. *Semin Thromb Hemost* 1999; 25:89-95.

- Waller PC, Evans SJW. A model for the future conduct of pharmacovigilance. *Pharmacoepidemiol Drug Saf* 2003; 12:17-29.

- Lynd LD, O'Brien BJ. Taking calculated risks: advances in risk-benefit evaluation using probabilistic simulation methods. *J Clin Epidemiol* 2004; 57: 795-803.

- Hauber AB, Johnson FR, Andrews EA. Risk-benefit analysis methods for pharmaceutical decision-making – Where are we now? *ISPOR Connections* 2006; 12(6):3-5.

- Garrison LP Jr, Towse A, Bresnahan BW. Assessing a structured, quantitative health outcomes approach to drug risk-benefit analysis. *Health Affairs* 2007; 26:684-695.

- Hughes DA, Bayoumi AM, Pirmohamed M. Current Assessment of risk-benefit by regulators: is it time to introduce decision analyses? *Clin Pharmacol Ther* 2007; 82: 123-7.

- **Honig P. Benefit and risk assessment in drug development and utilization: a role for clinical pharmacology. *Clin Pharmacol Ther* 2007; 82:109-12.**

- Johnson FR, Ozdemir S, Mansfield C, Hass S, Miller DW, et al.. Crohn's disease patients' risk-benefit preferences: Serious adverse event risks versus treatment efficacy. *Gastroenterology* 2007; 133(3):769-79.

- Kirkwood CW. Strategic Decision Making: Multiobjective Decision Analysis with Spreadsheets. Wadsworth Publishing Co, Belmont, CA, USA, 1996.

- Keeney RL. Value-Focused Thinking: A Path to Creative Decision-making. Harvard University Press, Cambridge, MA, USA 1992.

ANNEX I

Proposed changes and guidance for the benefit risk assessment section of the CHMP assessment reports

---

BENEFIT RISK ASSESSMENT

The aim of this section is to identify the key observations and the uncertainties that drive the benefit risk assessment. It is important to avoid unnecessary repetition of technical details already described elsewhere, particularly concerning the methods and the results of the various tests and trials. Here, only the key findings should be briefly identified but no extensive description should be provided.

- First, it is recommended to **identify the main evidence and the uncertainties** that are considered key for the benefit–risk assessment. In this respect, a list of benefit and risk criteria is provided. The list is extensive, and what needs to be included has to be considered on a case by case basis.

- Second, important benefits, risks are compared to each other in the specific therapeutic context, and a conclusion is made on the benefit-risk balance, explaining as much as possible, principles, relationships between the data and the conclusions, and unsettled issues.

Guidance is provided on how to describe as objectively as possible and how to be explicit about the arguments to support the conclusions. This is done, for example, by describing weights given to the expected benefits and the perception of what are acceptable levels of risk relative to these benefits in the specific context.

Compared to the former template, the main differences are in terms of structure and recommendations to document the subjective judgements explicitly. The aim is to avoid repetition and separate enumeration of quality topics, non-clinical issues, clinical efficacy, and safety results, without clearly stated relationship to the conclusions. Instead, the new structure encourages a description of significant findings and uncertainties in terms of their impact on the assessment of benefits and risks.

Although **the proposed template has been designed with the final CHMP assessment report in mind**, similar templates should be developed for all assessment reports and the section could be updated as the scientific review is conducted.

Introduction

The objective of this introductory section is to briefly summarise the background of the disease and its treatments (e.g., life-threatening vs. self-limited disease, availability of treatments) for determining the medical need in terms of benefits and the acceptable risks. This may be complex if the indication includes different situations (multiple indications, populations or dosages) with different benefit-risk categories.

- Briefly state the problem statement (the details should be left to the Introduction section, at the beginning of the CHMP assessment report, see current templates). Ensure that the claimed therapeutic indication is clearly stated. Specify the therapeutic alternatives that are relevant for this benefit-risk assessment, including other treatment modalities, their purpose or intended outcome (a new treatment is evaluated against the background of currently available treatment options and standard of care).

- Discuss in general terms the aims of treatments and attempt to establish bounds of acceptability – namely criteria against which a drug must perform. For instance, define

Demonstrated benefits and uncertainties

The aim of this section is to identify the benefits, and discuss them critically. **Only the important results and issues that have an impact on the benefit-risk balance should be described.** In addition, **unresolved issues or uncertainties should be identified** and their impact on the balance assessment should be clearly stated.

There is a primary requirement for convincingly demonstrated efficacy. Benefits are usually described as the positive results for an individual or a population, and the probability of achieving such results. As a possible guide for this section, consider describing any of the following points. (This is not a list of mandatory points to be described. The need to discuss or not each point has to be judged on a case by case basis).

For main trials,

- Describe the main benefits versus comparator, for example, in terms of primary endpoint(s), and main secondary endpoint(s). Discuss and the size of the effect and the statistical evidence (confidence intervals and p-values). Consider describing benefits in relevant subgroups (e.g. as defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphism).

For other benefits, if these are key in the benefit-risk assessment, consider the following

- Describe benefits as observed in non-pivotal trials and extensions.

- Describe other available benefit outcome measures (including patient reported outcomes, patient preference, etc., as relevant).

- Describe the observed patient compliance in clinical trials.

- Describe the potential of the new treatment, based, e.g., on any known benefits for the pharmaceutical class.

Review the results critically. Summarise the most important findings of the scientific assessment of efficacy. The purpose is to describe the strength of evidence and uncertainties. Consider any of the following:

- Discuss the choice of dose, comparator, and endpoints (including surrogates, as appropriate).

- Describe important methodological flaws or deficiencies. Refer to guidelines or scientific literature if useful and describe how deviations from guidelines or scientific advice, if any, have been justified.

- Describe the impact of methodological deficiencies on the estimated benefit, e.g. consider any issues of multiplicity, exploratory techniques, post hoc analyses, etc.

- Have measurements and scales been validated? What are the unsettled issues? Is there a need for further studies?

- Describe any negative studies and studies showing no difference.

- Describe the quality of the supportive scientific literature.

- Describe any other issues that may have an impact on the estimated benefits.

- Are the results consistent across different factors, e.g. pivotal trial(s) and supportive studies, all submitted studies and literature, different populations, centres, doses, etc.?

Demonstrated risks and uncertainties

The aim of this section is to give a high level summary of the probability that important negative events will happen. Only those risks that are part of the benefit-risk balance and risks that must be accommodated should be referred to. When considering the importance of different events, it may be useful to refer to the intensity of the adverse event (severity for example), time of the event (onset, duration), and time period over which the probability applies. This should not be a detailed description of the safety profile which is described elsewhere.

In addition, unresolved issues or uncertainties regarding potential risks should be identified.

- Present **the most important non-clinical safety findings** that have not been adequately addressed by clinical data. If present, refer to key findings for example in terms of toxicity (including repeat-dose toxicity, reproductive/ developmental toxicity, nephrotoxicity, hepatotoxicity, genotoxicity, carcinogenicity etc.), general pharmacology (cardiovascular, including QT interval prolongation; nervous system, etc.), and drug interactions. The relevance of the findings to the use in humans should be discussed.

- With regard to **clinical findings**, refer to **the most important** toxicity and other risks that have been described in the clinical safety section of the report, i.e. summarise what were the most important adverse drug reactions (or events). State to what extent these risks are considered to be the major contributors to a risk profile.

- On a case-by-case basis, consider for instance discussing the impact of the following safety aspects:

  - The overall incidence of adverse effects.

  - The most serious/important identified risks.

  - The duration and whether the observed reactions are reversible.

  - Possible mechanisms (preclinical data on toxicity and general pharmacology).

  - Known and potential interactions.

  - Limitations of the data set (e.g. missing data, potential risk factors, subgroups of patients not investigated but potentially susceptible to adverse effects). Discuss the implications of such limitations with respect to predicting the safety of the product.

  - The duration of performed/on-going safety studies and evaluate the need of results from long-term studies. Discuss if the safety profile has been quantified and characterized over an appropriate duration of time consistent with the intended use.

  - Risk versus standard of care, comparative drugs of the same pharmacological class. Discuss class-effects.

  - Discuss the potential of off-label use and risks associated with this use.

- Consider discussing identified and potential pharmacokinetic and pharmacodynamic interactions, potential for overdose, potential for abuse and misuse, potential for transmission of infectious agents, potential for misuse for illegal purposes, potential for off-label use, etc., provided these elements could impact the benefit-risk balance significantly.

The EU-RMP Template may be useful as a basis for the evaluation, i.e. considering the important identified and potential risks and the missing important information. Much of the data needed should be available in quantitative terms as specified in the RMP Template.

Benefit-risk balance

The aim of this section is to compare benefits and risks described above, putting in perspective alternative therapies or interventions (where possible and relevant), and to conclude on whether the benefit-risk balance is positive in the specified target population(s).

The evaluation of the balance should take into account the observed benefits and harms, as well as the uncertainties and risks.

Under Community law (Regulation 726/2004), in the interest of public health, authorisation decisions under the centralised procedure should be taken on the basis of the objective scientific criteria of quality, safety and efficacy of the medicinal product concerned, to the exclusion of economic and other considerations such as "cost-effectiveness".

The assessment of the benefit-risk balance should be based on the available tests and trials, which are designed to determine the efficacy and safety of the product under normal conditions of use (Directive 2001/83), and which are generally performed under ideal conditions.

It is important to be explicit about the perspectives of different stakeholders that are taken into account in the assessment of the benefit-risk balance, in particular the perspectives of patients and treating physicians.

There are no standard quantitative methods to be recommended for evaluating the balance of benefits and risks. Generally, the evaluation of the balance relies on balancing benefits and harms as objectively as possible, each consisting of several different events of different importance and estimated with variable precision.

The estimation of the balance is often not precise and large approximations are commonly used. This is generally not a problem when the benefits are clearly much larger than the risks (or vice-versa). If benefits and risks are expressed in terms of the same event (e.g., deaths) then the balance is also easily quantified. Similarly, the balance compared to other treatments is easily quantified if the different treatments differ only in terms of one type of event (e.g., magnitude of an effect or frequency of an adverse event).

However, when the difference is less clear-cut, and the benefits and risks consist of different types of events, it is important to identify and estimate all contributing factors as precisely as possible, and to describe the importance given to the various factors in as much detail as possible. Also, it is important to assess the impact of any significant approximations on the conclusions.

It is important to consider the different regulatory options for approval (standard marketing authorisation, conditional marketing authorisation, authorisation under exceptional circumstances). If applicable, discuss the eligibility and requirements for these different regulatory options.

Generally, it will be important to describe the following (the level of detail should be assessed on a case by case basis):

- Amount of available evidence to characterise the benefit-risk balance. Availability of comparative data and limitations and potential pitfalls of the comparative analyses.

- Interpret magnitude of key benefits and risks from the perspectives of different stakeholders, in particular the perspectives of patients and treating physicians.

- Discuss the level of risk acceptability that corresponds to the perceived degree of clinical benefit in the specific context.

- State the relevant benefits wherever possible in a way that is comparable to the risks (e.g., potential lives saved as a result of treatment vs. potential lives lost as a result of adverse

- Describe how the benefit-risk balance might vary across different factors, e.g., different patient or disease characteristics. Be wary of uncritical use of overall expression of risk or benefit as these are rarely evenly distributed over a population over time.

- Discuss the sensitivity of the benefit-risk balance assessment to different assumptions. For example, describe the "worst case scenario" if assumptions are violated.

- The following potential points should be considered, as appropriate. This is not a list of mandatory points to be described. The need to discuss or not each point has to be judged on a case by case basis.

  - When the proposed treatment is less effective as compared to available options, discuss the impact of loss of efficacy.

  - If the balance is assessed to be negative, describe the harm (e.g., in terms of lack of efficacy, toxicity) that the drug might cause if used in the claimed indication (cf. the importance of sensitivity analyses, as described below).

  - Describe how the benefit-risk balance is expected to evolve over time (e.g., when late side effects emerge or long-term efficacy decreases).

  - Describe outstanding issues, submission of additional reports by the company to address those issues, hearings and advisory group recommendations.

  - Make reference to the evaluation of the pharmacovigilance plan and risk minimisation plan (if any). Describe any communication of particularly significant information to the medical profession, patients or the public that is required. Describe restrictions to product availability or usage.

  - Describe the need for further studies (e.g., the need for studies to improve the benefit-risk balance with further optimisation studies, the need for intensive additional follow-up measures or specific obligations, and the need for further development including any paediatric development plans).

  - Describe the involvement of scientific experts, patients, consumers or consumer advocates, and other stakeholders in the benefit-risk assessment.

- Provide a clear conclusion on the benefit risk being positive or not for every claimed indication