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Implementing Benefit-Risk Assessment for the Periodic Benefit-Risk Evaluation Report

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Abstract

Background: In 2012, the International Conference on Harmonisation (ICH) E2C (R1) guideline for periodic safety update reporting (PSUR) for medicines was revised. Several new concepts that expanded the scope of the report were added, including a new section focused on benefits and an additional section focused on integrated benefit-risk (B-R) assessment. These changes are reflected in the new title of the report, namely, the Periodic Benefit-Risk Evaluation Report (PBRER). Recently, structured frameworks have been developed by the pharmaceutical industry and regulatory agencies to facilitate B-R analysis for medicines. *Methods:* This manuscript provides suggestions for incorporating the elements of a structured B-R assessment into the PBRER and also includes practical approaches for implementing the ICH guidelines for the B-R analysis section. *Results:* The main components of a B-R assessment for the PBRER include decision context; key benefits and key risks; strengths, limitations, and uncertainties of the evidence; risk management; and the overall B-R conclusions. *Conclusions:* A structured, systematic approach to defining a medicine's B-R profile will help ensure compliance with this ICH objective for the PBRER.

Keywords

benefit-risk assessment, Periodic Benefit-Risk Evaluation Report (PBRER), periodic safety update report (PSUR), benefit-risk framework, International Conference on Harmonisation (ICH)

Introduction

Following regulatory approval of a medicine, pharmaceutical companies must meet various postmarketing regulatory requirements. One requirement is to submit periodic safety update reports (PSURs) to regulatory authorities worldwide. In 1996, the International Conference on Harmonisation (ICH) published the ICH E2C guideline for preparing PSURs for marketed drugs with an addendum to the guideline finalized in 2003 (ICH E2C[R1]).[1] Until 2012, the focus of the PSUR was on relevant new safety information collected over the defined period of the report in the context of patient exposure to determine if changes should be made to reference safety information, to ensure optimal and safe use of the medicine.

With increasing recognition that a medicine's safety is more meaningfully understood when considered together with its benefits, the ICH E2C(R1) guideline was revised and was published as a Step 4 guideline (ICH E2C[R2]) in 2012. This guideline marked a new focus for periodic reporting, moving from a narrow focus on periodic safety updates to a broader scope of periodic benefit-risk (B-R) evaluation; as such, the document was given the new title of Periodic Benefit-Risk Evaluation Report (PBRER). The PBRER now includes important efficacy and effectiveness information in addition to safety data, and there is a separate section devoted entirely to providing an integrated B-R assessment for each of the medicine's approved indications and populations.

Both the ICH E2C(R2) guideline and EMA Good Pharmacovigilance Practices (GVP) for the PBRER contain instructions on what information to include in the integrated B-R assessment.[2,3] However, the implementation of new guidelines invariably creates some uncertainty for those responsible for creating the document as a guideline cannot, by nature, be prescriptive or provide extreme detail. For the PBRER, the content is particularly important because the totality of the information, including the B-R assessment, contributes to regulatory decision making, including whether to maintain, restrict, or revoke a medicine's marketing license. Although further clarification for completing the PBRER was recently provided in a question-and-answer document issued by the ICH E2C(R2) implementation working group,[4] there continues to be discussion among pharmaceutical companies focused on defining best practices for

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Table 1. Section 18 of the PBRER Per ICH Guideline.

Section 18. Integrated Benefit-Risk Analysis for Approved Indications
Section 18.1. Benefit-Risk Context
Section 18.2. Benefit-Risk Analysis Evaluation

Abbreviations: ICH, International Conference on Harmonisation; PBRER, Periodic Benefit-Risk Evaluation Report.

completing the B-R assessment for the PBRER. Thus, in this manuscript, the ICH E2C(R2) guideline for the PBRER and EMA GVP Module VII(R1) for the PSUR[i] are reviewed with a focus on Section 18, "Integrated Benefit-Risk Analysis for Approved Indications," to provide practical approaches and ideas for implementing the guidelines for this section.

Development of Structured B-R Assessment Frameworks

Evaluating the benefits and risks of a medicine is at the center of decision making for many stakeholders, including patients, health care providers, payers, regulators, and the pharmaceutical industry. Until recently however, few processes or tools existed to help make B-R decisions transparent and defensible. Over the past decade, methods to implement a more structured approach to B-R assessment have been developed or endorsed by regulatory agencies and the pharmaceutical industry.[5-11] Although some differences exist among the various B-R frameworks, the main components across the frameworks are largely similar. These components include the following:

- decision context;
- key benefits and key risks;
- strengths, limitations, and uncertainties of the evidence;
- risk management; and
- overall benefit-risk conclusions.

Use of a framework to provide information relevant to a medicine's B-R profile helps to ensure transparency in decision making and to facilitate communication of B-R decisions across a broad range of stakeholders. Thus, use of a structured approach is ideal for completing the integrated B-R assessment within the PBRER.

Benefit-Risk Assessment for the PBRER

Per the PBRER guideline, "When a drug is approved for marketing, a conclusion has been reached that, when used in accordance with approved product information, its benefits outweigh its risks. As new information about the drug emerges during marketing experience, B-R evaluation should be carried out to determine whether benefits continue to outweigh risks."[2] This approach supports the awareness that a medicine's B-R profile may change over time.[2,9,12] Thus, the benefits and risks should be re-evaluated not only as new safety and efficacy/effectiveness data emerge but also when important changes external to the medicine occur, such as new developments in the therapeutic environment or in knowledge of the disease state. Periodic evaluation helps to ensure that changes in a medicine's B-R profile will be detected early and then acted upon if the changes have a negative impact. Steps to improve the B-R profile may be implemented through risk minimization activities such as revisions to labeling and communications to prescribers and patients, including educational materials. In some cases, risk minimization may not be possible and the medicine's marketing authorization may be restricted or revoked.

Table 1 shows the main headers suggested in the ICH E2C(R2) PBRER guideline for Section 18 (Integrated Benefit-Risk Analysis for Approved Indications). The intent of Section 18 is to provide an integrated and critical analysis of information relevant to the B-R profile that was presented in previous sections of the PBRER. Although the ICH-recommended format and content for section 18 incorporates many of the elements of structured B-R assessment, Table 2 shows an expanded table of contents that more explicitly covers these elements while also retaining ICH formatting recommendations.[2,6,8-10]

Table 2. Suggested Formatting for Section 18 of the PBRER Using Additional Elements of a Structured Benefit-Risk Assessment.

Section 18. Integrated Benefit-Risk Analysis for Approved Indications
18.1. Benefit-Risk Context
18.1.1. Medical Need
• Condition to be treated/prevented/diagnosed
• Severity and seriousness of the condition (eg, chronic, acute, life-threatening)
• Population to be treated (eg, adults, children)
18.1.2. Important Alternative Therapies
• Pharmacologic
• Nonpharmacologic (eg, surgery, physical therapy, diet/exercise)
• None (eg, no available alternatives, watchful waiting, palliative care)
18.2 Benefit-Risk Analysis Evaluation
18.2.1. Benefit-Risk Assessment Methodology
• Explain the methodology used (eg, qualitative, quantitative) and provide information on assumptions, judgment, or weighting.
18.2.2. Key Benefits
• List the key benefits.
• Briefly state the clinical importance of each key benefit.
18.2.3. Key Risks
• List the key risks.
• Briefly state the clinical importance of each key risk.
18.2.4. Integrated Benefit-Risk Evaluation
• Provide a succinct evaluation of all elements of a structured benefit-risk assessment: medical need, therapeutic environment, key benefits, key risks, strengths, limitations, and uncertainties of the evidence, and risk management. This discussion should lead to a transparent and defensible conclusion as to whether, in the context of cumulative knowledge, the benefits of the medicine outweigh the risks or vice versa.

Abbreviation: PBRER, Periodic Benefit-Risk Evaluation Report.

Section 18.1 of the PBRER: Benefit-Risk Context

The "Medical Need" and "Important Alternative Therapies" subsections of Section 18.1 should be completed thoroughly and thoughtfully since information on context forms the basis for critically evaluating and applying clinical judgment to determine whether the benefits of a medicine outweigh its risks. For example, the B-R profile of a medicine for an acute, non–life-threatening condition with multiple alternative therapies will be evaluated quite differently than the B-R profile of a medicine for a life-threatening disease with no or few alternative therapies. Within the medical needs section, the disease/condition should be described in terms of its epidemiology, duration, severity, and seriousness, with the target population specific to the indication clearly defined. The impact of the disease on public health and quality of life should also be described, as applicable.

The content of the "Important Alternative Therapies" section will vary depending on the disease/condition as there may be many, few, or no alternative therapies. Alternative pharmacologic treatments can be approved or off-label if they are generally recognized as legitimate treatment options (eg, endorsed by practice guidelines, supported by published clinical trial data, or commonly used because of an absence of approved treatments). However, only the most important alternatives should be included in the PBRER (eg, the most commonly prescribed treatments or classes of treatments for the specific patient population/indication, including standard of care therapies). Although there is no limit on the number of alternatives specified in the ICH guidelines, critical thinking should be applied to narrow the choice usually to only 3 or 4 alternatives that are considered the most "important" for comparison with the medicinal product being evaluated. The benefits and risks of each alternative therapy or class of therapy should be summarized with a focus on data/endpoints that permit a comparison with the medicine under evaluation (absolute or comparative efficacy/effectiveness), if possible. A similar exercise should be performed to evaluate important nonpharmacologic therapies, such as surgery, psychotherapy, laser therapy, etc. If no alternative therapies exist, this should be stated, as should other important recognized alternatives, including watchful waiting or palliative care.

Section 18.2 of the PBRER: Benefit-Risk Analysis Evaluation

Benefit-Risk Assessment Methodology

The methodology and reasoning used to develop the B-R assessment should be stated in the PBRER.[2] Currently, formal quantitative methods are not typically used for the B-R analysis, although nearly all B-R assessments are based on quantitative data. Further, there is no regulatory requirement for the application of quantitative methods for the B-R analysis (eg, multicriteria decision analysis), and if used, the methodology must be clearly explained.[2,10] For qualitative assessments, the description should convey that the B-R assessment was based on a comprehensive framework that structured and facilitated the integration of clinical and scientific data with expert clinical judgment, allowing for a systematic and transparent evaluation of the overall B-R profile.

Table 3. Considerations for Determining Key Benefits and Key Risks.

Key Benefit: A favorable effect with substantial impact on the overall B-R profile
- Benefits that are clinically important due to effect size, duration of effect, generalizability, and/or demonstrated efficacy in patients who do not respond to other therapies; these benefits are often determined by the primary and secondary efficacy outcomes of pivotal trials.
- Benefits that are important to patients or offer significant differentiation from important alternative therapies such as benefits related to health outcomes, real-word use (ie, effectiveness), or convenience.
- Benefits that are not necessarily limited to efficacy such as a reduction in toxicity vs important alternative therapies.

Key Risk: An unfavorable effect with substantial impact on the overall B-R profile
- Risks that are clinically important because of their seriousness, frequency, toxicity, unpredictability, irreversibility, or inability to be prevented.
- Risks that result in risk minimization activity beyond labeling.
- Risks that are significantly different from important alternative therapies.
- Lack of efficacy in a subgroup, if the product is used extensively in this subgroup in clinical practice, or loss of efficacy over time on an important endpoint.
- Risks that regulators are concerned about, such as those with missing information (eg, lack of long term-data).

Note: The choice of which benefits and risks are considered "key" may differ among stakeholders, as each has a different viewpoint and/or responsibility with regard to the medicinal product (eg, patients, regulators, physicians, payers, industry). Since the regulator is the stakeholder for the PBRER, the viewpoint and concerns of the regulator should be considered when deciding on what benefits and risks are most impactful on the B-R profile of the medicine (eg, those having public health impact).

Key Benefits

For qualitative B-R assessments, deciding which benefits have substantial impact on a medicine's B-R profile (ie, the "key benefits") relies on expert clinical/medical judgment of all available clinical and scientific data regarding the favorable effects of the medicine. To facilitate thoughtful decision making, it is useful to assemble a cross-functional team (eg, individuals from medical, safety, regulatory, health outcomes, statistics) with members knowledgeable about the medicine and therapeutic area. Some considerations for assessing whether or not a benefit is a key benefit are listed in Table 3. The data sources (eg, placebo-controlled vs observational) should also be considered, because the strengths and limitations of a data set may impact the choice of whether a benefit should be considered "key." When writing

the "Key Benefit" subsection of Section 18.2, it is helpful to provide a concise list of the key benefits (eg, a bullet point list conveys this important information clearly). For most medicines, it is likely that only 2 or 3 benefits substantively impact the overall B-R profile and, thus, only these should be included in the assessment. For example, the key benefits of a cancer therapy may be

- improved overall survival,
- improved progression-free survival, and
- maintenance of quality of life.

Although the medicine likely has other important benefits (eg, improved objective response rate and disease control rate), the 3 key benefits listed above were judged to be the most clinically relevant for this medicine and to have the most substantial impact on the overall B-R profile.

After choosing the key benefits, a brief summary highlighting their clinical importance (eg, duration, generalizability, effect size) should be included in this section. A full description of the strengths, limitations, and uncertainties of evidence supporting the key benefits should not be included, since this is provided in Section 17 (Benefit Evaluation).

Key Risks

Table 3 presents a list of considerations for assessing each risk to determine whether it has a substantial impact on the B-R profile (ie, key risk). Similar to the procedure outlined above for deciding key benefits, key risks for a qualitative B-R assessment should be chosen based on expert clinical/medical judgment of all available data regarding the unfavorable effects of the medicine. Providing a concise list of the key risks makes the choice transparent to the reviewer. For example, the key risks for a cancer therapy may be

- serious infusion reactions,
- pulmonary toxicity, and
- arterial thromboembolism.

Although the medicine likely has other important risks (eg, myelosuppression), the 3 key risks were those judged to be the most clinically relevant for this medicine and to have the most substantial impact on the overall B-R profile. After choosing the key risks, a brief summary highlighting their clinical importance (eg, seriousness, frequency, reversibility, preventability, impact on patients) can also be included in this section. A full description of the strengths, limitations, and uncertainty of evidence for the risks should not be included in Section 18 because it is provided in Section 16 (Signal and Risk Evaluation).

Integrated Benefit-Risk Evaluation

The final subsection suggested for Section 18.2 is the "Integrated Benefit-Risk Evaluation" (Table 2). Only the most relevant information related to each element of the B-R framework (medical need, alternative therapies, key benefits, key risks, risk management) should be brought forward to this section (ie, do not restate details of the efficacy and safety data from Sections 16 and 17). If risk mitigation activities beyond labeling (eg, long-term observational studies, registries, health care provider letters) are ongoing or planned, these should be summarized briefly to convey how the programs will help to minimize risk, ensure that the drug is directed to only those patients for whom the risk is considered acceptable, and/or optimize the benefit-risk profile. In addition, the impact on the B-R profile of the strengths, limitations, and uncertainties of the evidence for both the benefits and risks should be discussed. Of note, economic considerations should not be considered in the B-R analysis.[2] The section should culminate in a defensible conclusion stating whether or not the benefits of the medicine outweigh the risks given the medical need, therapeutic environment, target population, strengths and limitations of the evidence, and risk mitigation plan.

Formatting Considerations for Medicines With Multiple Indications

Many medicines are approved for more than one indication that often involve distinct disease states or conditions, or are approved for distinct populations (eg, pediatric and adult). Per the ICH guideline, "A B-R profile is specific to an indication and population."[2] For medicines with more than one indication or population, separate B-R profiles should be provided where clinically appropriate. Separation allows a thorough discussion of the context (target population, epidemiology, and alternative therapies), key benefits, key risks, etc, for each indication/population.

From a practical standpoint, it facilitates writing as well as review of the PBRER if Sections 18.1 and 18.2 are grouped by indication, rather than working through all indications in Section 18.1 before moving on to Section 18.2. Table 4 shows an example of how to format Section 18, by indication, for a product with 2 indications. This method becomes particularly helpful for products with 3 or more indications, as the information for each indication will be grouped and not dispersed across multiple subsections of the document. A similar "by indication" organization should also be considered for Section 17. Note that the suggested by-indication format in Table 4 is not part of the ICH E2C(R2) guideline for the PBRER or EMA GVP Module VII for the PSUR[2,8] and does not align exactly with the suggested section numbering in the guideline. However, it does retain the recommended elements of the guidelines (ie, Sections on B-R context and B-R analysis evaluation for each indication/population).

Conclusion

"The main objective of a PBRER is to present a comprehensive, concise, and critical analysis of new or emerging information on the risks of the medicinal product, and on its benefit in approved indications, to enable an appraisal of the product's overall B-R profile."[2] A structured, systematic approach to

Table 4. Suggested Organization of Section 18 of the PBRER for Medicinal Products with >1 Indication.

Section 18. Integrated Benefit-Risk Analysis for Authorized Indications
Section 18.1. Integrated Benefit-Risk Analysis for Drug X for Indication #1.
18.1.1. Benefit-Risk Context
18.1.1.1. Medical Need
18.1.1.2. Important Alternative Therapies
18.1.2. Benefit-Risk Analysis Evaluation
18.1.2.1. Benefit-Risk Assessment Methodology
18.1.2.2. Key Benefits
18.1.2.3. Key Risks
18.1.2.4. Integrated Benefit-Risk Evaluation
Section 18.2. Integrated Benefit-Risk Analysis for Drug X for Indication #2
18.2.1. Benefit-Risk Context
18.2.1.1. Medical Need
18.2.1.2. Important Alternative Therapies
18.2.2 Benefit-Risk Analysis Evaluation
18.2.2.1. Benefit-Risk Assessment Methodology
18.2.2.2. Key Benefits
18.2.2.3. Key Risks
18.2.2.4. Integrated Benefit-Risk Evaluation

Abbreviation: PBRER, Periodic Benefit-Risk Evaluation Report.

defining a medicine's B-R profile will help ensure compliance with this ICH objective for the PBRER. Using elements common to a number of established qualitative B-R frameworks allows information relevant to a medicine's B-R profile to be conveyed in a transparent fashion that can be readily understood by various stakeholders.

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Note

i. Although the EU adopted the ICH E2C(R2) format and content, they retained the previous PSUR title.

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