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**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**

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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 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

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., Pharmacovigilance 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

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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 the minimally significant clinical benefits worth detecting. This could be based on therapeutic guidelines.

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 reactions). In this respect, avoid the use of relative expressions of benefits and risks in isolation. The true medical impact is better expressed using absolute values (together with indication of the precision of the estimates).
- 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