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ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)

Step 5

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Table of contents

1. Introduction

The Periodic Benefit-Risk Evaluation Report (PBRER) described in this guideline is intended to be a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) among the ICH regions.

This guideline defines the recommended format and content of a PBRER and provides an outline of points to be considered in its preparation and submission.

Definitions of many technical terms used in the guideline are included in a glossary (Appendix A); the first mention of a term in the guideline is identified with an asterisk (*).

1.1. Background

When a new medicinal product is approved for marketing, demonstration of safety and efficacy are generally based on data from a limited number of patients, many studied under the controlled conditions of randomised trials. Often, higher risk subgroups and patients with concomitant illnesses that require use of other drugs are excluded from clinical trials, and long-term treatment data are limited. Moreover, patients in trials are closely monitored for evidence of adverse events. In clinical practice, monitoring is less intensive, a broader range of patients are treated (age, co-morbidities, drugs, genetic abnormalities), and events too rare to occur in clinical trials may be observed (e.g., severe liver injury). These factors underlie the need for continuing analysis of relevant safety, efficacy,[1] and effectiveness[1] information throughout the lifecycle of a medicinal product – promptly, as important findings occur – and periodically – to allow an overall assessment of the accumulating data. Although the majority of new information will be safety-related, new information about effectiveness, limitations of use, alternative treatments, and many other aspects of the drug's place in therapy may be pertinent to its benefit-risk assessment.

The ICH Guideline E2C, Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs, achieved *Step 4* in 1996, and was intended to harmonise the periodic reporting requirements to regulatory authorities and to provide, in a common format, the worldwide interval safety experience of a medicinal product at defined times post-approval. At that time, the focus of the Periodic Safety Update Report (PSUR) was on relevant new safety information in the context of patient exposure, to determine if changes were needed to the reference safety information* (RSI) in order to optimise the continued safe use of the product. The guideline was revised in 2003, to provide needed clarification, guidance and flexibility.

Since that time, the pharmacovigilance environment has evolved, prompting reassessment of the role of the PSUR in the spectrum of safety documents submitted to regulatory authorities. This reassessment highlighted several factors that led to consensus for revision and refocus of the guideline, to enhance its usefulness in light of advances in the field:

- Significant progress in the technology and science of pharmacovigilance, including electronic submission of individual case safety reports (ICSRs) to regulatory authorities, automated data mining techniques, and more attention to benefit-risk evaluation;
- Greater emphasis on proactive and documented risk management planning;
- Increasing recognition that meaningful evaluation of important new risk information should be undertaken in the context of a medicinal product's benefits; and
- Overlap in the content of ICH Guidelines related to pharmacovigilance documentation.

[1] The terms efficacy and effectiveness are not standardised, and have different meanings across some regions. See Section 2.6.

As noted above, the primary objective of the PSUR was to provide a comprehensive picture of the safety of approved medicinal products. With recognition that the assessment of the risk of a medicinal product is most meaningful when considered in light of its benefits, the proposed report would provide greater emphasis on benefit than the PSUR, particularly when risk estimates change importantly. In such cases there will need to be an overall explicit evaluation of benefit-risk. Consequently the name of the proposed report is the "Periodic Benefit-Risk Evaluation Report" (PBRER). The PBRER would also provide greater emphasis on the cumulative knowledge regarding a medicinal product, while retaining a focus on new information.

A formal evaluation of benefit is a new feature of the PBRER; however, it is recognised that a concise discussion of benefit will usually be sufficient, unless the safety or benefit-risk profile has changed significantly during the reporting interval. Thus, the level of detail provided in certain sections of the PBRER (e.g., evaluation of safety and efficacy data, evaluation of safety signals,* and benefit-risk evaluation) should be proportional to the medicinal product's known or emerging important risks and to evidence of emerging important benefits.

As the scope of the PBRER has been extended to include benefit as well as safety, the reference information for the report also needs to take this new factor into account. It is generally impractical for marketing authorisation holders (MAHs) to have one reference information source that:

- encompasses all parameters that contribute towards the benefit-risk evaluation, (i.e., benefit, efficacy/effectiveness, indication(s) and safety information);
- is common to all ICH regions; and
- addresses all circumstances, (e.g., generics, products licensed in one country only).

Therefore, this guideline proposes more practical options that MAHs can consider in selecting the most appropriate reference product information for the PBRER. These proposals incorporate the original ICH E2C concept of reference safety information (e.g., Company Core Safety Information* [CCSI]), with the addition of the approved indications for the product. This reference product information may be the Company Core Data Sheet* (CCDS) or another document proposed by the MAH (see Section 2.4).

The important baseline efficacy and effectiveness information summarised in section 17.1 of the PBRER will form the basis (or "reference") for the benefit evaluation, irrespective of the reference product information used by the MAH.

The frequency of submission of reports to regulatory authorities is subject to national or regional regulatory requirements, and may differ, depending on a number of factors. The guideline includes advice on managing different frequencies of PBRER submission in different regions.

One of the motivating factors behind revision of the ICH E2C(R1) guideline was the desire to enhance efficiency by decreasing the duplication of effort required for the preparation of various regulatory documents. This guideline has been developed, therefore, such that corresponding sections of the PBRER, DSUR (ICH E2F), and safety specification of a risk management plan (ICH E2E) can be identical in content. (See also Section 1.4, Relation of the PBRER to Other ICH Documents.)

1.2. Objectives

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 benefit-risk profile. The PBRER should contain an evaluation of new information relevant to the medicinal product that became available to the MAH during the reporting interval, in the context of cumulative information by:

- summarising relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- summarising any important new efficacy/effectiveness information that has become available during the reporting interval;
- examining whether the information obtained by the MAH during the reporting interval is in accord with previous knowledge of the medicinal product's benefit and risk profile; and
- where important new safety information has emerged, conducting an integrated benefit-risk evaluation for approved indications.

When appropriate, the PBRER should include proposed action(s) to optimise the benefit-risk profile.

Urgent safety information should be reported through the appropriate mechanism; the PBRER is not intended to be used to provide initial notification of significant new safety information or to provide the means by which new safety concerns* are detected.

1.3. Scope of the PBRER

The main focus of each PBRER is the evaluation of relevant new safety information from the available data sources, placed within the context of any pertinent efficacy/effectiveness information that may have become available since the international birth date* (IBD), the date of the first marketing approval in any country in the world, or the development international birth date (DIBD), the date of first authorisation for the conduct of an interventional clinical trial in any country.[2] All pertinent new safety and efficacy/effectiveness information discovered during the reporting interval[3] should be discussed in the appropriate sections of the PBRER.

For the purposes of this guideline, sources of available information refer to data regarding the active substance(s) included in the medicinal product or the medicinal product that the MAH may reasonably be expected to have access to, and that are relevant to the evaluation of the safety or benefit-risk profile (see also Appendix E, Examples of Sources of Information That May Be Used in the Preparation of the PBRER). For example, there may be less information available to the MAH regarding a generic product as compared to a product for which the MAH is the innovator, and only a published report may be accessible for a clinical trial not sponsored by the MAH. On the other hand, for a MAH-sponsored clinical trial, the MAH will have access to patient level data towards evaluation of the product's benefit-risk. When desired by the MAH, a list of the sources of information used to prepare the PBRER can be provided as an appendix to the report.

The PBRER should include cumulative knowledge of the product while retaining focus on new information, i.e., the overall safety evaluation and integrated benefit-risk evaluation will take into account cumulative information. Because clinical development of a drug frequently continues following marketing approval, relevant information from post-marketing studies or clinical trials in unapproved indications or populations should also be included in the PBRER. Similarly, as knowledge of the safety of a medicinal product may be derived from evaluation of data associated with uses other than the approved indication(s), such knowledge would be reflected in the risk evaluation, where relevant and appropriate.

[2] For the purpose of this document, the terms "authorisation" and "authorised" refer to clinical trials and the terms "approval" and "approved" refer to marketing applications.
[3] This guideline should not serve to limit the scope of information to be provided in the evaluation of benefit-risk of a medicinal product. Please refer to the applicable laws and regulations in the countries and regions in which the PBRER is to be submitted.

1.4. Relation of the PBRER to other ICH documents

At present, some ICH countries and regions accept submission of separate types of periodic reports to fulfil national and regional requirements within the post-approval period: the PSUR (ICH Guideline E2C(R1)) for periodic reporting of the safety of approved medicinal products, the DSUR (ICH Guideline E2F) for periodic reporting on the safety of medicinal products that remain in clinical development, and the safety specification component of ICH Guideline E2E that might be submitted at the time of marketing application and/or PSUR submission to aid in the planning of pharmacovigilance activities. As these documents have different regulatory purposes, different periodicities, and can be reviewed by different divisions within a single regulatory authority, each document needs to be complete in its own right – a comprehensive document that can stand alone. Nevertheless, overlap and inconsistencies between the content of the DSUR, PSUR, and safety specification can lead to inefficiencies in the production of the documents by the MAH.

Modular approach

This guideline aims to facilitate flexibility by encouraging the use of individual sections that are common to more than one report – "modules" that can be used for different regulatory authorities and for different purposes. Therefore, the PBRER has been developed in such a way that the content of several sections may be used for sections of other documents as a basis for a modular approach. For example, if the DIBD of a DSUR for a medicinal product is aligned to the IBD of the PBRER for the same product as suggested in ICH E2F, the content of a number of sections of the DSUR can also be used in the PBRER when the data lock points (DLPs) are the same, i.e., when each report covers an interval of one year based on the IBD.

Appendix D of this guideline lists the PBRER sections that can be shared with either the DSUR (ICH E2F) or safety specification of a risk management plan (ICH E2E), if appropriate.

The use of common sections across the PBRER, DSUR and safety specification as a modular approach has a number of advantages:

- maximizes the utility of the modules across multiple regulatory documents;
- promotes consistency across the PBRER, DSUR and Safety Specification;
- avoids unnecessary duplication of effort;
- is expected to improve efficiency for MAHs in the preparation of these documents;
- facilitates flexible utilisation of existing sections (modules) when, for example, the PBRER covers different time intervals or needs to be submitted at different times to multiple different authorities. In these circumstances, only modules that include new information or new evaluation would need to be updated when submitting the PBRER.

Although currently out of scope for ICH E2C(R2), it is envisioned that the modular approach proposed, based on common sections across various documents, will ultimately facilitate development of electronic modules for use in future regulatory submissions.

2. General principles

2.1. Single PBRER for an active substance

The PBRER should provide information on all approved indications, dosage forms, and regimens for the active substance, with a single DLP. In some circumstances, it will be appropriate to present data by

indication, dosage form, dosing regimen, or population (e.g., children vs. adults) within the relevant section(s) of the PBRER. In exceptional cases, submission of separate PBRERs might be appropriate, for example, an active substance used in two formulations for systemic and topical administration in entirely different indications. In these cases, the regulatory authorities should be notified and their agreement obtained, preferably at the time of approval.

2.2. PBRERs for fixed dose combination product

For combinations of substances also marketed individually, information for the fixed combination may be reported either in a separate PBRER or included as separate presentations in the report for one of the individual substances, depending on the circumstances. Listing related PBRERs is considered important.

2.3. Products manufactured and/or marketed by more than one company

Each MAH is responsible for submitting PBRERs for its own products.

When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PBRER to the regulatory authorities should be clearly specified in the written agreement.

When data received from a partner company(ies) might contribute meaningfully to the safety, benefit, and/or benefit-risk analyses and influence the reporting company's product information, these data should be included and discussed in the PBRER.

2.4. Reference information

An objective of a PBRER is to evaluate whether information obtained during the reporting interval is in accord with previous knowledge on the product's benefit and risk profile, and to indicate whether changes should be made to the reference product information. Having one reference source of information that can be applied across the three ICH regions would facilitate a practical, efficient, and consistent approach to the benefit-risk evaluation and make the PBRER a unique report accepted in all countries and regions.

The reference product information for the PBRER would include "core safety" and "approved indications" components. In order to facilitate the assessment of benefit and benefit-risk by indication in the evaluation sections of the PBRER, the reference product information document should list all approved indications in ICH countries or regions. It is likely that these indications will also apply in other countries or regions. However, when the PBRER is also to be submitted to other countries in which there are additional locally approved indications, these indications may either be added to the reference product information or handled as a regional appendix/appendices as considered most appropriate by the MAH. The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarised in Section 17.1 of the PBRER.

The following possible options can be considered by MAHs in selecting the most appropriate reference product information for a PBRER:

- Company Core Data Sheet

In accordance with ICH E2C (R1) recommendations, it is a common practice for MAHs to prepare their own CCDS, which includes sections relating to safety, indications, dosing, pharmacology, and other information concerning the medicinal product. The core safety information contained within the CCDS is referred to as the CCSI. A practical option is for MAHs to use the latest CCDS in effect at the end of

the reporting interval as the reference product information for both the risk sections of the PBRER as well as the main approved indications for which benefit is evaluated.

When the CCDS for a medicinal product does not contain information on approved indications, the MAH should clearly specify which document is used as the reference information for the approved indications in the PBRER.

- Other options for the reference product information

When there is no CCDS or CCSI for a product, e.g., where the product is approved in only one country or region or for established/generic products on the market for many years, the MAH should clearly specify the reference information being used. This may comprise national or regional product information such as the US Package Insert (USPI) or European Summary of Product Characteristics (SmPC), or the Japanese package insert, as appropriate. The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarised in Section 17.1 of the PBRER.

Where the reference information for approved indications is a separate document to the RSI, the version current at the DLP of the PBRER should be included in Appendix 1.

The MAH should continuously evaluate whether any revision of the reference product information/RSI is needed whenever new safety information is obtained throughout the reporting interval. Significant changes to the reference product information/RSI made during the interval should be described in Section 4 of the PBRER ("Changes to Reference Safety Information") and include:

- changes to contraindications, warnings/precautions sections of the RSI;
- addition of ADR(s) and interactions;
- addition of important new information on use in overdose; and
- removal of an indication or other restrictions for safety or lack of efficacy reasons.

Significant changes to the RSI made after the DLP but before submission of the PBRER should be included in Section 14 of the report (Late Breaking Information), if feasible.

If stipulated by applicable regional requirements, the MAH should provide, in a regional appendix, information on any final, ongoing, or proposed changes to the national or local authorised product information.

2.5. Level of detail within PBRER

The level of detail provided in certain sections of the PBRER should depend on the medicinal product's known or emerging important benefits and risks. This approach is applicable to those sections of the PBRER in which there is evaluation of safety data, efficacy/effectiveness data, safety signals, and benefit-risk. Therefore, the extent of information provided in such PBRER sections will vary among individual PBRERs.

For example, when there is important new safety information, a detailed presentation of that information should be included, plus the relevant benefit information, in order to facilitate a robust benefit-risk analysis. Conversely, when little new important safety information has become available during the reporting interval, a concise summary of baseline benefit information should be sufficient, and the benefit-risk evaluation would consist primarily of an evaluation of updated interval safety data.

2.6. Efficacy/Effectiveness

For the purpose of this guideline, evidence on benefits in clinical trials and in everyday medical practice should be reported. Because the terms are not harmonized across regions, the terms

'efficacy/effectiveness' are used in this guideline to clarify that information from both clinical trials and everyday medical practice are within the scope of the information on benefit to be included within the PBRER. In some regions, efficacy refers to evidence of benefit from controlled clinical trials while effectiveness implies use in everyday medical practice. Conversely, in other regions, this distinction is not made.

2.7. Benefit-risk evaluation

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, benefit-risk evaluation should be carried out to determine whether benefits continue to outweigh risks, and to consider whether steps need to be taken to improve the benefit-risk balance through risk minimisation activities, e.g., labelling changes, communications with prescribers, or other steps.

2.8. Periodicity and PBRER data lock point

2.8.1. International birth date and data lock point

Each medicinal product should have an IBD: the IBD is the date of the first marketing approval for any product containing the active substance granted to any company in any country in the world. When a report contains information on different dosage forms, formulations, or uses (indications, routes and/or populations), the date of the first marketing approval for any of the various authorisations should be regarded as the IBD and, therefore, determine the DLP for purposes of the PBRER. The DLP is the date designated as the cut-off for data to be included in a PBRER. Through PBRERs prepared with harmonised DLPs based on a common IBD, the same updated safety and benefit-risk information can be reviewed globally by different regulatory authorities.

When a separate PBRER is prepared for a fixed-dose combination product (see Section 2.2), the DLP for that PBRER can be based on either the earliest IBD of one of the component active substances, or the IBD of the first marketing approval anywhere in the world for the fixed-dose combination.

When clinical development of a medicinal product continues following marketing approval, if desired by the sponsor/MAH, the beginning of the DSUR reporting interval can be synchronized with the IBD-based cycle, so that both the DSUR and PBRER can be prepared at the same time, using the same DLP. This approach will facilitate use of the proposed common sections/modules for both the PBRER and DSUR when both are submitted annually (see Appendix D).

2.8.2. Managing different frequencies of PBRER submission

The need for the submission of a PBRER and the frequency of report submission to regulatory authorities are subject to national or regional regulatory requirements, and usually depend on such factors as approval dates, the length of time the product has been on the market, and the extent of knowledge of the benefit-risk profile of the product. The PBRER format and content are intended to apply to periodic reports that cover reporting periods of 6 months or longer. Once a drug has been marketed for several years, national or regional regulation may allow the frequency of submission to be extended to longer time intervals, e.g., greater than one year for products considered to have an established and acceptable profile or considered to be low risk; however, more frequent PBRERs may continue to be required in other regions. As a result, the following scenarios may be encountered by MAHs:

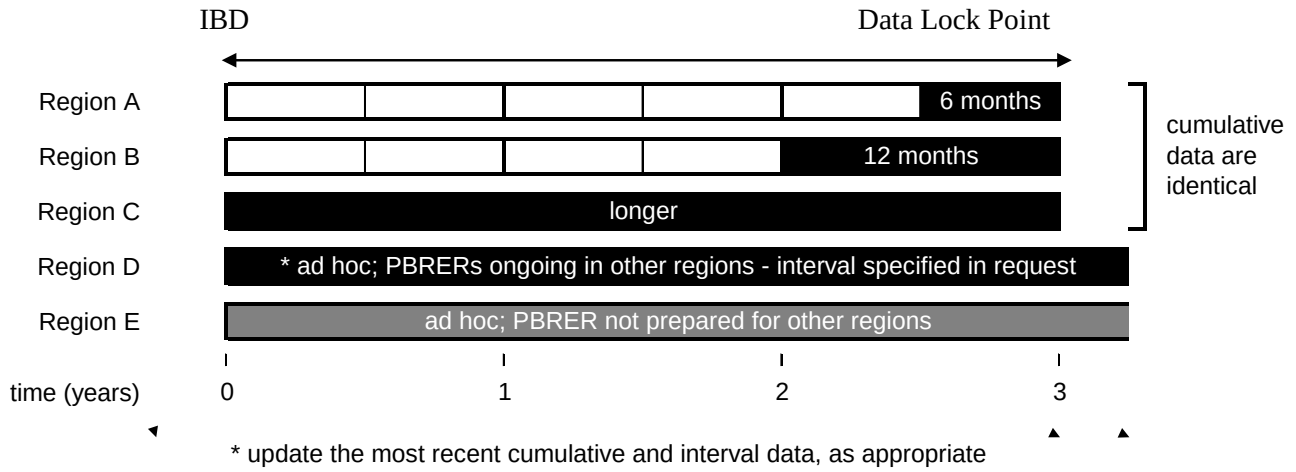
- PBRERs may be required on 6-monthly, annual, and less frequent submission timetables simultaneously across different regions.
- Changes in reporting frequency may also apply after important additions or changes in clinical use are approved (e.g., new indication[s] and/or new population[s]). In these circumstances, it is possible that the reporting interval will be shortened, even for older products with a previously reduced frequency of PBRER submission.
- An *ad hoc* PBRER may be requested by a regulatory authority (see Section 2.8.2.1 of this guideline).

Independent of the length of the interval covered by the report:

- Each PBRER should be stand-alone and reflect new and cumulative information currently available to the MAH.
- Regulators will normally accept use of the IBD to determine the DLP for PBRERs. Where national or regional requirements differ from this, the MAH may wish to discuss with the relevant regulatory authority. Use of a single harmonised IBD and DLP for each product is important in order to reduce the burden of work involved in preparing PBRERs, and respects the original purpose of the PBRER – to prepare a single worldwide summary on a product that can be submitted to different regulatory authorities.
- For newly approved products, a 6-monthly periodicity applies in many regions, for at least the first 2 years after approval.
- For PBRERs submitted on a routine/regular basis, the reports should be based on cumulative data, with interval data sets of 6 months, or multiples thereof.
- Sections that provide interval information are likely to need to be updated for each PBRER, and the content used in the previous PBRER can be reviewed and reused for sections where no new information has arisen since preparation of the last PBRER, if appropriate. Following review, it may be determined that sections providing evaluation of cumulative data may not need to be updated if the content remains up to date with current information. See Figure 1.
- In situations when an MAH is preparing PBRERs on both a six-monthly and annual basis for different regulatory authorities, the regulatory authority requiring a PBRER on a six-month cycle may accept PBRERs containing 12-month interval data. See Figure 2. MAHs should discuss the acceptability of this approach with the relevant regulatory authority(ies).

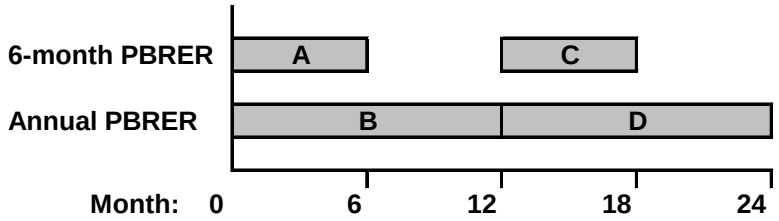
Figure 1: Submission of PBRERs Based on the Same Data Lock Point, with Various Reporting Periods.

Shading indicates period of interval data.
For all reports, the cumulative data reflect all data from the IBD/DIBD**.



** Cumulative Clinical Trial Summary Tabulation of Serious Adverse Events & Clinical Trial Exposure data only

Figure 2: Submission of 6-Month and Annual PBRERs



Region 1 requires 6-monthly PBRER, and receives PBRER A, B, C, and D (assuming agreement has been reached with pertinent regulatory authority[ies]).

Region 2 requires annual PBRER, and receives PBRER B and D.

2.8.2.1. Ad hoc ("for cause") PBRERs

Ad hoc PBRERs are reports outside the routine reporting requirements, and may be requested by some regulatory authorities. Where an *ad hoc* report is requested and a PBRER has not been prepared for a number of years, it is likely that a completely new report will need to be prepared by the MAH.

2.8.3. Time interval between data lock point and the submission

As a result of the expanded scope of the PBRER, the time interval between the DLP and submission of PBRERs should be as follows:

- PBRERs covering intervals of 6 or 12 months: within 70 calendar days;
- PBRERs covering intervals in excess of 12 months: within 90 calendar days;
- *ad hoc* PBRERs: 90 calendar days, unless otherwise specified in the *ad hoc* request.

The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission. Where national or regional requirements differ from the above, the MAH should discuss the timeline for submission with the relevant regulatory authority.

2.9. Format and presentation of PBRER

2.9.1. Format

The recommended format and content of the PBRER, including table of contents, section numbering, and content of each section, is outlined below.

The full ICH Guideline E2C(R2) format should be used for all PBRERs. When no relevant information is available or a PBRER section is not applicable, this should be stated. Particular sections of the PBRER may share content with other regulatory reports, e.g., documents described in ICH guidelines E2E and E2F. It may be possible for the MAHs to take advantage of the modular approach of the PBRER (i.e., sections that can be separated and submitted independently or combined with other documents) to facilitate such regulatory needs, maximize the utility of the content, and reduce duplicate work.

2.9.2. Presentation

The recommended table of contents, including section numbering, for the PBRER is provided below:

Title Page

Executive Summary

Table of Contents

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns
   - 5.1 Cumulative Subject Exposure in Clinical Trials
   - 5.2 Cumulative and Interval Patient Exposure from Marketing Experience
6. Data in Summary Tabulations
   - 6.1 Reference Information

3. Guidance on contents of the PBRER

All sections should be completed, and when no information is available, this should be stated. Note that Section “3.N” of this guideline provides guidance on the content of Section “N” of the PBRER. For example, “Reference Information,” described in Section 3.6.1 of this guideline corresponds to Section 6.1 of the PBRER.

Title Page

The title page of the PBRER should include the following information:

- Date of the report;
- Medicinal product(s);

- IBD;
- Reporting interval;
- MAH(s) name(s) and address(es); and
- Any statement on the confidentiality of the information included in the PBRER.

Executive summary

This section should provide a concise summary of the most important information contained in the report.

The following information should be included in the Executive Summary:

- Introduction;
- Reporting interval;
- Medicinal product(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);
- Estimated cumulative exposure of clinical trial subjects; interval and cumulative post-approval exposure;
- Number of countries in which the medicinal product is approved;
- Summary of overall benefit-risk evaluation (based on Section 18.2 of the PBRER);
- Actions taken or proposed for safety reasons, e.g., significant changes to the reference product information, other risk minimisation activities; and
- Conclusions.

Table of Contents

3.1. Introduction

- Section 1 of the PBRER should include:
- IBD;
- reporting interval;
- medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);
- a brief description of the approved indication(s) and population(s);
- a brief description and explanation of any information that has not been included in the PBRER; and
- the rationale for submission of multiple PBRERs for the medicinal product, if applicable.

3.2. Worldwide marketing approval status

Section 2 of the PBRER should provide a brief narrative overview including date of first approval, indication(s), approved dose(s), and where approved, if applicable.

3.3. Actions taken in the reporting interval for safety reasons

Section 3 of the PBRER should include a description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsor of a clinical trial(s), regulatory authorities, data monitoring committees, or ethics committees that had:

- A significant influence on the benefit-risk profile of the approved medicinal product; and/or
- An impact on the conduct of a specific clinical trial(s) or on the overall clinical development programme.

The reason(s) for each action should be provided, if known, and additional relevant information should be provided when appropriate. Relevant updates to previous actions should also be summarised in this section. Examples of significant actions taken for safety reasons include:

Actions related to investigational drugs:*

- Refusal to authorise a clinical trial for ethical or safety reasons;
- Partial[4] or complete clinical trial suspension or early termination of an ongoing clinical trial* because of safety findings or lack of efficacy;
- Recall of investigational drug or comparator;
- Failure to obtain marketing approval for a tested indication, including voluntary withdrawal of a marketing application;
- Risk management activities, including:
  - protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion/exclusion criteria, intensification of subject monitoring, limitation in trial duration);
  - restrictions in study population or indications;
  - changes to the informed consent document relating to safety concerns;
  - formulation changes;
  - addition by regulators of a special safety-related reporting requirement;
  - issuance of a communication to investigators or healthcare professionals; and
  - plans for new studies to address safety concerns.

Actions related to marketed drugs:

- failure to obtain or apply for a marketing approval renewal;
- withdrawal or suspension of a marketing approval;
- suspension of supply by the MAH;
- risk management activities including:
  - significant restrictions on distribution or introduction of other risk minimisation measures;

[4] "Partial suspension" might include several actions (e.g., suspension of repeat dose studies, but continuation of single dose studies; suspension of trials in one indication, but continuation in another, and/or suspension of a particular dosing regimen in a trial but continuation of other doses).

- significant safety-related changes in labelling documents that could affect the development programme, including restrictions on use or population treated;
- communications to health care professionals; and
- new post-marketing study requirement(s) imposed by regulator(s).

3.4. Changes to reference safety information

Section 4 of the PBRER should list any significant changes to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, adverse drug reactions (ADRs), overdose, and interactions; important findings from ongoing and completed clinical trials;* and significant non-clinical findings (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the PBRER.

A clean version of the reference document that is current at the DLP of the PBRER should be included in Appendix 1. A track change version of the reference information is not required.

3.5. Estimated exposure and use patterns

Sections 5.1 and 5.2 of the PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. Section 5.1 of the PBRER should provide information on cumulative exposure in clinical trials. Section 5.2 should provide cumulative and interval exposure in the marketed setting. Brief descriptions of the method(s) used to estimate the subject/patient exposure should be provided, as well as the limitations thereof. Consistent methods for calculating patient exposure should be used across PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PBRER introducing the change.

3.5.1. Cumulative subject exposure in clinical trials

Section 5.1 of the PBRER should include the following information, if applicable, presented in tabular format (see Appendix B, Tables 1-3 for examples):

- Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD. It is recognised that for older products, precise data might not be available.
- More detailed cumulative subject exposure in clinical trials should be presented if available, e.g., sub-grouped by age, sex, and racial/ethnic group for the entire development programme.
- Important differences among trials in dose, routes of administration, or patient populations can be noted in the tables, if applicable, or separate tables can be considered.
- If clinical trials have been or are being performed in special populations (e.g., pregnant women; patients with renal, hepatic, or cardiac impairment; or patients with relevant genetic polymorphisms), exposure data should be provided, as appropriate.
- When there are substantial differences in duration of exposure between subjects randomised to the investigational medicinal product or comparator(s), or disparities in duration of exposure between clinical trials, it can be useful to express exposure in subject-time (subject-days, -months, or -years).

- Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, depending on the type of adverse reaction, particularly when subjects are exposed to a single dose. Such data can be presented separately with an explanation as appropriate.
- If the serious adverse events (SAEs) from clinical trials are presented by indication in the summary tabulations, the patient exposure should also be presented by indication, where available.
- For individual trials of particular importance, demographic characteristics should be provided separately.

3.5.2. Cumulative and interval patient exposure from marketing experience

Separate estimations should be provided for interval exposure (since the DLP of the previous PBRER) and, when possible, cumulative exposure (since the IBD). See Appendix B, Tables 4 and 5 for examples. The estimated number of patients exposed should be provided when possible, along with the method(s) used to determine the estimate. If an estimate of the number of patients is not available, alternative estimated measures of exposure should be presented along with the method(s) used to derive them, if available. Examples of alternative measures of exposure include patient-days of exposure and number of prescriptions. Only if such measures are not available, measures of drug sales, such as tonnage or dosage units, may be used. The concept of a defined daily dose may also be used to estimate patient exposure.

The data should be presented according to the following categories:

1. Post-approval (non-clinical trial) exposure:

An overall estimation of patient exposure should be provided.

In addition, the data should be routinely presented by indication, sex, age, dose, formulation, and region, where applicable.

Depending upon the product, other variables may be relevant, such as number of vaccination courses, route(s) of administration, and duration of treatment.

When there are patterns of reports indicating a safety signal, exposure data within relevant subgroups should be presented, if possible.

2. Post-approval use in special populations:

Where post-approval use has occurred in special populations, available information regarding cumulative patient numbers exposed and the method of calculation should be provided. Sources of such data include non-interventional studies designed to obtain this information, including registries. Populations to be considered for discussion include, but might not be limited to:

- Paediatric population;
- Elderly population;
- Pregnant or lactating women;
- Patients with hepatic and/or renal impairment;
- Patients with other relevant co-morbidity;
- Patients with disease severity different from that studied in clinical trials;
- Sub-populations carrying relevant genetic polymorphism(s); and

- Patients of different racial and/or ethnic origins.

3. Other post-approval use:

If the MAH becomes aware of patterns of use of the medicinal product considered relevant for the interpretation of safety data, provide a brief description thereof. Examples of such patterns of use may include overdose, drug abuse, misuse, and use beyond that recommended in the reference product information (e.g., an anti-epileptic drug used for neuropathic pain and/or prophylaxis of migraine headaches). Such patterns may be regional. If known, the MAH may briefly comment on whether use beyond that recommended in the reference product information is supported by clinical guidelines, clinical trial evidence, or an absence of approved alternative treatments. Quantitative use information should be provided, if available. For purposes of identifying patterns of use outside the terms of the reference product information, the MAH should use the appropriate sections of the reference product information that was in effect at the DLP of the PBRER (e.g., approved indication, contraindications).

3.6. Data in summary tabulations

PBRER Sections 6.1 to 6.3 should present cumulative summary tabulations of SAEs from clinical trials and post-marketing sources that have been reported to the MAH since the DIBD. At the discretion of the MAH, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

3.6.1. Reference information

Section 6.1 of the PBRER should specify the version(s) of the coding dictionary used for analyses of adverse reactions.

3.6.2. Cumulative summary tabulations of serious adverse events from clinical trials

Section 6.2 of the PBRER should provide background for the appendix that provides a cumulative summary tabulation of SAEs reported in the MAH's clinical trials, from the DIBD to the DLP of the current PBRER. The MAH should explain any omission of data (e.g., clinical trial data might not be available for products marketed for many years). The tabulation(s) should be organised by system organ class (SOC), for the investigational drug, as well as for the comparator arm(s) (active comparators, placebo) used in the clinical development programme. Data can be integrated across the programme. Alternatively, when useful and feasible, tabulations of SAEs can be presented by trial, indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the SAEs.

Appendix B, Table 6 of this guideline provides an example of summary tabulations of SAEs from clinical trials. The following points should be considered:

- In general, the tabulation(s) of SAEs from clinical trials should include only those terms that were used in defining the case as serious; they should not include non-serious events.
- When the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level and SOC should be presented in the summary tabulations.
- The tabulations should include blinded and unblinded clinical trial data. Unblinded SAEs might originate from completed trials and individual cases that have been unblinded for safety-related

reasons (e.g., expedited reporting), if applicable. Sponsors/MAHs should not unblind data for the specific purpose of preparing the PBRER.

- Certain adverse events in clinical trials can be excluded from the clinical trials summary tabulations, but such exclusions should be explained in the report. For example, adverse events that have been defined in the protocol as "exempt" from special collection and entry into the safety database because they are anticipated in the patient population, and those that represent study endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).
- Causality assessment is generally useful for the evaluation of individual rare ADRs. Individual case causality assessment has less value in the analysis of aggregate data, where group comparisons of rates are possible. Therefore, the summary tabulations should include all SAEs for the investigational drug, active controls, and placebo. It may be useful to give rates by dose.

3.6.3. Cumulative and interval summary tabulations from post-marketing data sources

Section 6.3 of the PBRER should provide background for the appendix that provides cumulative and interval summary tabulations of adverse reactions, from the IBD to the DLP of the current PBRER. As described in ICH Guideline E2D, for marketed medicinal products, spontaneously reported* adverse events usually imply at least a suspicion of causality by the reporter, and should be considered to be adverse reactions for regulatory reporting purposes. The tabulation should include:

- serious and non-serious adverse drug reactions from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities;
- serious adverse reactions from non-interventional studies; and
- solicited reports* of serious adverse reactions.

The tabulation should include interval and cumulative data presented side-by-side (see Appendix B, Table 7), and should be organised by SOC.

For special issues or concerns, additional tabulations of adverse reactions can be presented by indication, route of administration, or other variables. This section should not serve to provide analyses or conclusions based on the data presented.

3.7. Summaries of significant safety findings from clinical trials during the reporting interval

This section of the PBRER should provide a brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the MAH's sponsored clinical trials that became available during the reporting interval of the report. The safety signals arising from clinical trial sources should be tabulated in Section 15 of the PBRER. Evaluation of the signals (whether or not categorised as refuted signals or either potential* or identified risks*) that were closed during the reporting interval should be presented in Section 16.2 of the PBRER. New information in relation to any previously known potential or identified risks and not considered to constitute a newly identified signal should be evaluated and characterised in Sections 16.3 and 16.4, respectively. Findings from clinical trials not sponsored by the MAH should be described in the relevant sections of the PBRER.

When relevant to the benefit-risk evaluation, information on lack of efficacy from clinical trials for treatments of non-life-threatening diseases in approved indications should also be summarised in this

section. Information on lack of efficacy from clinical trials with products intended to treat or prevent serious or life-threatening illnesses should be summarised in Section 13 of the PBRER.

When possible and relevant, data categorized by sex and age (particularly children versus adult), indication, dose, and region should be presented.

A listing of any MAH-sponsored post-marketing interventional trials with the primary aim of identifying, characterising, or quantifying a safety hazard, or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval should be included in an appendix. The listing should include the following information for each trial:

- Study ID (e.g., protocol number or other identifier);
- Study title (abbreviated study title, if applicable);
- Study type (e.g., randomized clinical trial, cohort study, case-control study);
- Population studied (including country and other relevant population descriptors, e.g., paediatric population or trial subjects with impaired renal function);
- Study start (as defined by the MAH) and projected completion dates;
- Status:
- Ongoing (clinical trial has begun);
- Completed (clinical study report is finalised).

3.7.1. Completed clinical trials

Section 7.1 of the PBRER should provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval. This information can be presented in narrative format or as a synopsis.[5] It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

3.7.2. Ongoing clinical trials

If the MAH is aware of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events), this section should briefly summarise the concern(s). It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

3.7.3. Long-term follow-up

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products.

3.7.4. Other therapeutic use of medicinal product

This section of the PBRER should include clinically important safety information from other programmes conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH Guideline E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single-patient investigational new drug applications [INDs], treatment INDs, and other organised data collection).

[5] Examples of synopses are provided in ICH E3 and CIOMS VII.

3.7.5. New safety data related to fixed combination terapies

Unless otherwise specified by national or regional regulatory requirements, the following options can be used to present data from combination therapies:

- If the product that is the subject of a PBRER is also approved or under development as a component of a fixed combination product or a multi-drug regimen, this section should summarise important safety findings from use of the combination therapy.
- If this PBRER is for a fixed combination product, this section should summarise important safety information arising from the individual components.

The information specific to the combination can be incorporated into a separate section(s) of the PBRER for one or all of the individual components of the combination.

3.8. Findings from non-interventional studies

This section should summarise relevant safety information or information with potential impact on the benefit or risk evaluations, from MAH-sponsored non-interventional studies that became available during the reporting interval (e.g., observational studies, epidemiological studies, registries, and active surveillance programmes). This should include relevant information from drug utilisation studies when applicable to multiple regions.

A listing of any MAH-sponsored post-marketing non-interventional study(ies) with the primary aim of identifying, characterising, or quantifying a safety hazard, confirming the safety profile of the medicinal product, or measuring the effectiveness of risk management measures that were completed or ongoing during the reporting interval should be included in an appendix (see Section 3.7 of this guideline for the information that should be included in the listing).

Final study reports completed during the reporting interval for the studies mentioned in the paragraph above should also be included in the regional appendix of the report where stipulated by regional requirements.

3.9. Information from other clinical trials and sources

3.9.1. Other clinical trials

This subsection should summarise information accessible to the MAH with reasonable and appropriate effort from any other clinical trial/study sources, including results from pooled analyses or meta-analyses of randomised clinical trials, and safety information provided by co-development partners or from investigator-initiated trials.

3.9.2. Medication errors

This subsection should summarise relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes. A potential medication error is the recognition of circumstances that could lead to a medication error, and may or may not involve a patient. Such information may be relevant to the interpretation of safety data or the overall benefit-risk evaluation of the medicinal product. A medication error may arise at any stage in the medication use process, and may involve patients, consumers, or healthcare professionals.

This information may be received by the MAH via spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other available information sources.

Signals or risks identified from any information source and/or category of reports should be presented and evaluated in the relevant section of the PBRER.

3.10. Non-clinical data

This section should summarise major safety findings from non-clinical *in vivo* and *in vitro* studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting interval. Results from studies designed to address specific safety concerns should be included in the PBRER, regardless of the outcome. Implications of the findings presented in PBRER Section 10 should be discussed in the relevant evaluation sections of the report.

3.11. Literature

This section should summarise new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts, relevant to the approved medicinal product that the MAH became aware of during the reporting interval. Literature searches for PBRERs should be wider than those for individual adverse reaction cases, and include studies reporting safety outcomes in groups of subjects. If relevant, information on active substances of the same class should be considered.

3.12. Other periodic reports

Unless otherwise specified by national or regional regulatory requirements, the MAH should prepare a single PBRER for a single active substance. However, if an MAH prepares multiple PBRERs for a single active substance (e.g., covering different indications, or formulations), this section should summarise significant findings from the other periodic reports if they are not presented elsewhere within this report.

When available, based on contractual agreements, the MAH should summarise significant findings from periodic reports provided during the reporting interval by other parties (e.g., sponsors, MAHs, other contractual partners).

3.13. Lack of efficacy in controlled clinical trials

Data from clinical trials indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for products intended to treat or prevent serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes) could reflect a significant risk to the treated population and should be summarised in this section.

3.14. Late-breaking information

This section should summarise information on potentially important safety and efficacy/effectiveness findings that arise after the DLP but while the PBRER is in preparation. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings and any action that the MAH, a data monitoring committee, or a regulatory authority has taken for safety reasons. New individual case reports should not be included unless they are considered to constitute an important index case (i.e., the first instance of an important event), an important safety signal, or

where they may add information to the evaluation of safety concerns already presented in the PBRER (e.g., a well-documented and unconfounded case report of aplastic anaemia in a medicinal product known to be associated with adverse effects on the bone marrow).

Any significant change proposed to the reference product information which has occurred after the DLP of the report but before submission should also be included in this section, where feasible. Such changes could include a new contraindication, warning/precaution, or new adverse drug reaction.

The data presented in this section should also be taken into account in the evaluation of risks and new information (see Section 3.16.3 of this guideline).

3.15. Overview of signals: new, ongoing, or closed

The general location for presentation of information on signals and risks within the PBRER is shown in Appendix F of this guideline. The purpose of Section 15 of the PBRER is to provide a high level overview of safety signals that were closed (i.e., the evaluation was completed) during the reporting interval as well as ongoing signals* that were undergoing evaluation, at the end of reporting interval. For the purposes of the PBRER, a signal should be included once it has undergone the initial screening or clarification step, and a determination made to conduct further evaluation by the MAH. It should be noted that a safety signal is not synonymous with a statistic of disproportionate reporting for a specific drug/event combination as a validation step is required. Signals may be qualitative (e.g., a pivotal individual safety case report, case series) or quantitative (e.g., a disproportionality score, findings of a clinical trial or epidemiological study). Signals may arise in the form of an information request or inquiry on a safety issue from a regulatory authority.

Decisions regarding the subsequent classification of these signals and the conclusions of the evaluation involve medical judgement and scientific interpretation of available data, which is presented in Section 16 of the PBRER.

A new signal is a signal that the MAH became aware of during the reporting interval. New clinically important information on a previously closed signal* that became available during the reporting period of the PBRER (i.e., a new aspect of a previously refuted signal or recognised risk likely to warrant further action to verify) would also constitute a new signal. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the DLP of the PBRER. Examples would include new information on a previously:

- closed and refuted signal, which would result in the signal being re-opened;
- identified risk which is indicative of a clinically significant difference in the severity of the risk, e.g., transient liver enzyme increases are identified risks and new information is received indicative of a more severe outcome such as hepatic failure; neutropenia is an identified risk and a well-documented and unconfounded case report of agranulocytosis is received;
- identified risk for which a higher frequency of the risk is newly found, e.g., in a subpopulation; and
- potential risk* which, if confirmed, would warrant a new warning, precaution, a new contraindication or restriction in indication(s) or population or other risk minimisation activities.

Within this section, or as an appendix, include a tabular listing of all signals ongoing or closed at the DLP of the PBRER. This table should include the following information. See Appendix C for an example.

- a brief description of the signal;
- date when the MAH became aware of the signal;

- status of the signal (closed or ongoing at the DLP);
- date when the signal was closed, if applicable;
- source of the signal;
- a brief summary of key data;
- plans for further evaluation; and
- actions taken or planned.

Detailed signal evaluations for closed signals are not to be included in this section but instead should be presented in Section 16.2 (Signal Evaluation) of the PBRER. Evaluation of new information in relation to any previously known identified and potential risks and not considered to constitute a newly identified signal* should be provided in Section 16.3 (Evaluation of Risks and New Information) of the PBRER.

When a regulatory authority has requested that a specific topic (not considered a signal) be monitored and reported in a PBRER, the MAH should summarize the result of the analysis in PBRER Section 15 if it is negative. If the specific topic becomes a signal, include it instead in the signal tabulation and discuss in PBRER Section 16.2.

3.16. Signal and risk evaluation

The purpose of Section 16 of the PBRER is to provide:

- A succinct summary of what is known about important identified and potential risks and important missing information* at the beginning of the reporting interval covered by the report (16.1);
- An evaluation of all signals closed during the reporting interval (16.2);
- An evaluation of new information with respect to previously recognised identified and potential risks (16.3);
- An updated characterisation of important potential and identified risks ,where applicable (16.4); and
- A summary of the effectiveness of risk minimisation activities in any country or region which may have utility in other countries or regions (16.5).

Appendix F of this guideline provides a flowchart to illustrate the mapping of signals and risks to specific sections of the PBRER.

The evaluation subsections should not summarise or repeat information presented in previous sections of the PBRER, but should instead provide an interpretation of the information, with a view towards characterising the profile of those risks assessed as important. As a general rule, it is not necessary to include individual case narratives in the evaluation sections of the PBRER; however, when integral to the scientific analysis of a signal or risk, a clinical evaluation of pivotal or illustrative cases (e.g., the first case of suspected agranulocytosis with an active substance belonging to a class known to be associated with this adverse reaction) should be provided.

3.16.1. Summary of safety concerns

The purpose of this section is to provide a summary of safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. These comprise:

- important identified risks;*
- important potential risks;* and
- important missing information.

The following factors should be considered when determining whether or not a risk is important:

- medical seriousness of the risk, including the impact on individual patients;
- its frequency, predictability, preventability, and reversibility;
- potential impact on public health (frequency; size of treated population); and
- potential for avoidance of a medical product with a preventive benefit as a result of public perception of risk.

For products with an existing safety specification, this section can be either the same as, or be derived from, the safety specification summary (according to ICH guideline E2E) at the start of the reporting interval of the current PBRER. For products without an existing safety specification, this section should provide information on the important identified and potential risks and important missing information associated with use of the product, based on pre- and post-approval experience. Important identified and potential risks may include, for example:

- important adverse reactions;
- interactions with other medicinal products;
- interactions with foods and other substances;
- medication errors;
- effects of occupational exposure; and
- pharmacological class effects.

The summary on important missing information should take into account whether there are critical gaps in knowledge for specific safety issues or populations that use the medicinal product.

3.16.2. Signal evaluation

Section 16.2 of the PBRER should summarize the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. A safety signal can be closed either because it is refuted or because it is determined to be a potential or identified risk following evaluation. Therefore, the two main categories to be included in this section are:

1. Those signals that, following evaluation, have been refuted as “false” signals based on medical judgment and a scientific evaluation of the currently available information.
2. Those signals that, following evaluation, have been categorised as either a potential or identified risk, including lack of efficacy.

For both categories of closed signals, a concise description of each signal evaluation should be included in order to provide to the regulatory authorities the basis upon which the signal was either refuted or considered to be a potential or identified risk by the MAH.

It is recommended that the level of detail provided in the description of the signal evaluation be proportionate to the medical significance of the signal, its public health importance, and the extent of

the available evidence. When multiple evaluations are included under both categories of closed signals, they can be presented in the following order:

- closed and refuted signals;
- closed signals that are categorised as important potential risks;
- closed signals that are categorised as important identified risks;
- closed signals that are potential risks not categorised as important; and
- closed signals that are identified risks not categorised as important.

Where applicable the closed signal evaluations can be presented by indication or population.

The description(s) of the signal evaluations can be included in this section of the PBRER, or in an appendix. Each signal evaluation should include the following information as appropriate:

- source of the signal;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms [e.g., PTs, HLTs, SOCs, etc.] or Standardised MedDRA Queries [SMQs] that were reviewed), and analytical approaches;
- results – a summary and critical analysis of the data considered in the signal evaluation; where integral to the assessment, this may include a description of a case series or an ICSR, e.g., an index case of well documented agranulocytosis or Stevens Johnson syndrome;
- discussion; and
- conclusion.

3.16.3. Evaluation of risks and new information

This section should provide a critical appraisal of new information relevant to previously recognised risks that is not already included in Section 16.2 of the PBRER, Signal Evaluation.

New information that constitutes a signal with respect to a previously recognised risk or previously refuted signal should be presented in the tabular summary in Appendix C and evaluated in Section 16.2 of the PBRER, if the signal is also closed during the interval of the PBRER.

Updated information on a previously recognised risk that does not constitute a signal should be included in this section. Examples include information that confirms a potential risk as an identified risk, or information that allows further characterisation of a previously recognised risk.

New information can be organised as follows:

1. new information on important potential risks;
2. new information on important identified risks;
3. new information on other potential risks not categorised as important;
4. new information on other identified risks not categorised as important;
5. update on important missing information.

The focus of the evaluation(s) is on new information which has emerged during the reporting interval of the PBRER. This should be concise and interpret the impact, if any, on the understanding and characterisation of the risk. Where applicable, the evaluation will form the basis for an updated

characterisation of important potential and identified risks in Section 16.4 of the report. It is recommended that the level of detail of the evaluation included in this section should be proportional to the available evidence on the risk and its medical significance and public health relevance.

The evaluation(s) of new information and missing information update(s) can be included in this section of the PBRER, or in an appendix. Each evaluation should include the following information as appropriate:

- source of the new information;
- background relevant to the evaluation;
- method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- results – a summary and critical analysis of the data considered in the risk evaluation;
- discussion;
- conclusion including whether or not the evaluation supports an update of the characterisation of any of the important potential and identified risks in Section 16.4 of the PBRER.

Any new information on populations exposed or data generated to address previously missing information should be critically assessed in this section. Unresolved concerns and uncertainties should be acknowledged

3.16.4. Characterisation of risks

This section will characterise important identified and important potential risks based on cumulative data (i.e., not restricted to the reporting interval), and describe important missing information.

Depending on the nature of the data source, the characterisation of risk may include, where applicable:

- frequency;
- numbers of cases (numerator); precision of estimate, taking into account the source of the data;
- extent of use (denominator) expressed as numbers of patients, patient-time, etc., and precision of estimate;
- estimate of relative risk; precision of estimate;
- estimate of absolute risk; precision of estimate;
- impact on the individual patient (effects on symptoms, quality or quantity of life);
- public health impact;
- patient characteristics relevant to risk (e.g., age, pregnancy/lactation, disease severity, hepatic/renal impairment, relevant co-morbidity, genetic polymorphism);
- dose, route of administration;
- duration of treatment, risk period;
- preventability (i.e., predictability, ability to monitor for a “sentinel” adverse reaction or laboratory marker);
- reversibility;
- potential mechanism; and

- strength of evidence and its uncertainties, including analysis of conflicting evidence, if applicable.

When missing information could constitute an important risk, it should be included as a safety concern. The limitations of the safety database (in terms of number of patients studied, cumulative exposure or long term use, etc.) should be discussed.

For PBRERs for products with several indications, formulations, or routes of administration, where there may be significant differences in the identified and potential risks, it may be appropriate to present risks by indication, formulation, or route of administration. Headings that could be considered include:

- Risks relating to the active substance;
- Risks related to a specific formulation or route of administration (including occupational exposure);
- Risks relating to a specific population; and
- Risks associated with non-prescription use (for substances that are available as both prescription and non-prescription products).

3.16.5. Effectiveness of risk minimisation (if applicable)

Relevant information on the effectiveness and/or limitations of specific risk minimisation activities for important identified risks that has become available during the reporting interval should be summarised in this section.

Insights into the effectiveness of risk minimisation activities in any country or region that may have utility in other countries or regions are of particular interest. Information may be summarised by region, if applicable and relevant.

When required for reporting in a PBRER, results of evaluations that are relevant to only one region and that became available during the reporting interval should be provided in regional appendices.

3.17. Benefit evaluation

PBRER sections 17.1 and 17.2 provide the baseline (17.1) and newly identified (17.2) benefit information that support the characterization of benefit described in Section 17.3 that in turn supports the benefit-risk evaluation in Section 18.

3.17.1. Important baseline efficacy/effectiveness information

This section summarises information on the efficacy/effectiveness of the medicinal product as of the beginning of the reporting interval, and provides the basis for the benefit evaluation. This information should relate to the approved indication(s) of the medicinal product listed in the reference product information (see Section 2.4).

For medicinal products with multiple indications, populations, and/or routes of administration, the benefit should be characterised separately by these factors, where relevant.

The level of detail provided in this section should be sufficient to support the characterisation of benefit in PBRER Section 17.3 and the benefit-risk assessment in Section 18.

3.17.2. Newly identified information on efficacy/effectiveness

New information on efficacy/effectiveness in approved indications that may have become available during the reporting interval should be presented in this section. For approved indications, new information on efficacy/effectiveness under conditions of actual use should also be described in this section, if available. New information about efficacy/effectiveness in uses other than the approved indication(s) should not be included, unless relevant for the benefit-risk evaluation in the approved indication. Information on indications approved during the reporting interval should also be included in this section. The level of detail provided in this section should be sufficient to support the characterisation of benefit in Section 17.3 and the benefit-risk assessment in Section 18.

New information on efficacy/effectiveness might also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines, emergence of resistance to anti-infective agents.

3.17.3. Characterisation of benefits

Section 17.3 of the PBRER provides an integration of the baseline benefit information (see Section 3.17.1) and any relevant new benefit information (see Section 3.17.2) that became available during the reporting interval for approved indications.

This section should provide a concise but critical evaluation of the strengths and limitations of the evidence on efficacy/effectiveness, considering the following, when available:

- a brief description of the strength of evidence of benefit, considering comparator(s), effect size, statistical rigor, methodological strengths and deficiencies, and consistency of findings across trials/studies;
- new information that challenges the validity of a surrogate endpoint, if used;
- clinical relevance of the effect size;
- generalizability of treatment response across the indicated patient population, e.g., information that demonstrates lack of treatment effect in a sub-population;
- adequacy of characterization of dose-response;
- duration of effect;
- comparative efficacy; and
- a determination of the extent to which efficacy findings from clinical trials are generalizable to patient populations treated in medical practice.

The level of detail provided in PBRER Section 17.3 should be sufficient to support the analysis of benefit-risk in Section 18.

When there are no new relevant benefit data, this section should provide a characterisation of the information in Section 17.1 of the PBRER.

When there is new positive benefit information and no significant change in the risk profile in this reporting interval, the integration of baseline and new information in this section should be succinct.

3.18. Integrated benefit-risk analysis for approved indications

Whereas PBRER Sections 16.4 and 17.3 present the risks and benefits, respectively, Section 18 should provide an integration and critical analysis of the key information in these sections as described below. Section 18 provides the benefit-risk analysis, and should not simply duplicate the benefit and risk characterization presented in Sections 16.4 and 17.3.

3.18.1. Benefit-risk context - medical need and important alternatives

This section should provide a brief description of the medical need for the medicinal product in the approved indications, and summarise alternatives (medical, surgical, or other; including no treatment).

3.18.2. Benefit-risk analysis evaluation

A benefit-risk profile is specific to an indication and population. For products approved for more than one indication, benefit-risk profiles should be evaluated and presented for each indication individually. If there are important differences in the benefit-risk profiles among populations within an indication, benefit-risk evaluation should be presented by population, if possible. The evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks, and should take into account the following points:

- Whereas previous sections will include all important benefit and risk information, not all benefits and risks contribute importantly to the overall benefit-risk evaluation. Therefore, the key benefits and risks considered in the evaluation should be specified. The key information presented in the previous benefit and risk sections should be carried forward for integration in the benefit-risk evaluation.
- Consider the context of use of the medicinal product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated.
- With respect to key benefit(s), consider its nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments. Consider the effect size. If there are individual elements of benefit, consider all (e.g., for therapies for arthritis: reduction of symptoms and inhibition of radiographic progression of joint damage).
- With respect to risk, consider its clinical importance, e.g., nature of toxicity, seriousness, frequency, predictability, preventability, reversibility, impact on patients, and whether it arose from off-label use, a new use, or misuse.
- The strengths, weaknesses, and uncertainties of the evidence should be considered when formulating the benefit-risk evaluation. Describe how uncertainties in the benefits and risks impact the evaluation. Limitations of the assessment should be discussed.

Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation:

- The assumptions, considerations, and judgement or weighting that support the conclusions of the benefit-risk evaluation should be clear.
- If a formal quantitative or semi-quantitative assessment of benefit-risk is provided, a summary of the methods should be included.

Economic considerations (e.g., cost-effectiveness) should not be included in the benefit-risk evaluation.

When there is important new information or an *ad hoc* PBRER has been requested, a detailed benefit-risk analysis is warranted.

Conversely, where little new information has become available during the reporting interval, the primary focus of the benefit-risk evaluation might consist of an evaluation of updated interval safety data.

3.19. Conclusions and actions

This section should provide a conclusion about the implications of any new information that arose during the reporting interval, in terms of the overall benefit-risk evaluation, for each approved indication, as well as for relevant subgroups, if appropriate.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis, the MAH should assess the need for further changes to the reference product information and propose changes as appropriate.

In addition and as applicable, the conclusion should include preliminary proposal(s) to optimise or further evaluate the benefit-risk balance, for further discussion with the relevant regulatory authorities. This may include proposals for additional risk minimisation activities.

These proposals should also be considered for incorporation into the risk management plan, e.g., the E2E pharmacovigilance plan and/or risk minimisation plan, as appropriate.

If required by applicable regional laws and regulations, the MAH should provide, in a regional appendix, information on any final, ongoing, or proposed changes to the national or local authorised product information.

3.20. Appendices to the PBRER

The PBRER should be accompanied by the following appendices, as appropriate, numbered as follows:

1. Reference Information;
2. Cumulative Summary Tabulation of Serious Adverse Events from Clinical trials and Interval/Cumulative Summary Tabulations from Marketed Experience;
3. Tabular Summary of Safety Signals (if not included in the body of the report);
4. Listing of interventional and non-interventional studies with a primary objective of post-authorization safety monitoring; and
5. List of the Sources of Information Used to Prepare the PBRER (when desired by the MAH).

The PBRER may also be accompanied by regional appendices, as needed, to fulfil national and regional requirements.

4. Appendices to this guideline

Appendix A – Glossary

Appendix B – Examples of Summary Tabulations

Appendix C – Example of a Tabular Summary of Safety Signals that Were Ongoing or Closed during the Reporting Interval

Appendix D – List of PBRER Sections that May be Shared with Other Regulatory Documents

Appendix E – Examples of Possible Sources of Information that May Be Used in the Preparation of the PBRER

Appendix F – Mapping of Signals and Risks to PBRER Sections

Appendix A

Glossary

Whenever possible the Working Group has used terms in use in other ICH Guidelines, or those previously proposed by Council for International Organizations of Medical Sciences (CIOMS) working groups. Generally, the definitions of terms previously defined in ICH documents are not repeated in this glossary, except for those of particular importance to the PBRER.

Item	Glossary Term	Source of Definition	Definition/Commentary
	Closed signal	ICH Guideline E2C(R2)	A signal for which an evaluation was completed during the reporting interval.
	Company Core Data Sheet (CCDS)	ICH Guideline E2C	A document prepared by the MAH containing, in addition to safety information, material related to indications, dosing, pharmacology and other information concerning the product.
	Company Core Safety Information (CCSI)	ICH Guideline E2C	All relevant safety information contained in the CCDS prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is the reference information by which listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected ad unexpected are determined for expedited reporting.
	Completed clinical trial	ICH Guideline E2F	Clinical trial for which a final study report is available.
	Identified risk	ICH Guideline E2F	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest. Examples of identified risks include: an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data; an adverse reaction observed in well-designed clinical trials or epidemiological studies for which the magnitude of the difference compared with the comparator group (placebo or active substance) on a parameter of interest suggests a causal relationship; and an adverse reaction suggested by a number of well documented spontaneous reports where causality is strongly supported by temporal relationship and biological plausibility, such as anaphylactic reactions or application site

Item	Glossary Term	Source of Definition	Definition/Commentary
			reactions.
	Important identified risk, important potential risk	ICH Guideline E2C(R2)	An identified risk or potential risk that could impact on the risk-benefit profile of the product or have implications for public health. What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, and the impact on public health. Normally, any risk that is likely to be included in the contraindications or warnings and precautions section of the product labelling should be considered important.
	Important missing information	ICH Guideline E2C(R2)	Critical gaps in knowledge for specific safety issues or populations that use the marketed product.
	International Birth Date	ICH Guideline E2C	The date of the first marketing authorisation for any product containing the active substance granted to any company in any country in the world.
	Investigational drug	ICH Guideline E2F	The term investigational drug is used in this guideline to indicate only the experimental product under study or development. Note: This term is more specific than “investigational medicinal product,” which includes comparators and placebos.
	Newly identified signal	ICH Guideline E2C(R2)	A signal first identified during the reporting interval, prompting further actions or evaluation. This term could also apply to a previously closed signal for which new information becomes available in the reporting interval prompting further action or evaluation.
	Ongoing clinical trial	ICH Guideline E2F	Trial where enrolment has begun, whether a hold is in place or analysis is complete, but for which a final clinical study report is not available.
	Ongoing signal	ICH Guideline E2C(R2)	A signal that remains under evaluation at the DLP.
	Potential risk	ICH Guideline E2F	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed. Examples of potential risks include: non-clinical safety concerns that have not been observed or resolved in clinical studies; adverse events observed in clinical trials or epidemiological studies for which the magnitude of the difference, compared with the comparator group (placebo or active substance, or unexposed

Item	Glossary Term	Source of Definition	Definition/Commentary
			group), on the parameter of interest raises a suspicion of, but is not large enough to suggest, a causal relationship; an event which is known to be associated with other products of the same class or which could be expected to occur based on the properties of the medicinal product.
	Reference safety information	ICH Guideline E2C(R2)	All relevant safety information contained in the reference product information (e.g., CCDS) prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the drug, except when the local regulatory authority specifically requires a modification. It is a subset of information contained within the MAH's reference product information for the PBRER. Where the reference product information is the Company Core Data Sheet (CCDS), the reference safety information is the Company Core Safety Information (CCSI).
	Safety concern	ICH Guideline E2C(R2)	An important identified risk, important potential risk, or important missing information.
	Signal	ICH Guideline E2C(R2)	Information that arises from one or multiple sources (including observations and experiments), that suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify further action to verify. For the purpose of Section 16.2 of the PBRER, signals relate to adverse effects.
	Solicited reports	ICH Guideline E2D	Solicited reports are those derived from organized data collection systems, which include clinical trials, registries, post-approval named patient use programs, other patient support and disease management programs, surveys of patients or healthcare providers, or information gathering on efficacy or patient compliance.
	Spontaneous report or spontaneous notification	ICH Guideline E2D	An unsolicited communication to a company, regulatory authority, or other organization that describes an ADR in a patient given one or more medicinal products and which does not derive from a study or any organized data collection scheme.

Appendix B

Examples of summary tabulations

Note: MAHs can modify these examples to suit specific situations, as appropriate.

Table 1 – Estimated Cumulative Subject Exposure from Clinical Trials

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

Treatment	Number of subjects
Medicinal product	
Comparator	
Placebo	

Table 2 – Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex*

	Number of subjects		
Age range	Male	Female	Total

* Data from completed trials as of [date]

Table 3 – Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group*

Racial group	Number of subjects
Asian	
Black	
Caucasian	
Other	
Unknown	
Total	

* Data from completed studies as of [date]

Table 4 – Cumulative Exposure from Marketing Experience

Indication	Sex		Age (years)				Dose (mg/day)			Formulation		Region				
	Male	Female	2 to 16	>16 to 65	> 65	unknown	<40	≥40	unknown	IV	Oral	EU	Japan	Mexico	US/Canada	other
Overall																
Depression																
Migraine																

Table 4 includes cumulative data obtained from month/day/year through month/day/year.

Table 5 – Interval Exposure from Marketing Experience

Indication	Sex		Age (years)				Dose (mg/day)			Formulation		Region				
	Male	Female	2 to 16	>16 to 65	> 65	unknown	<40	≥40	unknown	IV	Oral	EU	Japan	Mexico	US/Canada	other
Depression																
Migraine																

Table 5 includes interval data obtained from month/day/year through month/day/year, where available.

Table 6 – Cumulative Tabulations of Serious Adverse Events from Clinical Trials

System Organ Class Preferred Term	Investigational Medicinal product	Blinded	Active comparator	Placebo
Investigations				
Alanine aminotransferase increased				
Aspartate aminotransferase increased				
Nervous System Disorders				
Syncope				
Headache				

Table 7 - Numbers of Adverse Drug Reactions by Term from Post-Marketing Sources

	Spontaneous, including regulatory authority and literature					Non-interventional post-marketing study and reports from other solicited sources*	
	Serious		Non-serious		Total Spontaneous	Serious	
	Interval	Cumulative	Interval	Cumulative	Cumulative	Interval	Cumulative
SOC 1							
MedDRA PT							
MedDRA PT							
MedDRA PT							
SOC 2							
MedDRA PT							
MedDRA PT							
MedDRA PT							
MedDRA PT							

*This does not include interventional clinical trials.

Appendix C

Example of a tabular summary of safety signals that were ongoing or closed during the reporting interval

Reporting Interval: DD-MMM-YYYY to DD-MMM-YYYY

Signal term	Date detected	Status (ongoing or closed)	Date closed (for closed signals)	Source of signal	Reason for evaluation & summary of key data	Method of signal evaluation	Action(s) taken or planned
Stroke	month/ year	ongoing	month/ year	meta-analysis (published trials)	statistically significant increase in frequency	review meta-analysis and available data	pending
SJS	month/ year	closed	month/ year	spontaneous case reports & one case report in Phase IV trial	Rash already an identified risk SJS not reported in pre authorisation CTs. 4 apparently unconfounded reports within 6 months of approval; plausible time to onset.	targeted follow up of reports with site visit to one hospital. Full review of cases by MAH dermatologist and literature searches	RSI updated with a Warning and Precaution DHPC sent to oncologists. Effectiveness survey planned 6 months post DHPC. RMP updated.

Explanatory notes

Signal term

A brief descriptive name of a medical concept for the signal. The description may evolve and be refined as the signal is evaluated. The concept and scope may, or may not, be limited to specific MedDRA term(s), depending on the source of signal.

Date detected (month/year)

Month and year the MAH became aware of the signal.

Status

Ongoing: Signal under evaluation at the DLP of the PBRER. Provide anticipated completion date, if known.

Closed: Signal for which evaluation was completed before the DLP of the PBRER.

Note: A new signal of which the MAH became aware during the reporting interval may be classified as closed or ongoing, depending on the status of signal evaluation at the DLP of the PBRER.

Date closed (month/year)

Month and year when the signal evaluation was completed.

Source of signal

Data or information source from which a signal arose. Examples include, but may not be limited to, spontaneous adverse event reports, clinical trial data, scientific literature, non-clinical study results, or information requests or inquiries from a regulatory authority.

Reason for evaluation

A brief summary of key data and rationale for further evaluation.

Actions taken or planned

State whether or not a specific action has been taken or is planned for all closed signals that have been classified as potential or identified risks. If any further actions are planned for newly or previously identified signals under evaluation at the DLP, these should be listed. Otherwise leave blank for ongoing signals.

Appendix D

List of PBRER sections that may be shared with other regulatory documents

		Potential shared module with
1	Introduction	
2	Worldwide Marketing Approval Status	E2F
3	Actions Taken in the Reporting Interval for Safety Reasons	Parts may be common to E2E and E2F
4	Changes to Reference Safety Information	
5	Estimated Exposure and Use Patterns	
5.1	Cumulative Subject Exposure in Clinical Trials	E2E and E2F
5.2	Cumulative and Interval Patient Exposure from Marketing Experience	E2E and E2F (cumulative only)
6	Data in Summary Tabulations	
6.1	Reference Information	
6.2	Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials	E2F
6.3	Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources	
7	Summaries of Significant Findings from Clinical Trials during the Reporting Period	
7.1	Completed Clinical Trials	E2F
7.2	Ongoing Clinical Trials	E2F
7.3	Long-Term Follow-up	E2F
7.4	Other Therapeutic Use of Medicinal Product	E2F
7.5	New Safety Data Related to Combination Therapies	E2F
8	Findings from Non-Interventional Studies	E2F
9	Information from Other Clinical Trials and Sources	E2F
10	Non-Clinical Data	E2F
11	Literature	E2F
12	Other Periodic Reports	
13	Lack of Efficacy in Controlled Clinical Trials	E2F
14	Late-Breaking Information	E2F, if reports cover same period and submitted at

		Potential shared module with
		same time
15	Overview of Signals: New, Ongoing, or Closed	
16	Signal and Risk Evaluation	
16.1	Summary of Safety Concerns	
16.2	Signal Evaluation	
16.3	Evaluation of Risks and New Information	
16.4	Characterisation of Risks	
16.5	Effectiveness of Risk Minimisation (if applicable)	
17	Benefit Evaluation	
17.1	Important Baseline Efficacy/Effectiveness Information	
17.2	Newly Identified information on Efficacy/ Effectiveness	
17.3	Characterisation of Benefits	
18	Integrated Benefit-Risk Analysis for Approved Indications	
18.1	Benefit-Risk Context - Medical Need and Important Alternatives	
18.2	Benefit-Risk Analysis Evaluation	
19	Conclusions and Actions	E2F
20	Appendices to the PBRER	

Appendix E

Examples of possible sources of information that may be used in the preparation of the PBRER

This list is not intended to be all inclusive; additional data sources may be used by the MAH to present safety and efficacy/effectiveness data in the PBRER and to evaluate the benefit-risk profile, as appropriate to the product and its known and important emerging benefits and risks (see also Introduction Section 1.3, Scope of the PBRER regarding sources of available information).

Examples of sources of information potentially relevant to the evaluation of benefits and risks that, if relevant, should be used in the preparation of the PBRER, include but are not limited to:

- non-clinical studies;
- clinical trials, including research in unapproved indications or populations;
- spontaneous reports (for example, on the MAH's safety database);
- MAH-sponsored websites (for additional information see ICH E2D Guideline, Post-approval Safety Data Management: Definitions and Standards for Expedited Reporting);
- observational studies such as registries;
- product usage data and drug utilization information;
- published scientific literature or reports from abstracts including information presented at scientific meetings;
- unpublished manuscripts;
- active surveillance systems (for example, sentinel sites);
- systematic reviews and meta-analyses;
- information arising from licensing partners, other sponsors or academic institutions/research networks;
- patient support programmes;
- investigations of product quality;
- information from regulatory authorities.

Appendix F

Mapping signals and risks to PBRER sections