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

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

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Fax +44 20 7418 8613

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EXECUTIVE SUMMARY

The assessment of the benefit risk 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 transparency, consistency and communication** of the benefit risk assessment by the CHMP.

The group reviewed some well-known models of benefit-risk assessment, and considered their practical applicability to the CHMP benefit-risk assessment. Many of the models' features are of interest, such as:

- Most important benefits and medically serious risks that drive the assessment are identified
- Explicit weights are assigned to individual benefits and risks depending on their importance
- Strength of evidence and uncertainty identified and quantified.

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

1) To integrate the most useful features of the models into CHMP guidelines and assessment report templates

1.1 It's recommended to:

- Use a structured and mainly qualitative approach
- Describe explicitly the importance of benefits and risks in the specific therapeutic context
- Describe uncertainties and their impact on the benefit-risk assessment

1.2 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. A proposal for modification is provided in Annex 4.

1.3 Pilot phase: before implementation, the modified templates should be tested (for example, by a small group of assessors using ongoing or completed applications), and revised as necessary.

1.4 Implementation phase: should consist of regular training and monitoring. The working group should monitor the implementation of the new template and benefit-risk assessment to determine the effectiveness of the templates and guidelines.

2) To further research into methodology of benefit risk assessment, involving further experts and assessors

2.1 To explore further development in methodologies for benefit/risk analysis, e.g. by organising workshops with specialists of decision-theory and regulators from other areas such as environment, food additives and chemicals where there is a great deal of experience, or setting up specific research projects (e.g., post doctorate research project).

2.2 To continue the process of a comprehensive review of available methods for benefit-risk assessment relevant to the CHMP and to maintain state of the art input from the field.

2.3 To explore further development in tailored methodologies for benefit/risk analysis.

2.4 The working group should be closely involved in the further research into methodology of benefit risk assessment

1. BACKGROUND AND PROBLEM STATEMENT

The assessment of the benefit risk in the context of a new drug application is a central element of the scientific assessment of a marketing authorisation application and related variations. The assessment requires evaluation of all relevant data and the use of judgment and arguments to establish as objectively as possible a sufficient level of confidence that a set level of quality, efficacy and safety have been demonstrated. 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".

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 currently detailed CHMP guidance on the principles and methodology for benefit risk assessment is lacking. The CHMP assessment report template provides summaries of the main evidence from the different parts of the dossier and sets out some main aspects of the actual benefit risk assessment. However there is no agreed approach on the methodology to estimate the overall benefit risk, and 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 transparency, consistency and communication of the benefit risk assessment in CHMP assessment reports.

2. EXAMPLES OF MODELS OF BENEFIT/RISK ASSESSMENT

The working group reviewed some well-known examples of models of benefit/risk assessment described in the literature. A preliminary assessment of these models was conducted. The aim of this review was to assess the need for conducting a more comprehensive review of available methods for benefit-risk assessment, and the need to explore further development in tailored methodologies for benefit/risk analysis. Basically there are two types of models: models used for individual clinical trials, and general models.

2.1 Models for individual clinical trials

- ***Number Needed to Treat/Number Needed to Harm (NNT/NNH)***

The method of NNT/NNH is a popular method described in the literature and used by health authorities. Basically the NNT is the number of patients who need to be treated to prevent one additional adverse outcome, and NNH the number of patients to be treated before one experience of an adverse treatment related outcome. NNT is usually computed as the inverse of the absolute risk reduction. The NNT is dependent on the baseline risk (*i.e.*, the incidence in the population to be treated) and the duration of treatment as well as the relative risk reduction.

A mathematical model has been developed to overcome the concern that NNT conveys the effort required to achieve a positive outcome without distinguishing between the presence or absence of treatment related adverse events, and NNH without accounting for the benefit of therapy (Mancini and Schulzer, 1999). The concepts of NNTu ("unqualified success", treatment success without treatment induced side effects) and NNHu ("unmitigated failure", lack of treatment success with treatment induced side effects) have been created, but not widely used so far. As for most other methods and models for quantitative B-R methods, this method does not incorporate clinical judgement, which is a key feature of benefit risk analysis.

The NNT/NNH method has some merits for clinicians and reimbursement bodies, because it is simple to use. However, there are limits to its usefulness in the context of CHMP scientific review:

- The method has been essentially adapted for one clinical trial with binary endpoints. It is unclear how it would account for multiple benefit risk variables and multiple adverse events of different seriousness.
- One important methodological problem in using NNT and NNH is that of inference. Being dependent on the background rate means that results are applicable only in settings with the same conditions as those existing where the data have been collected.

2.2 General models

• The “Principle of three” and the TURBO models

These two models were both developed for the reassessment of marketed medicines in case of new safety issues. Both are described in the report of the CIOMS Working Group IV entitled: “Benefit risk balance for marketed drugs: evaluating safety signals” (CIOMS Working Group IV, 1998).

Briefly, the “Principle of three” grading system is a model based on the concepts of seriousness, duration, and incidence as related to disease indication, disease amelioration by the medicine, and the adverse effects ascribed to the medicine. Each parameter is rated as high, medium, or low. The methodology is essentially based on the visible weighing of the scores for the “level of improvement produced by the medicine” against the scores for “the adverse effects” criteria.

A third dimension, i.e., the seriousness, duration, and incidence of disease is used to determine how much the benefit must outweigh the risks (see table 1, annex 1). A numerical scale is used for the qualitative terms (low=1, medium=2, high=3). In the report of the CIOMS Working Group IV, the model was applied to three examples (felbamate, dipyron and quinine) to illustrate its applicability.

The TURBO (“Transparent Uniform Risk Benefit Overview”) model is a quantitative and graphical approach to benefit risk analysis. This method tries to quantify the benefit and risks of a medicine in a given indication and both factors are then displayed on a TURBO diagram. The risk factor “R” is defined as the sum of two risks: the risk associated with the most medically serious adverse effect (score from 1 to 5), and the risk associated with the second most serious adverse effect or the most frequent adverse effect (score from 1 to 2). The Benefit factor “B” is calculated in a similar way, as the sum of the primary benefit, and the ancillary benefit (see tables 1 and 2, annex 2). The R factor and B factor are placed in the TURBO diagram and a T score expressing the intrinsic benefit risk analysis ranging from 1 to 7 is assigned. In the CIOMS IV publication, T scores were not attributed to all cells (see table 3, annex 2).

Possible drawbacks that limit the usefulness of the “Principle of Three” and the TURBO models are:

- There is a significant gap between a comprehensive list of benefit and risk criteria on one hand, and the few criteria incorporated in these models on the other hand.
- Many criteria used are not well defined with regard to the scores to be attributed.
- These models have been developed for already marketed medicines, and this is a limitation, and none of them have been validated, which may explain why their use is very limited.

• Multi criteria decision analysis (MCDA)

This model uses an algorithm that combines value judgements along multiple dimensions. Decision analysis is widely used in business and government decision-making and common applications include managing research and development programs, deciding whether to launch a new product or a new venture, developing ways to respond to environmental risks, and various studies in medicine.

With this method, the first step is to identify a list of relevant benefit and risk criteria that are evaluated for determining the benefit risk profile, and to organise them (see e.g., annex 3). Then the method can be summarised as follows:

- Score the options on each criterion, using numerical values between two reference points and either a fixed, but not necessarily linear, scale or a relative preference scale;
- Assign weights to each criterion to reflect their relative importance in the decision;
- Calculate the product of the options score times weight for each criterion, then add them for both benefits and risks;
- Examine the result, compare the total scores of benefits and risks, and use sensitivity analyses which are built into the computer program to determine the importance of selected criteria.

The main advantages of the MCDA method, in terms of usefulness for the CHMP scientific assessment, can be summarised as follows.

- The model is able to combine numerically judgements and data by assigning weights to the scores given for each of the benefit risk criteria in a transparent way;
- The balance of benefits and risks can be evaluated likewise between treatment arms, against placebo, or against active control;
- The model considers a comprehensive and structured list of possible benefit and risk criteria considered to be of potential relevance,
- It offers the flexibility to include one or more additional benefit and risk criteria and thus could be extended to comparable clinical situations,
- It allows a numerical balancing of the benefit risk of a medicine and to compare the balance between treatment arms against placebo and /or active control, and by,
- It allows performing a subsequent sensitivity analysis, exploring the dependency of the conclusions on the chosen weights,
- It requires a discussion about the subjective weights and allows the assessors to discuss a comprehensive benefit risk profile of a new medicine, therefore being a useful training tool.

The main disadvantages in terms of the CHMP assessment are:

- There is a danger that decision over relies on the numerical outcome of the analysis from the model
- The model consists of linear combinations of single values (point estimates calculated from the data, the arbitrary value chosen as the weight) and does not incorporate uncertainty about the estimation (e.g., confidence intervals around the point estimates) or variation in the subjective perceptions about the appropriate weights by different assessors. As a result, the available information is drastically reduced.
- Although it is interesting to visualise how changes in one value or weight affect the conclusions, the models treat all values and weights as independent of each other, which is unrealistic. Lacking a plausible dependence structure, the results of sensitivity analyses can be misleading and are of limited value. To implement a plausible dependence structure would be very complex due to the many items.
- The process of setting up a model is time consuming, requiring building up a complex model for every situation. Furthermore, a specific model may be needed for each therapeutic area or even product or indication.
- There could be significant divergences between industry's versus regulators' choice for weights. The discussion on benefit risk assessment may be shifted to discussion on values and weighting factors for implementation of the model, reducing complex issues to over simplified abstract quantities.
- The focus is on decision-making, comparing quantitatively the overall value of different treatments, rather than highlighting and contrasting the qualitative differences.

2.3 Other Methods

Besides the few examples described above, there is a large body of research developed by pharmaco-epidemiologists or derived from pharmaco-economics, introducing numerous quantitative methods developed for benefit-risk assessment and tested to varying degrees. *Several of these models are referenced at the end of this document. Some of them have been used essentially in the pharmacovigilance field or for purposes of reimbursement.* Most of these models are still in the research domain and their validity and usefulness have still to be tested. Importantly, inherently to the practice of epidemiology, many models developed by pharmaco-epidemiologists allow to incorporate uncertainties formally.

- Given the active research in the field of decision-making, it is important to conduct a comprehensive review of available methods for benefit-risk assessment relevant to the CHMP, and to maintain state of the art input from the field.
- Given the knowledge and experience within the EMEA and CHMP, it is important to explore further development in tailored methodologies for benefit/risk analysis.

3. DISCUSSION

Numerical models aiming to weigh all the available efficacy and safety data and value judgements as objectively and explicitly as possible into a single mathematical construct do not adequately reflect the intellectual process of assessing the empirical evidence, accommodating risks and balancing risks and benefits. Although the models may be helpful to stimulate a structured discussion on what data are important and what are the reasoned justifications for the weight given to each piece of information, in practice, they can still be quite complex (defeating the purpose of simplifying the task), may convey a misleading feeling of precision, and may shift the focus on overall numerical summaries at the expense of information on the qualitative differences.

- Quantitative benefit-risk assessment is not expected to replace qualitative evaluation
- Expert judgement is expected to remain the cornerstone of benefit-risk evaluation for the authorisation of medicinal products.

Although by and large it was felt by the working group that the use of numerical models may not be currently the best option in practice, some of the key principles of the examples reviewed, namely the requirement to be explicit about what data are important and how much weight is given to each important data leading to increased transparency and ease in communication, should not be discarded. Furthermore, the need for a structured approach to benefit-risk assessment (what elements should be considered) has been recognised and the available models with some adaptation can be very useful as a basis. All these aspects could be reflected into CHMP guidance and templates for the benefit-risk assessment.

- An important area for improvement would be to make much more explicit the criteria on which a benefit-risk evaluation are being made by experts

Lastly, applied decision-making theory applied to regulatory decisions is a moving field. Even if no single mathematical modelling is suitable in practice to conducting benefit-risk assessment in the context of the CHMP, 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. Quantitative approaches to benefit-risk might also be useful for the continuous evaluation of products post-approval. Furthermore, it might be interesting to follow the approaches used in different regulatory contexts (e.g., environment, food safety). 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.

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- Given the knowledge and experience within the EMEA and CHMP, it is important 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 main steps:

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2.6 The working group should be closely involved in the further research into methodology of benefit risk assessment

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ANNEX 1

Table 1: “Principle of three” grading system

	High	Medium	Low
Disease			
Seriousness			
Duration			
Incidence			
LEVEL OF IMPROVEMENT PRODUCED BY THE MEDICINE			
Seriousness			
Duration			
Incidence			
ADVERSE EFFECTS OF THE MEDICINE			
Seriousness			
Duration			
Incidence			

ANNEX 2

Table 1: Calculating the R-score associated with the most serious adverse effect (R₀)

ESTIMATED Attributable risk	FREQUENCY					5
	Common				4	
	Not uncommon			3		
	Rare		2			
	Very rare	1				
		Minor	Slight	Moderate	Severe	Very severe
Estimated severity						

Table 2: Calculating the B-score associated with the benefit in the given indication (B₀)

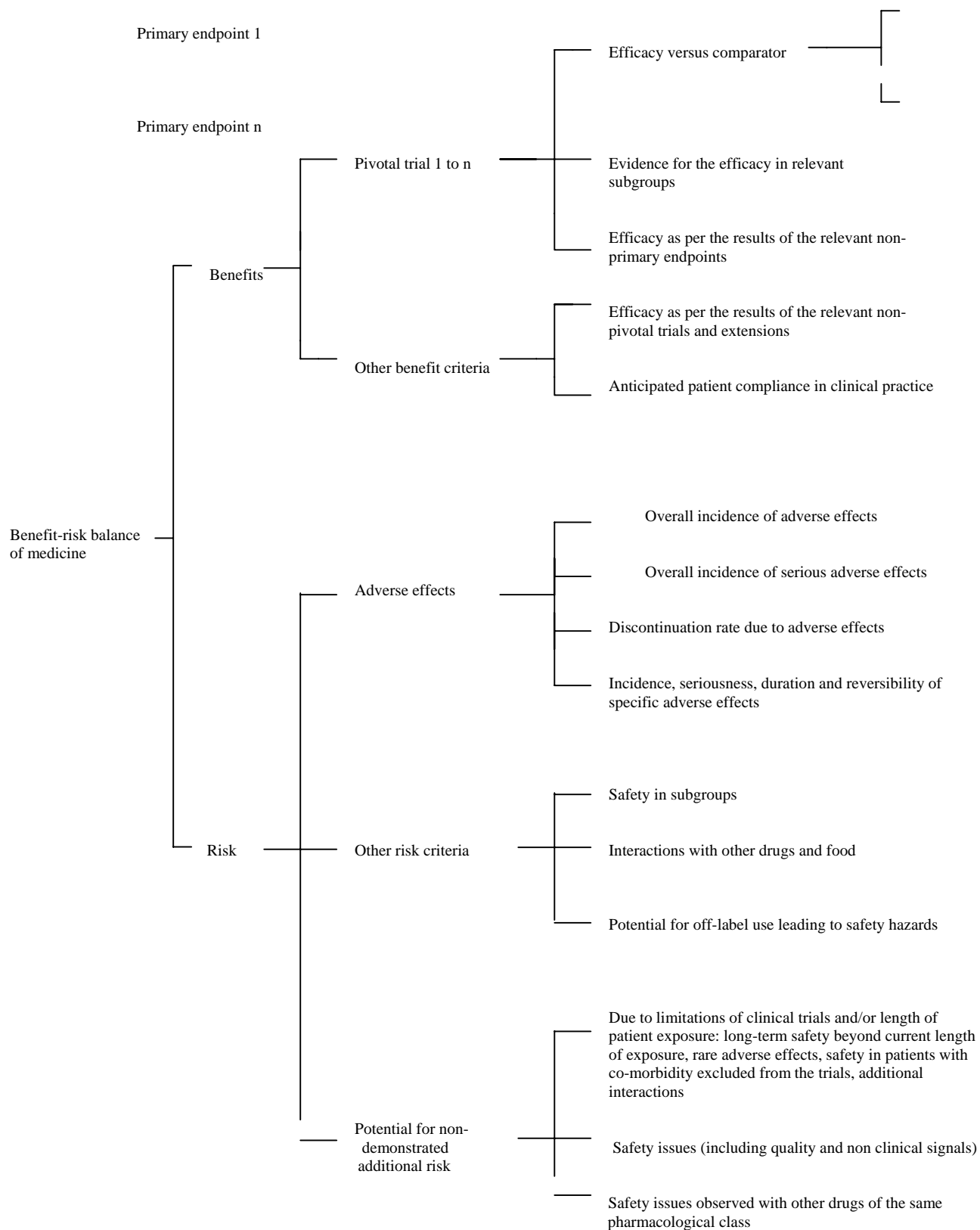
PROBABILITY of benefit	NEARLY ALWAYS					5
	Frequent				4	
	Common			3		
	Not uncommon		2			
	Rare	1				
		Minor	Slight	Moderate	Marked	Major
Degree of benefit						

Table 3: The TURBO diagram

R-factor							
7	T = 1	T = 2	T = 3				T = 4
6						T = 4	
5					T = 4		T = 7
4				T = 4		T = 6	
3			T = 4		T = 5		
2		T = 4					
1	T = 4						
	1	2	3	4	5	6	7
	B-factor						

ANNEX 3

Multi Criteria Decision Analysis: Value tree for benefit-risk assessment (modified from 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.)



ANNEX 4

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

BENEFIT RISK ASSESSMENT

The proposed structure of the CHMP assessment report template aims to provide guidance on important elements that should be considered when making the benefit risk balance assessment, and how the assessment should be documented.

- First, it is recommended to describe factually the observed effects and uncertainties in terms of important benefits and risks. In this respect a list of benefit and risk criteria is provided.
- Second, important benefits, risks and uncertainties are compared to each other in the specific therapeutic context.

Since balancing benefits and risks can be a complex multidimensional judgement, guidance is provided on how to be as objective as possible and 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 explicitly the subjective judgements. The aim is to avoid separate enumeration of quality and 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 define the background (e.g., life-threatening vs. self-limiting disease, availability of treatments) for determining what is the medical need in terms of benefits and what are the acceptable risks. This may be complex if the indication includes different situations (multiple indications, populations, 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 always 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, explain what are minimally significant clinical benefits worth detecting. This could be based on therapeutic guidelines.

Benefits

The aim of this section is to discuss critically the benefits. **Only the important results and issues that have an impact on the benefit-risk balance should be described.** 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 benefits versus comparator, in terms of primary endpoint(s), and main secondary endpoint(s). Refer to point estimates and statistical evidence (confidence intervals and p-values). Describe benefits in relevant subgroups (e.g. as defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphism).

For other benefits,

- Describe benefits as observed in non-pivotal trials and extensions.
- 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, choice of endpoints (including surrogates, as appropriate).
- Describe important methodological flaws or deficiencies (refer to guidelines or scientific literature if useful, and describe how these 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, 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 if any, different populations, centres, doses.

Risks

The aim of this section is to describe the probability that a negative event will happen. It is always important to include information on intensity (severity for example), time of the event (onset, duration) and time period over which the probability applies. Only describe those risks that are part of the benefit-risk balance described below, or risks that must be accommodated.

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

Summarise factually **the most important** toxicity and other risks, i.e. describe the most important adverse drug reactions (or events), in terms of incidence, seriousness, and reversibility. State to what extent these risks are considered to be the major contributors to a risk profile. Only describe those risks that are part of the benefit-risk balance described below, or risks that must be accommodated.

- Describe the overall incidence of adverse effects
- Describe the most serious/important identified risks
- Describe the duration and whether the observed reactions are reversible

- Describe possible mechanisms (preclinical data-toxicity/general pharmacology)
- Describe known and potential interactions
- Describe limitations of data set (missing data, potential risk factors or evaluated-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.
- Describe 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
- Discuss risk versus 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 transmission of infectious agents, potential for misuse for illegal purposes, potential for off-label use, etc.

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.

It is important to state the perspective according to which the benefit-risk evaluation has to be made. This is generally understood as the perspective of a physician when considering treatment prevention or diagnosis for an average patient that falls within the claimed therapeutic indication, considering ideal conditions (“efficacy”). If a different perspective is considered more relevant, this should be clearly stated. Practical considerations about how the treatment is expected to perform under real conditions of use (“effectiveness”) or about the value of such treatment in terms of the society (“cost-effectiveness”), whether in absolute or relative terms, are outside the scope of the CHMP benefit-risk assessment.

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 as objectively as possible benefits and harms, each consisting of several different events of different importance and estimated with variable precision. Where possible, it is useful to compare the balance with that of other therapeutic options.

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, conditional marketing authorisation, authorisation under exceptional circumstances). *If applicable, discuss the eligibility and requirements for these different regulatory options*

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).

- Amount of available evidence to characterise the benefit risk
- Availability of comparative data and limitations and potential pitfalls of the comparative analyses.
- When the proposed treatment is less effective as compared to available options, discuss the impact of loss of efficacy.
- Clinical relevance of endpoints used in these comparisons should be considered.
- 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).
- 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.
- Discuss the level of risk acceptability that corresponds to the perceived degree of clinical benefit in the specific context.
- Describe how the benefit risk is expected to evolve over time (e.g., when late side effects emerge or long-term efficacy decreases).
- 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 to different assumptions. Describe the “worst case scenario” if assumptions are violated.
- During the final stages of the assessment, 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., need for studies to improve the benefit risk balance with further optimisation studies, the need for intensive additional follow-up measures or specific obligations necessary, the need for further development including any paediatric development plans).
- Describe the involvement of scientific experts, patients, consumers or consumer advocates, and other stakeholders