



Communication of the benefit risk profile in the Clinical Overview section of an application for marketing approval of a new medicinal product

by Sarah Hemingway

Introduction

Many people involved in the drug development process will contribute to interpretation of the clinical data and evaluation of benefit risk, and the role of the Communicator is to work with this team to organise the different elements of benefit risk evaluation and document a clear, balanced view of the clinical value of the product. According to Regulatory guidance (ICH M4E [1]), the Clinical Overview is the document within a pharmaceutical registration dossier in which the applicant should present the overall analysis of the benefits and risks of the product in its intended use. The purpose of this article is to help Communicators understand elements of the benefit risk evaluation, and propose questions and points that should be addressed during the processes of critically evaluating a new product and preparing a Clinical Overview.

An ineffective drug is obviously of no value, and no drug is completely safe—hence the decision to market a new medicine is based on an evaluation of the benefit risk balance. The question that must be addressed is: *“Do the benefits outweigh the risks in relation to the intended clinical use?”*

Thus the Clinical Overview must critically assess the value of a new product in the indication for which it might be marketed, based on clinical trial data presented and summarised in the application. Furthermore, the Clinical Overview explains and justifies the content of the proposed prescribing information for the product. Labelling text follows a prescribed format, designed to include the basic information on the product needed by a prescriber to reach a benefit risk decision in relation to the potential treatment of an individual patient. Labelling is then translated into patient information, which influences patient perception of benefit risk of a prescribed medication.

Analysis of benefit risk is a complex process; quantitative techniques have been proposed [2-5], but the issues vary between products and the evaluation may rely on clinical judgement alone. The case for approval of a product is made in the following 5 stages:

- Clarify the unmet medical need that is addressed by the new medicine
- Confirm that the clinical database is adequate to characterise the benefits and risks
- Present the analysis of clinical benefit
- Present the analysis of clinical risk
- Address the key question: ‘Do the benefits outweigh the risks?’

Unmet medical need

A new medication is introduced to address an unmet medical need, represented either by patients who receive no treatment (who experience discomfort and disruption of daily activities, with consequent social impact, and in whom there may be a risk of the condition deteriorating), or those in whom there are drawbacks associated with the existing treatment (e.g. limited efficacy, adverse drug reactions (ADR) or over-complex dosing regimens). The acceptability of the balance between benefit and risk for a new therapy may depend upon the severity of the condition to be treated: for potentially life-threatening illness, a higher level of risk may be more acceptable than in less serious conditions. Where treatment already exists, benefit risk will need to be compared with current therapy, and it may be appropriate to refer to published clinical guidelines, in which the benefit risk profiles of existing therapies are evaluated and treatment algorithms proposed.

The ‘Product Development Rationale’ section of the Clinical Overview must address the question: “What is the unmet medical need for this product?” Having identified the unmet need, the applicant should then set out the criteria that a drug must meet (or surpass) in order to be judged to have met the unmet need with an acceptable balance of benefit and risk.

Adequacy of the clinical data to support evaluation of benefit risk

Before attempting to show how the benefits of a new medicine outweigh the risks, consideration should be given to the question of whether the clinical database is adequate to characterise the benefits and risks: if either the benefits or the risks are not well enough understood, the application may be judged to be premature. Furthermore, the impact of any major issues of data quality on the conclusions must be addressed. The Clinical Overview should include a statement, with justification, that the information on a new medicine is adequate to support a conclusion on the benefit risk.

Communicating clinical benefit

Efficacy

Efficacy is (clearly) the most important determinant of benefit: the drug must be shown to be efficacious in the patient population in which it is to be indicated. Points to be discussed when presenting conclusions on clinical efficacy are noted in Box 1.

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Box 1: Critical evaluation of clinical efficacy

- Are the trial methodology and endpoints used for efficacy evaluation valid and relevant to the intended use?
- Is the population studied representative of the population indicated in the prescribing information?
- Are the methods of statistical analysis robust and appropriate?
- Is the size of the effect on efficacy variables shown to be clinically relevant?
- Is the medication effective in important patient subgroups? (e.g. young/elderly, males/females, normal/impaired renal function, normal/impaired hepatic function, disease variants, e.g. degrees of severity or commonly used co-medication)
- How does the choice of control groups (placebo and/or active) support the assessment of clinical benefit? (Comparison with an active control may help assess the overall clinical utility of a new product)
- Are the design of the clinical programme and analysis of the data in accordance with regulatory guidance (both published guidelines and any specific agency advice received during development of the product)?

If the clinical trial population was too broad and not homogeneous, i.e. there is clear evidence that there were groups of responders and non-responders, it might be possible to characterise the responder group, based on a measurable biological characteristic; a confirmatory clinical study in the identified subgroup could well be necessary. Alternatively, the prescribing information may need to recommend use of a trial with the drug, with discontinuation in case of poor response. (If the eligible population is defined too narrowly, e.g. in terms of a specific biomarker, patients who could benefit from treatment might be excluded unnecessarily.)

Patient Reported Outcomes

'Quality of life' assessment and other Patient Reported Outcomes (PRO) may contribute important evidence of benefit, provided that the instruments used are fully validated and appropriately applied [6,7].

Patient acceptability

Patient acceptability may provide a component of clinical benefit. For example, it may be possible to demonstrate that the new therapy contributes to a better clinical outcome by offering a more acceptable formulation or frequency of administration, resulting in improved patient compliance with medication compared with the existing standard treatment. Other patient benefits of a new product over existing treatment could include reductions in laboratory testing, dietary restriction or concomitant medication. For a new drug, such characteristics are unlikely to provide a sufficiently compelling benefit in the absence of an efficacy or safety advantage. However, there may be benefits of replacing an old formulation with an improved one.

Communicating clinical risk

At the time of submitting a marketing application for a new medicine, the extent of patient exposure is too limited to adequately characterise a low frequency ADR; hence the novelty of the compound itself constitutes a risk. The risk of a rare ADR can only be assessed with extended exposure in the post-marketing context, but other risks can be described on the basis of clinical trial safety data. For a new indication or formulation of an established product the risk may be more easily characterised using existing post-marketing data. Useful questions for the evaluation of risk are noted in Box 2 (for a detailed consideration of risk evaluation refer to the FDA Reviewer Guidance on Conducting a Clinical Safety Review [8]).

Box 2: Possible sources of clinical risk

- *What are the ADR observed in the clinical trial population?*
The evaluation includes analysis of adverse events (AE) in the entire patient population, in the population with the labelled indication, and in the subgroups that may have differing susceptibility to ADR, usually young/elderly, males/females, normal/impaired renal function, normal/impaired hepatic function, disease variants, e.g. degrees of severity, good/poor prognosis, and presence of commonly used comedications
- *Are there adverse effects that might be expected, based on the pharmacological activity of the product or class effects associated with related products?*
- *Are there unconfirmed safety 'signals' based on low-frequency AE observed in clinical trials?*
Such signals may not be fully characterised at the time of an application if they represent rare ADRs
- *Are there fatal AE or other serious or significant AE that warrant particular attention?*
AE that lead to discontinuation of treatment or require specific intervention, marked laboratory abnormalities, or potentially important abnormalities (e.g. a single seizure or syncopal episode) should always be fully discussed
- *Do variable bioavailability, drug interactions or other pharmacokinetic characteristics result in unpredictable exposure to the drug or an active metabolite?*
In assessing such risks, the focus should be on changes in exposure that are large enough to be clinically relevant
- *Do unwanted pharmacological effects occur at therapeutic doses?*
Unwanted effects may be either an exaggeration of the desired effect, or other effects, e.g. QT prolongation, sedation
- *Are there risks shown in toxicology studies in animals, but for which there may be no clinical evidence, e.g. carcinogenicity, or teratogenicity?*
The existence of biological data indicating that such a finding is species-specific is helpful in assessing the extent of the risk it represents, but a potential risk remains until there has been extensive exposure in patients, without ill-effect

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Risk Management

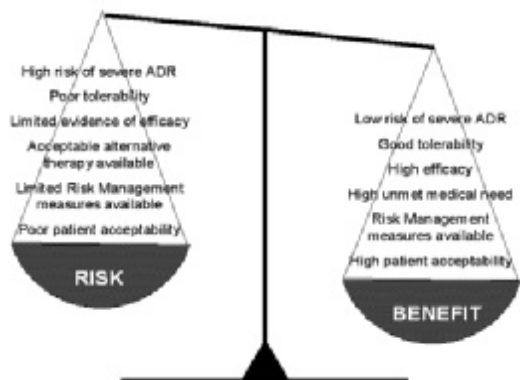
The team should address the question: “What measures are needed to minimise the risk of treatment?”

Availability of measures to mitigate known or potential adverse effects are relevant to the overall assessment of risk; e.g. a risk associated with variable plasma exposure to the drug might be overcome by dose adjustment, based on the results of monitoring drug effect or plasma concentrations, either at the onset of treatment or regularly throughout the time a patient receives the medication. Alternatively, it may be possible to identify a patient characteristic or a biomarker that helps to select at-risk patients so that they can be excluded from treatment. More usually, measures such as product labelling, prescriber and patient education, enhanced monitoring, or restricted prescribing are adopted to minimise risk (refer to the guidance on documentation of risk management measures [9-11]).

The key question: ‘Do the benefits outweigh the risks?’

Ideally, a new product should provide a high level of benefit with low risk. However, if the unmet medical need is high, a product with limited (but demonstrable) efficacy or a recognised risk may still be a useful medicine and receive marketing approval; major factors influencing the benefit risk analysis are shown in Figure 1.

Figure 1: Factors influencing the benefit risk analysis



In presenting the benefit risk conclusion, it may be helpful to consider the following points:

- How to compare benefits and risks? Some efficacy measures are less clinically significant and some risks are more acceptable than others – is there a single variable that can be applied that combines both benefit and risk, or is it possible to objectively apply ‘weighting’ in assessing benefits in relation to risks [2-5]?
- Is the benefit risk appropriate to the intended use?
 - If the unmet need is high (a serious or life-threatening medical condition, for which there is no effective therapy, or an existing therapy with poor safety), a greater level of risk, or greater variability in efficacy may be acceptable. If the unmet need is low

(a non-serious medical condition, or availability of an existing effective and well tolerated therapy), the efficacy must be higher and more reproducible, and risk must be lower.

- The evaluation should take account of whether the product is a preventive medicine or intended for treatment of an existing condition: for a preventive medicine it is important to weigh the risk of no, or inadequate, prophylaxis against the benefit risk of the medication, whereas for a treatment the question is how tolerable is the condition (or how beneficial and safe is existing therapy) compared with benefits and risks of the new product. Benefit may need to be greater and risk lower for a preventive medicine that may be used long-term by relatively healthy people.
- Has the correct dose been selected to optimise the benefit risk? The dose should be high enough for predictable efficacy, but with good tolerability and minimum risk of ADRs. Is dose adjustment needed to optimise benefit risk for some patient subgroups (e.g. those with intrinsic or extrinsic factors affecting drug exposure)? Would dose titration enhance benefit or reduce risk?
- Is benefit risk the same across the indicated patient population – are risks or benefits more evident in some subgroups? If the overall benefit risk balance in the clinical trial population is less favourable in relation to unmet need, is there a patient subgroup in whom the benefit risk may be more favourable, either because of a better response to the new treatment or because these patients are less well managed on existing treatment? In such a case, the indication might be adapted to maximise the benefit risk ratio.
- Do PRO and patient acceptability contribute to benefit, particularly for a medication intended for long-term administration?
- How might the product fit into current treatment guidelines—should it be adopted as first-line or second-line treatment?
- Do the measures needed to mitigate a possible risk require a high degree of physician education and patient understanding and compliance? A key question in evaluating risk management measures is “How effectively can risk management be applied?” Is the benefit risk acceptable in patients who may, for any reason, not comply with labelled precautions, or escape the risk management measures altogether?
- If the application is for a new indication or new formulation of an approved drug, does the new information alter the benefit risk profile?

At present, the benefits and risks of a new medicine are judged on the basis of analysis of clinical study data in the indicated population. For the future, the possibilities of individualised medicine—the ability to select patients who will benefit or exclude those who are at risk of a serious ADR - may result in a very different approach to analysis of benefit risk.

Conclusion

The Clinical Overview section of a Common Technical Document application for marketing authorisation represents an important opportunity for the applicant to present the benefit risk profile of a new medicine, in the context of current therapy for the indication and the unmet medical need for a new treatment. The approach to evaluating and documenting benefit risk, and providing a realistic appraisal of the place of the new agent in treatment protocols, will vary according to the type of medication and its intended use, and can be complex. However, using questions such as those described in this article, a Communicator working with the team responsible for authoring the Clinical Overview can make a significant contribution by facilitating the processes of critically evaluating a new product and describing its benefit risk profile.

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A journal rejected your Nobel Prize paper?

Jan Miguel Campanario is looking for a journal to publish his research. His paper¹ has been rejected by 6 journals to date although it was mentioned in an editorial in *Nature*². His research was by questionnaire to winners of Nobel prizes. He found that 36 Nobel laureates had initially received rejections from scientific journals of their manuscripts relating to research for which they had subsequently received a Nobel Prize. In most instances he concluded the rejection had been because of resistance to scientific discovery. The reasons he put forward for this were:

- new theories or discoveries often clashed with the orthodox views held by referees
- referees did not appreciate the potential or interest of new discoveries because, e.g. they were not derived from accepted knowledge or did not relate to the current body of knowledge.

1 <http://www2.uah.es/jmc/nobel.html>

2 Coping with peer rejection *Nature* 2003;425(6959):645

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Ig Nobel weapons for author's editors

Medical literature is entrenched by an unnecessarily complex writing style, the aim of which is more to impress readers with the author's intellectual prowess than to enlighten them. The Ig Nobel Prize for literature this year should have important consequences for medical literature. The award was made to Daniel Oppenheimer, who is a professor of psychology at Princeton University in the USA, for his research report "Consequences of erudite vernacular utilization irrespective of necessity: problems with using long words needlessly" (*Applied Cognitive Psychology* 2006;20(2):139-156). Oppenheimer's findings show that readers believe authors who use simple, clear language to be generally cleverer than those who use unnecessarily long words and complicated language.

Oppenheimer presented students with samples of graduate school applications, sociology dissertation abstracts and translations of works by Descartes. He adjusted the text and font style to produce samples of the same text that were easy to read and samples that were difficult to read. Students rated the intelligence of the authors of the simple text as higher than that of those who had written the text that was difficult to read.

Sadly these findings are unlikely to deter authors from writing text that is difficult to understand, but they have potential in the armoury of an author's editor confronted with an author who insists that simple language is unscientific. And another piece of armoury, if anyone can find it, would be data that show papers with simpler wording have higher citation rates. Professor Oppenheimer told me that several people had mentioned such data to him but he has never seen an original paper reporting these results.

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