Guideline on Periodic Benefit Risk Evaluation Report (PBRER)

NATIONAL MEDICINES REGULATORY AUTHORITY

NORRIS CANAL ROAD, COLOMBO 10, SRI LANKA

Content

Periodic Benefit Risk Evaluation Report

1. Introduction

Periodic Benefit Risk Evaluation Reports (PBRERs) are pharmacovigilance documents for preparation and submission by marketing authorization holders at defined time points during the post-authorization phase with objective to provide a comprehensive, concise and critical evaluation of the risk-benefit balance of a medicinal product taking into account new or emerging information in the context of cumulative information on risks and benefits.

For the purposes of lifecycle benefit-risk management, it is necessary for the marketing authorization holder to continue evaluating the risks and benefits of a medicine in everyday medical practice and long term use in the post-authorization phase. This may extend to evaluation of populations and endpoints that could not be investigated in the pre-authorization clinical trials. A different risk-benefit balance may emerge as pharmacovigilance reveals further information about safety. The marketing authorization holder should therefore reevaluate the risk-benefit balance of its own medicinal products in populations exposed.

Urgent safety information should be reported through the appropriate mechanism. **A PBRER is not intended, in the first instance, for notification of significant new safety or efficacy information or to provide the means by which new safety issues are detected**. It is acknowledged that the review of the data in the PBRER may lead to new safety issues being identified.

2. Evaluation of the risk-benefit balance within PBRERs

The risk evaluation should be based on all uses of the medicinal product. The scope includes evaluation of safety in real medical practice including use in unauthorized indications and use which is not in line with the product information. If use of the medicinal product is identified where there are critical gaps in knowledge for specific safety issues or populations, such use should be reported in the PBRER (e.g. use in paediatric population or in pregnant women). Sources of information on use outside authorization may include drug utilization data, information from spontaneous reports and publications in the literature.

The scope of the benefit information should include both clinical trial and real world data in authorized indications.

The integrated benefit-risk evaluation should be performed for all authorized indications and should incorporate the evaluation of risks in all use of the medicinal product (including use in unauthorized indications).

3. Principles of preparation of PBRER

3.1. Single PBRER for an active substance

Unless otherwise specified by competent authorities, the marketing authorization holder shall prepare a single PBRER for all its medicinal products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures.

Where relevant, data relating to a particular indication, dosage form, route of administration or dosing regimen, shall be presented in a separate section of the PBRER and any safety concerns shall be addressed accordingly. There might be exceptional scenarios where the preparation of separate PBRERs might be appropriate, for instance, in the event of different formulations for entirely different indications. In this case, agreement should be obtained from the NMRA preferably at the time of authorization.

Case narratives shall be provided in the relevant risk evaluation section of the PBRER where integral to the scientific analysis of a signal or safety concern. In this context, the term "case narratives" refers to clinical evaluations of individual cases rather than the CIOMS narratives.

3.2. Reference information

An objective of a PBRER is to evaluate whether or not the information obtained during the reporting interval is in accordance with previous knowledge on the product's benefit and risk profile, and to indicate whether changes should be made to the reference product information.

3.2.1. Selection of reference product information

The following possible options can be considered by the marketing authorization holders when selecting the most appropriate reference product information for a PBRER:

- ***Company Core Data Sheet (CCDS)***

  It is a common practice for marketing authorization holders 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 company core safety information (CCSI).

When the CCDS for a medicinal product does not contain information on approved indications, the marketing authorization holder 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 established/generic products on the market for many years, the marketing authorization holder should clearly specify the reference information being used. This may comprise product information from reference country.

3.2.2. Reference product information and different PBRER sections

- The reference product information for the PBRER should 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 all countries. When there are additional locally authorized indications, these indications may be either added to the reference product information or handled as a national appendix as considered most appropriate by the marketing authorization holder. The basis for the benefit evaluation should be the baseline important efficacy and effectiveness information summarized in the PBRER section 17.1 ("Important baseline efficacy and effectiveness information")

- The marketing authorization holder should consider the reference product information/reference safety information upon examining the information which has emerged during the reporting interval to determine whether it has generated new signals, led to the identification of new potential or identified risks or contributed to knowledge of previously identified risk, and where relevant, this should be discussed in PBRER section 16 ("Signal and risk evaluation")

- The marketing authorization holder should continuously evaluate whether any revision of the reference product information/reference safety information is needed whenever new safety information is obtained during the reporting interval and ensure that significant changes made over the interval are described in PBRER section 4 ("Changes to the reference safety information"). These changes may include:

i. Changes to contraindications, warnings/precautions sections of the RSI;
ii. Addition of ADR(s) and interactions;
iii. Addition of important new information on use in overdose;
iv. Removal of an indication or other restrictions for safety or lack of efficacy reasons.

- Significant changes to the reference product information made after the e data lock point to (DLP) but before submission of the PBRER should be included in PBRER section 14 ("Late Breaking Information") of the report, if feasible.

A practical option is for marketing authorization holders to use the latest CCDS/reference product information **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. A clean copy of this RSI should be provided as an appendix to the PBRER. The reference product information should be dated and version controlled.

3.3. Sources of information for preparation of PBRER

Sources of efficacy, effectiveness and safety information that may be used in the preparation of PBRERs include -for examples by not restricted to- the following:

- non-clinical studies;
- spontaneous reports (e.g. on the marketing authorization holder's safety database);
- active surveillance systems (e.g. sentinel sites);
- investigations of product quality;
- product usage data and drug utilization information;
- clinical trials, including research in unauthorized indications or populations;
- observational studies, including registries;
- patient support programs;
- systematic reviews and meta-analysis;
- marketing authorization holders sponsored websites;
- published scientific literature or reports from abstracts, including information presented at scientific meetings;
- unpublished manuscripts;
- licensing partners, other sponsors or academic institutions and research networks;
- medicines authorities (worldwide).

4. Periodicity, data lock point and Submission of PBRER

4.1. Routine PBRER submission and EURD list

In light of the continuous evaluation of the risk-benefit balance, the marketing authorization holders shall submit the PBRERs at defined time points during the post-authorization phase. For harmonization, the harmonized international birth date (EU reference date), periodicity, data lock points and the dates of PBRER submission for each active substance and combination of active substances as defined in the "list of EU reference dates" (EURD) is adopted in the context of this guideline. This list is maintained & published by the European Medicines Agency (EMA) on the following link https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/periodic-safety-update-reports-PBRERs

4.1.1. Data lock point

The data lock point (DLP) is the date designated as the cut-off for data to be included in a PBRER

4.1.2. Objectives of the list of EU reference dates and frequency of submission of PBRERs:

- **Prioritize the periodic re-evaluation of the risk-benefit balance**: the periodicity is defined on the basis of a risk-based approach in order to prioritize the periodic re-evaluation of the risk-benefit balance of active substances in a way that best protects public health and rationalize the resources for PBRER preparation and assessment by marketing authorization holders and the NMRA respectively for product with high risk.

  In this risk based approach, the PBRER periodicity is defined based not only on the length the product has been on the market but also on its risk profile. Hence, products with high risk profile are granted more frequent PBRER cycle e.g. 6 month or annual. On the other hand, products considered to have an established and acceptable profile or considered to be low risk are granted less frequent PBRER cycle e.g. 5, 6, 8, 10 years or longer as propionate to the product safety profile

- **PBRER Single assessment and reassessment of the risk-benefit balance** of an active substance: the list enables the harmonization of PBRER submissions for medicinal products containing the same active substance or combination of active substances for different marketing authorization holders, thus enables the NMRA to conduct single assessment for these PBRERs based on the totality of available data on the benefits and risks.

4.1.3. Products with requirements to submit PBRER

- The submission of latest PBRER is required **during product authorization** of biological products and new medicinal products
- **Biological products:**
  The submission of PBRER post authorization is required for all biological products innovators and biosimilar according to the submission frequency and dates in the EURD list
- **Medicinal products**
  - The submission of PBRER post authorization is required for all **medicinal products** innovators and generics having a submission frequency in the EURD list equals to or less than 2 years in the EURD list (e.g. 6 months, 1 year, 2 years).
  - Medicinal products innovators and generics with PBRER frequency more than 2 years in the EURD list, the PBRER should be prepared by the marketing authorization holder according to the specified frequency & DLP for the purpose of continuous evaluation of risk- benefit balance. The submission of these PBRERs will be made only upon NMRA request. Taking onto consideration that if the marketing authorization holder identified information that affects the risk benefit balance of the product; this should be notified immediately to the NMRA as emerging safety issue.
- For Medicinal products with active substances not included in the EURD list, a PBRER submission frequency of 2 years should be followed.

4.1.4. Submission modalities

PBRER should be submitted electronically via email (vigilance@nmra.gov.lk).

4.2. Ad hoc ("for cause") PBRERs

Ad hoc PBRERs are reports outside the routine reporting requirements, and may be requested by the NMRA. 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.

4.3. Time interval between data lock point and the PBRER submission

- Routine PBRERs covering intervals of 6 or 12 months: within 70 calendar days;
- Routine 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.

5. Content of PBRER

The PBRER shall be single stand–alone document based on all available data including interval as well as cumulative information:

- Interval information, it shall focus on new information which has been obtained during the reporting interval (i.e. emerged since the data lock point of the last PBRER), and examine whether this information is in accordance with previous knowledge of the medicinal product's benefit and risk profile
- Cumulative information should be taken into account when performing the overall safety evaluation and integrated benefit-risk assessment
- When appropriate, the PBRER should include proposed action(s) to optimize the benefit-risk profile.

The format and content of the PBRER, including table of contents, section numbering, and content of each section, are outlined below:

- Part I: Title page including signature
- Part II: Executive Summary
- Part III: Table of Contents

1. Introduction
2. Worldwide marketing authorization 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
    - 6.2. Cumulative summary tabulations of serious adverse events from clinical trials
    - 6.3. Cumulative and interval summary tabulations from post-marketing data sources
7. Summaries of significant findings from clinical trials during the reporting interval

- 7.1. Completed clinical trials
- 7.2. Ongoing clinical trials
- 7.3. Long-term follow-up
- 7.4. Other therapeutic use of medicinal product
- 7.5. New safety data related to fixed combination therapies

8. Findings from non-interventional studies
9. Information from other clinical trials and sources
   - 9.1. Other clinical trials
   - 9.2. Medication errors
10. Non-clinical Data
11. Literature
12. Other periodic reports
13. Lack of efficacy in controlled clinical trials
14. Late-breaking information
15. Overview of signals: new, ongoing or closed
16. Signal and risk evaluation
    - 16.1. Summaries of safety concerns
    - 16.2. Signal evaluation
    - 16.3. Evaluation of risks and new information
    - 16.4. Characterization of risks
    - 16.5. Effectiveness of risk minimization (if applicable)
17. Benefit evaluation
    - 17.1. Important baseline efficacy and effectiveness information
    - 17.2. Newly identified information on efficacy and effectiveness
    - 17.3. Characterization of benefits
18. Integrated benefit-risk analysis for authorized indications
    - 18.1. Benefit-risk context – Medical need and important alternatives
    - 18.2. Benefit-risk analysis evaluation
19. Conclusions and actions
20. Appendices to the PBRER

6. PBRER national appendix

An appendix is required for PBRER submission in post-authorization phase. The appendix should provide information specific to Sri Lanka and includes the following sections:

- **National appendix subsection on "Proposed product information"**

  In this sub-section, the marketing authorization holder should provide a track change version of the proposed product information (SmPC and package leaflet) based on the evaluation addressed in the PBRER. These should be based on all national authorized indications.

  All the SmPCs and packages leaflets covered by the PBRER and in effect at the data lock point, should be reviewed to ensure that they reflect the appropriate information according to the cumulative data included and analyzed in the PBRER.

  Amendments to the product information should not be postponed or delayed until the PBRER submission and amendments not related to the information presented in the PBRER, should not be proposed within the PBRER procedure. It is the obligation of the marketing authorization holder to submit a variation in accordance with the Regulation on variations to the terms of a marketing authorization. A brief description of ongoing procedures (e.g. variations) to update the product information should be provided in this section.

- **National appendix subsection on "Proposed additional pharmacovigilance and risk minimization activities"**
  This sub-section should include proposals for additional pharmacovigilance and additional risk minimization activities based on the conclusions and actions of the PBRER, including a statement of the intention to submit a RMP or an updated RMP when applicable.

7. Renewal of marketing authorizations and Addendum to Clinical Overview

Marketing authorizations need to be renewed after 5years on the basis of a re-evaluation of the risk-benefit balance in order to continue to be valid to place the product on the market.

Within the renewal application, **an addendum to clinical overview (ACO)** should be included and addressing the current benefit/risk balance for the product on the basis of a consolidated version of safety/efficacy data accumulated since the previous marketing authorization date till the 90 days before the renewal application submission

PBRER/s covering the same period are also accepted.

The Addendum to the Clinical Overview should contain the following information**:

1. History of pharmacovigilance system inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned) and an analysis of the impact of the findings overall on the benefit/risk balance of the medicinal product.
2. Worldwide marketing authorization status
3. Actions taken for safety reasons (worldwide)
4. Significant changes made to the Reference Information (RI) during the period covered
5. Meaningful differences between the RI and the proposals for the Summary of Product Characteristics. A proposed SmPC, Package leaflet and Labelling should also be provided
6. Estimated exposure and used patterns
7. Data in summary tabulations
8. Summaries of significant safety and efficacy findings from clinical trials and non-interventional studies
9. Literature
10. Risk evaluation
11. Benefit evaluation
12. Benefit-risk balance
13. Late-breaking information

** Marketing authorization holders should consider the PBRER guidelines for the preparation of the above sections of the clinical overview.

This Addendum should be signed and accompanied by the CV of the expert. The clinical expert should have the necessary technical or professional qualifications and may, but should not necessarily, be the same qualified person responsible for pharmacovigilance.

In any event, the following clear conclusive statement "Clinical Expert Statement" is required:

- Confirm that no new clinical data are available which change or result in a new risk-benefit evaluation.
- Confirm that the product can be safely renewed at the end of a 5-year period, or any action recommended or initiated should be specified and justified.

- Confirm that the NMRA have been kept informed of any additional data significant for the assessment of the benefit/risk ration of the product concerned.
- Confirm that the product information is up to date with the current scientific knowledge including the conclusions of the assessments and recommendations made publicly available.

For more guidance on the structure, process, preparation of PBRER and templates, refer to:

- the *EMA Guideline on good pharmacovigilance practices (GVP) Module VII*
- ICH guideline E2C (R2) on periodic benefit-risk evaluation report (PBRER)

The GVP Modules on Product- or Population-Specific Considerations should be consulted as applicable when preparing a PBRER