	Title: Guideline for Periodic Benefit-Risk Evaluation Reports (PBRERs)	
Rev No: 00	**Doc No: PBSL/GL/057**	Version no. 02
Issue date: 25th Nov. 2025	**Effective date: 28 Nov 2025**	Approved by: Registrar

Adopted By PBSL	
Start of public Consultation	
End of public Consultation	
Agreed by QMS committee	
Approved by Board	

Pharmacy Board of Sierra Leone

PMB 322

Central Medical Stores Compound

New England Ville

Freetown

	Title: Guideline for Periodic Benefit-Risk Evaluation Reports (PBRERs)	
Rev No: 00	**Doc No: PBSL/GL/057**	Version no. 02
Issue date: 25th Nov. 2025	**Effective date: 28 Nov 2025**	Approved by: Registrar

Table of Contents

1. INTRODUCTION 5

A. BACKGROUND 4
B. OBJECTIVES 6
C. SCOPE 6

2. GENERAL PRINCIPLES 7

A. SINGLE PSUR/ PBRER FOR AN ACTIVE SUBSTANCE 7
B. PSURS/ PBRERS FOR FIXED DOSE COMBINATION PRODUCT 7
C. PRODUCTS MANUFACTURED AND/OR MARKETED BY MORE THAN ONE COMPANY 7
D. REFERENCE INFORMATION 7
E. EFFICACY/EFFECTIVENESS 8
F. BENEFIT-RISK EVALUATION 9
G. PERIODICITY AND TIMELINES OF PSUR/ PBRER SUBMISSION 9

3. CONTENTS AND FORMAT OF THE PSUR/ PBRER 11

4. GUIDANCE ON CONTENTS OF THE PSUR/ PBRER 14

A. PART I: TITLE PAGE 14
B. PART II: EXECUTIVE SUMMARY 14
C. PART III: TABLE OF CONTENTS 14
1. Introduction 14
2. Worldwide Marketing Approval Status 15
3. Actions Taken in the Reporting Interval for Safety Reasons 15
4. Changes to Reference Safety Information 16
5. Estimated Exposure and Use patterns 16
6. Data in Summary tabulations 18
7. Summaries of significant safety findings from clinical trials during the reporting interval 20
8. Findings from Non-Interventional Studies 21
9. Information from Other Clinical Trials and Sources 22
10. Non-Clinical Data 22
11. Literature 22
12. Other Periodic Reports 23
13. Lack of Efficacy in Controlled Clinical Trials 23
14. Late-Breaking Information 23
15. Overview of Signals: New, Ongoing, or Closed 23

16. Signal and Risk Evaluation 25
17. Benefit Evaluation 29
18. Integrated Benefit-Risk Analysis for Approved Indications 30
19. Conclusions and Actions 32
20. Appendices to the PSUR/ PBRER 32

5. APPENDICES 33

A. GLOSSARY 33
B. REFERENCES 37

Acknowledgement

The Pharmacy Board wishes to express sincere thanks and appreciation to Paul Ehrlich Institute for their support in strengthening pharmacovigilance systems in Sierra Leone.

Executive summary

This Guideline outlines the suggested structure and content for a periodic benefit-risk evaluation report (PBRER) and highlights key considerations for its creation and submission. Unless the PBSL specifies otherwise, the responsibility for preparing and submitting PBRERs lies with the Marketing Authorization Holders (MAH).

Abbreviations

ADR	Adverse drug reaction
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information

CHMP	Committee for Medicinal Products for Human Use
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh)
DIBD	Developmental international birth data
DLP	Data lock point
DSUR	Development Safety Update Report
EURD-list	European Union Reference dates list
IBD	International birth date
ICSR	Individual case safety report
ICH	International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IND	Investigational new drug
MAH	Marketing authorisation holders
MedDRA	Medical Dictionary for Regulatory Activities
PBRER	Periodic benefit risk evaluation report
PBSL	Pharmacy Board of Sierra Leone
PRAC	Pharmacovigilance Risk Assessment Committee (PRAC)
PSUR	Periodic safety update report
QPPV	Qualified person responsible for Pharmacovigilance
RSI	Reference safety information
SAE	Serious adverse event

1.0 Introduction

In pursuance to the Pharmacy and Drugs Act 2001 this guideline is developed by The Pharmacy Board of Sierra Leone (PBSL), hereafter referred to as the PBSL, to define a common standard for periodic benefit-risk evaluation reporting on marketed products (including approved drugs that are under further study) in Sierra Leone. Benefit-risk evaluation should be

carried out throughout the lifecycle of a medical product to promote and protect public health and to enhance patient safety through effective risk minimisation. After granting marketing authorization it is still necessary to continue evaluating the benefits and risks of medical products in actual use and/or long-term use, to confirm that the benefit-risk balance remains favourable.

This Guideline defines the recommended format and content of a periodic benefit-risk evaluation report (PBRER) and provides an outline of points to be considered in its preparation and submission. Unless otherwise specified by the PBSL, it is the Marketing Authorization Holders (MAH) to prepare and submit PBRERs.

This Guideline is adopted from "ICH HARMONISED TRIPARTITE GUIDELINE PERIODIC BENEFIT-RISK EVALUATION REPORT (PBRER) E2C(R2)"[1] and the Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1) of the European Medicines Agency and adapted for Sierra Leone. The International Conference on Harmonisation is a project that brings together regulatory bodies and research-based industry from different regions of the word. Purpose of ICH is to harmonize regulatory requirements in order to avoid duplication. The adoption of the ICH E2C(R2) guideline will allow the PBSL and Marketing Authorization Holders (MAH) to:

- increase accountability;
- align product vigilance with international best practices;
- support the life cycle approach to product vigilance;
- strengthen the link between risk assessment and regulatory actions to minimize risk;
- minimize international regulatory burden and improve reviewing efficiency of submissions.

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, and effectiveness 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 PBRER is a pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product for submission by marketing authorisation holders at defined time points during the post-authorisation phase.

As noted above, the primary objective of the PSUR is 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". 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 feature of the PSUR/ 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 PSUR/ 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 PSUR/ PBRER has been extended to include benefit as well as safety, the reference information for the report also needs to consider this new factor into account. It is generally impractical for 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).

In Sierra Leone PSURs/PBRERs are generally requested routinely for:

- Pharmaceuticals;
- Biologics;
- Biotechnology products;
- Radiopharmaceuticals;
- Preventative and therapeutic vaccines
- Generic products;
- Herbal Medicines; and
- Homeopathic medicinal products.

2.0 Objectives

The main objective of this guideline 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 PSUR/ 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:

- Summarizing relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product;
- Summarizing 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 PSUR/ PBRER should include proposed action(s) to optimize the benefit-risk profile. Urgent safety information should be reported through the appropriate mechanism; the PSUR/ 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.

3.0 Scope

The main focus of each PSUR/ PBRER guideline 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 authorization for the conduct of an interventional clinical trial in any country.

All pertinent new safety and efficacy/effectiveness information discovered during the reporting interval should be discussed in the appropriate sections of the PSUR/ PBRER.

The PSUR/ 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 PSUR/ 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.

4.0 Requirements and general principles

a. Single PSUR/ PBRER for an active substance

The PSUR/ PBRER should provide information on all approved indications, dosage forms, and regimens for the active substance, with a single data lock point (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 PSUR/ PBRER. In exceptional cases, submission of separate PSURs/ 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.

b. PSURs/ PBRERs for fixed dose combination products

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

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

Each MAH is responsible for submitting PSURs/ PBRERs for its own products. When companies are involved in contractual relationships (e.g., licensor-licensee), respective responsibilities for preparation and submission of the PSUR/ 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 PSUR/ PBRER.

d. Reference information

An objective of a PSUR/ 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.

The reference product information for the PSUR/ 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 PSUR/ PBRER, the reference product information document should list all approved indications not only in Sierra Leone but worldwide. When the PSUR/ 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 of the PSUR/ PBRER.

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

- Company Core Data Sheet (CCDS)*

In accordance with ICH E2C (R1) recommendations [1], 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 Company Core Safety Information (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 PSUR/ 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 PSUR/ 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. The basis for the benefit evaluation should be the baseline important efficacy/effectiveness information summarized in the

Section Important Baseline Efficacy/Effectiveness Information of the PSUR/ PBRER.

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

Significant changes to the RSI made after the DLP but before submission of the PSUR/ PBRER should be included in the section "Late Breaking Information".

e. 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 PSUR/ PBRER.

f. 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 minimization activities, e.g., labelling changes, communications with prescribers, or other steps.

g. Periodicity and Timelines of PSUR/ PBRER Submission

Each marketing authorisation holder shall be responsible for submitting PSURs/ PBRERs for its own products and should submit PSURs/ PBRERs to

the PBSL according to defined timelines based on the IBD. Each medicinal product should have an IBD. 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 PSUR/ PBRER. The DLP is the date designated as the cut-off for data to be included in a PSUR/ PBRER. The PBSL will normally accept use of the IBD to determine the DLP for PSURs/ PBRERs. Provisions are available in Sierra Leone for the MAH to synchronize the PSUR/ PBRER DLP with the IBD. As necessary, the MAH should consult the PBSL and request adjustment of the PSUR/ PBRER DLP to the IBD, as necessary.

When a separate PSUR/ PBRER is prepared for a fixed-dose combination product (see Section 2b), the DLP for that PSUR/ 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 Development Safety Update Report (DSUR)* reporting interval can be synchronized with the IBD based cycle, so that both the DSUR and PSUR/ 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 PSUR/ PBRER and DSUR when both are submitted annually (see Appendix D in ICH E2C(R2)[1]).

The PBSL may waive the obligation to submit PSURs/ PBRERs routinely for generic medicinal products, well established use medicinal products, homeopathic medicinal products and traditional herbal medicinal products. For such products, PSURs/ PBRERs shall be submitted where there is a condition in the marketing authorisation or when requested by the PBSL on the basis of concerns relating to pharmacovigilance data or due to the lack of PSURs/ PBRERs for an active substance after its authorisation. The PBSL shall assess PSURs/ PBRERs to determine whether there are new risks or whether risks have changed or whether there are changes to the risk-benefit balance of medicinal products.

In situations where an MAH is preparing PSURs/ PBRERs on annual basis or longer period for different regulatory authorities based on the IBD and the PBSL requires a six-month cycle, the most recent PSUR/ PBRER with a longer period will be acceptable to the PBSL after consultation. The PBSL may also request for Ad hoc ("for cause") PSURs/ PBRERs.
Ad hoc PSURs/ PBRERs are reports outside the routine reporting requirements. Where an ad hoc report is requested and a PSUR/ 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.

The need for the submission of a PSUR/ PBRER and the frequency of report submission to the PBSL 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 following prioritisation criteria should be taken into account when defining the frequency of submission for a given active substance or combination of active substances:

- information on risks or benefits that may have an impact on public health;
- new product for which there is limited safety information available to date (includes pre- and post-authorization experiences)
- significant changes to the product (e.g. new indication has been authorized, new pharmaceutical for or route of administration broadening the exposed patient population);
- vulnerable patient populations/poorly studied patient populations, missing information (e.g. children, pregnant women) while these populations are likely to be exposed in the post-authorization setting;
- signal* of/potential for misuse, medication error, risk of overdose or dependency;
- the size of the safety database and exposure to the medical product;
- medical products subjected to additional monitoring.

Concerning submission and frequency of reporting, PBSL may refer to the EURD list if applicable [9]. The EURD list provides the following information for each active substance/combination. It contains

- frequency of PSUR submission;
- data lock point;
- submission date;

- requirements for the submission of PSURs for generic, well-established use, homeopathic and traditional herbal products.

The EURD list is a legally binding document in Sierra Leone as well and MAHs are legally
responsible for complying with its requirements. EMA updates the EURD list every
month, following adoption by the Committee for Medicinal Products for Human Use
(CHMP) and Coordination Group for Mutual Recognition and Decentralised Procedures –
Human (CMDh), after consultation with the Pharmacovigilance Risk Assessment
Committee (PRAC).

The PSUR/ 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 PSURs/ PBRERs may continue to be required in other regions. As a result, the following scenarios may be encountered by MAHs:

- PSURs/ 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.
- Ad hoc PSUR/ PBRER may be requested by the PBSL.

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

- For newly approved products, a 6-monthly periodicity applies, for at least the first 2 years after approval.
- For PSURs/ 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 PSUR/ PBRER, and the content used in the previous PSUR/ PBRER can be reviewed and reused for sections where no new information has arisen since preparation of the last PSUR/ 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 of the ICH-E2C(R2) guideline[1].
- In situations when an MAH is preparing PSURs/ PBRERs on both a six-monthly and annual basis for different regulatory authorities, the PBSL requiring a PSUR/ PBRER on a six-month cycle may accept PSURs/ PBRERs containing 12-month interval data. See Figure 2 of the ICH-E2C(R2) guideline [1]. MAHs should discuss the acceptability of this approach with the PBSL.

Time interval between data lock point and the PSUR/ PBRER submission

The day of DLP is day 0 of the 70- or 90-calendar day interval between the DLP and report submission. Time interval between data lock point and the submission is as following:

- within 70 calendar days of the data lock point (day 0) for PSURs/ PBRERs covering intervals up to 12 months (including intervals of exactly 12 months); and
- within 90 calendar days of the data lock point (day 0) for PSURs/ PBRERs covering intervals in excess of 12 months;
- the timeline for the submission of ad hoc PSURs/ PBRERs requested by the PBSL will normally be specified in the request, otherwise the ad hoc PSURs/ PBRERs should be submitted within 90 calendar days of the data lock point (DLP).

h. Contents and Format of the PSUR/ PBRER

a. Content of the PSUR/ PBRER

The PSUR/ PBRER should focus on summary information, scientific safety assessment and integrated benefit-risk evaluation. The PSUR/ PBRER shall provide summaries of data relevant to the benefits and risks of the medical product, including results of all studies with a consideration of their potential

impact on the marketing authorization. Each PSUR/ PBRER should be stand-alone and reflect new and cumulative information currently available to the MAH

The PSUR/ PBRER should be based on all available data and should focus on new information, which has emerged since the DLP.

The level of detail provided in certain sections of the PSUR/ PBRER should depend on the medicinal product's known or emerging important benefits and risks. This approach is applicable to those sections of the PSUR/ 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 PSUR/ PBRER sections will vary among individual PSURs/ PBRERs.

Because of clinical development of a medical product frequently continues following marketing authorization, relevant information from post-authorization studies or clinical trials in unauthorized indications or populations should also be included in the PSUR/ PBRER. Similarly, as knowledge of the safety of a medical product may be derived from evaluation of other data associated with off-label use, such knowledge should be reflected in the risk-evaluation where relevant and appropriate.
For reference information concerning risk minimization activities please consider VII.B.4. in the GVP [2]. The risk evaluation should be based on all uses of the medical product, also including uses in authorized indications.

In preparation of the PSUR/ PBRER examples of sources of efficacy, effectiveness and safety information should be used. These may be used by the MAH to present safety, efficacy and effectiveness information in the PSUR/ PBRER and to evaluate the risk-benefit balance as appropriate to the product and its known and emerging important benefits and risks. Compared to the product for which the MAH is the innovator, there may be less information available to the MAH on a generic product. For example, only a published report may be accessible for a clinical trial not sponsored by the MAH. The MAH may consider providing as an appendix to the report list of the information sources used to prepare the PSUR/ PBRER (see Appendix E of E2C(R2) guideline [1]).

Particular sections of PSUR/ PBRER may share content with other regulatory reports. It may be possible for the MAH to take advantage of the modular

approach of the PSUR/ 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.

b. Format of the PSUR/ PBRER

The required format of PSURs/ PBRERs in Sierra Leone are based on those described in the ICH-E2C(R2) guideline [1]. The report is described as PSUR in the GVP Module VII of the EMA [2]. The full format should be used for all PSURs/ PBRERs of Sierra Leone. When no relevant information is available or a section is not applicable, this should be stated.

Part I: Title Page
Part II: Executive Summary
Part III: 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
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 Period
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

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 Summary 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/Effectiveness Information
17.2 Newly Identified information on Efficacy/Effectiveness
17.3 Characterization of Benefits
17.4 Effectiveness of Risk Minimization (if applicable)

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
20. Appendices to the PSUR/ PBRER

i. Guidance on Contents of the PSUR/ PBRER

a. Part I: Title Page

The title page of the PSUR/ 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.

The title page should include a signature. It is at the discretion of the Qualified person responsible for Pharmacovigilance (QPPV) to determine the

most appropriate person to sign the document according to the MAH structure and responsibilities. A statement of the QPPV should be included.

b. Part II: 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 and 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 authorized;
- summary of overall benefit-risk evaluation (based on the "Benefit-Risk Analysis Evaluation of the PSUR/PBRER);
- actions taken or proposed for safety reasons, e.g., significant changes to the reference product information, other risk minimization activities; and
- conclusions.

C. Part III: Table of Contents

1. Introduction

Section 1 of the PSUR/ PBRER should include:

- IBD and 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 PSUR/ PBRER; and
- the rationale for submission of multiple PSUR/ PBRER for the medicinal product, if applicable.

2. Worldwide Marketing Approval Status

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

3. Actions Taken in the Reporting Interval for Safety Reasons

Section 3 of the PSUR/ 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 summarized in this section.
Examples of significant actions taken for safety reasons include:

Actions related to investigational uses

- refusal to authorise a clinical trial for ethical or safety reasons;
- partial[1] 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;

[1] "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).

- issuance of a communication to investigators or healthcare professionals;
- plans for new studies to address safety concerns.

Actions related to marketing experience:

- failure to obtain or apply for a marketing approval renewal;
- withdrawal or suspension of a marketing approval;
- actions taken due to the product defects and quality issues;
- suspension of supply by the MAH;
- risk management activities including:
  - significant restrictions on distribution or introduction of other risk minimisation measures;
  - 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 the PBSL.

4. Changes to Reference Safety Information

Section 4 of the PSUR/ PBRER should list any significant changes to the reference safety information within the reporting adverse drug reactions (ADR)* interval. These should include:

- changes to contraindications, warnings/precautions sections ;
- addition of ADR 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.

Such changes might include information relating to contraindications, warnings, precautions, 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 PSUR/ PBRER.

5. Estimated Exposure and Use patterns

Sections 5.1 and 5.2 of the PSUR/ PBRER should provide estimates of the size and nature of the population exposed to the medicinal product. Section 5.1 of the PSUR/ 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 PSURs/ PBRERs for the same product. If a change in the method is appropriate, both methods and calculations should be provided in the PSUR/ PBRER introducing the change.

5.1 Cumulative subject exposure in clinical trials

Section 5.1 of the PSUR/ PBRER should include the following information, if applicable, presented in tabular format (see Appendix B, Tables 1-3 for examples in the ICH E2C(R2) Guideline [1]):

- 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 recognized 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.

5.2. Cumulative and Interval Patient Exposure from Marketing Experience

Separate estimations should be provided for interval exposure (since the DLP of the previous PSUR/ PBRER) and, when possible, cumulative exposure (since the IBD). See Appendix B, Tables 4 and 5 in ICH E2C(R2) [1] 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);
- 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 PSUR/ PBRER (e.g., approved indication, contraindications).

6. Data in Summary tabulations

PSUR/ 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.

6.1. Reference information Section

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

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

Section 6.2 of the PSUR/ 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 PSUR/ 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, 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. 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 system organ class 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 reasons (e.g., expedited reporting), if applicable. Sponsors/MAHs should not unblind data for the specific purpose of preparing the PSUR/ 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.

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

6.3 of the PSUR/ 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 PSUR/ PBRER. As described in ICH Guideline E2D [3], 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 individual case safety reports (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 in the ICH guideline E2C (R2)[3]), and should be organised by system organ class.

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.

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

This section of the PSUR/ 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 "Overview of Signals: New, Ongoing or

Closed" of the PSUR/ 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 "Signal Evaluation" of the PSUR/ 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 ("Evaluation of Risks and New Information" and 16.4 "Characterization of Risks" respectively. Findings from clinical trials not sponsored by the MAH should be described in the relevant sections of the PSUR/ 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 "Lack of Efficacy in Controlled Clinical Trials"of the PSUR/ 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) or completed (clinical study report is finalised).

7.1. Completed Clinical Trials

Section 7.1 of the PSUR/ 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[2] It could include information that supports or refutes previously identified safety concerns, as well as evidence of new safety signals.

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.

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.

7.4. Other Therapeutic Use of Medicinal Product

This section of the PSUR/ 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 [3] (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).

7.5. New Safety Data Related to Fixed Combination Therapies

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 PSUR/ PBRER is also approved or under development as a component of a fixed combination product or a

[2] Examples of synopses are provided in ICH E3 [4] and CIOMS VII [5]

multi-drug regimen, this section should summarise important safety findings from use of the combination therapy.

- If this PSUR/ 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 PSUR/ PBRER for one or all of the individual components of the combination.

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.

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.

9. Information from Other Clinical Trials and Sources

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 metaanalyses of randomised clinical trials, and safety information provided by co-development partners or from investigator-initiated trials.

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 PSUR/ PBRER.

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 PSUR/ PBRER, regardless of the outcome. Implications of the findings presented in PSUR/ PBRER Section 10 should be discussed in the relevant evaluation sections of the report.

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 PSURs/ 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.

12. Other Periodic Reports

Unless otherwise specified by national or regional regulatory requirements, the MAH should prepare a single PSUR/ PBRER for a single active substance. However, if an MAH prepares multiple PSURs/ 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).

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.

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 PSUR/ 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), or an important safety signal, or where they may add information to the evaluation of safety concerns already presented in the PSUR/ 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 "Evaluation of Risks and New Information" of this guideline).

15. Overview of Signals: New, Ongoing, or Closed

The general location for presentation of information on signals and risks within the PSUR/ PBRER is shown in Appendix F of ICH E2C(R2) [1]. The purpose of this 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 PSUR/ 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 such as the PBSL.

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 "Signal and Risk Evaluation" of the PSUR/ 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 PSUR/ 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 PSUR/ 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 PSUR/ PBRER. This table should include the following information:

- 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 PSUR/ 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 PSUR/ PBRER. When a regulatory authority has requested that a specific topic (not considered a signal) be monitored and reported in a PSUR/ PBRER, the MAH should summarize the result of the analysis in PSUR/ PBRER Section 15 ("Overview of Signals: new, Ongoing, or Closed") if it is negative. If the specific topic becomes a signal, include it instead in the signal tabulation and discuss in PSUR/ PBRER Section 16.2 ("Signal Evaluation").

16. Signal and Risk Evaluation

The purpose of this section of the PSUR/ 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 the ICH E2C(R2) Guideline [1] provides a flowchart to illustrate the mapping of signals and risks to specific sections of the PSUR/ PBRER.

The evaluation subsections should not summarise or repeat information presented in previous sections of the PSUR/ 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 PSUR/ 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.

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;*
- 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 [7]) at the start of the reporting interval of the current PSUR/ 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.

16.2. Signal Evaluation Section

16.2 of the PSUR/ 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 PSUR/ 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 or Standardized MedDRA Queries 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 individual case, e.g., an index case of well documented agranulocytosis or Stevens Johnson syndrome;
- discussion; and
- conclusion.

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 "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 in ICH E2C(R2) [1] and evaluated in Section 16.2 of the PSUR/ PBRER, if the signal is also closed during the interval of the PSUR/ 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 PSUR/ 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 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 PSUR/ 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; and
- conclusion including whether or not the evaluation supports an update of the characterization of any of the important potential and identified risks in Section 16.4 of the PSUR/ 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.

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 PSURs/ 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).

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 PSUR/ 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.

17. Benefit Evaluation

PSUR/ 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.

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 PSUR/ PBRER Section 17.3 and the benefit-risk assessment in Section 18.

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.

17.3 Characterisation of Benefits

Section 17.3 of the PSUR/ 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 PSUR/ 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 PSUR/ 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.

18. Integrated Benefit-Risk Analysis for Approved Indications

Whereas PSUR/ 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.

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).

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 PSUR/ 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.

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 PBSL. This may include proposals for additional risk minimisation activities.

These proposals should also be considered for incorporation into the risk management plan, as stipulated by PBSL Guideline for Risk management plan.

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 in formation.

20. Appendices to the PSUR/ PBRER

The PSUR/ 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 PSUR/ PBRER (when desired by the MAH).

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

5.0 Glossary

Glossary Term	Source definitio	Definition/Commentary
Adverse drug reaction (ADR)	[3]	A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of disease or for modification of physiological function.
Adverse event	[3]	Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with the prodcut. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding for example), symptom or disease temporarily associated with the use of the medicine.
Adverse event of special interest	[3]	An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or programme, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterise and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (e.g., regulators) might also be warranted.
Closed Signal	[1]	A signal for which an evaluation was completed during the reporting interval.
Company Core Data Sheet (CCDS)	[1]	A document prepared by the MAH containing, in addition to safety information, material related to insications, dosing, pharmacology and other information concerning the product.

Company Core Safety Information (CCSI)	[1]	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 product, except when the local regulatory authority specially requires a modification. It is the reference information by which is listed and unlisted are determined for the purposes of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.
Completed clinical trial	[6]	Clinical trial for which a final study report is available.
Data lock point (DLP)	[1]	The date (month and day) designated as the cut-off for data to be included in a DSUR. It is based on the Development International Birth Date (DIBD).
Development Safety Update Report (DSUR)	[6]	Pharmacovigilance document of a comprehensive, thoughtful annual review and evaluation of pertinent safety information collected during the reporting period related to a drug under investigation, whether or not it is marketed.
Developmental international birth data (DIBD)	[6]	Date of first approval (or authorisation) for conducting an interventional clinical trial in any country.
European Union reference dates (EURD) list	[8]	The European Union reference dates (EURD) list is a comprehensive list of active substances and combinations of active substances contained in medicinal products subject to different marketing authorisations, together with the corresponding EU reference dates, frequencies for submission of periodic safety update reports and related data lock points.
Investigational Drug	[6]	The term is used to indicate only the experimental product under study or development.

Identified risk	[6]	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 reactions.
Important identified risk; important potential risk	[1]	An identified risk or potential risk that could have an impact on the risk-benefit balance of the product or have implications for public health.
Important missing information	[1]	Critical gaps in knowledge for specific safety issues or populations that use the marketed product.
Individual case safety report (ICSR)	[8]	An Individual Case Safety Report is a document providing the most complete information related to an Individual Case at a certain point of time. An ICSR may also be referred to as Safety Report.
International birth date (IBD)	[1]	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	[6]	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	[1]	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	[6]	Trial where enrolment has begun, whether a hold is in place or analysis is complete, but without a final clinical study report available.
Ongoing signal	[1]	A signal that remains under evaluation at the DLP.
Periodic benefit risk evaluation report (PBRER)	[1]	A PBRER is a format of safety report which is used as a basis for the Periodic Safety Update Report (PSUR). The report is produced by MAH at defined time points after a medicine has been given marketing authorisation. The motive of the report is to provide comprehensive and up-to-date information about the safety of a medicine.
Periodic safety update report (PSUR)	[1]	A regularly updated document of the world-wide safety experience of a medicinal product at defined times during post-registration period.
Potential risk	[6]	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. An example is toxicological findings seen in non-clinical safety studies which have not been observed or resolved in clinical studies. An important potential risk is a potential risk that could have an impact on the benefit-risk 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 precautions section of the product information should be considered important.
Reference safety information (RSI)	[1]	All relevant safety information contained in the reference product information 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 of the PBRER. Where the

		reference product information is the CCDS, the reference safety information is the CCSI.
Safety concern	[1]	An important identified risk, important potential risk, or important missing information.
Serious adverse event (SAE)	[3]	A serious adverse event or reaction is any untoward medical occurrence that at any dose: experience is an adverse drug experience that results in • results in death; • an adverse drug experience that places the patient at immediate risk of death from the adverse drug experience as it occurred (not including an adverse drug experience that might have caused death had it occurred in a more severe form); • inpatient hospitalization or prolongation of existing hospitalization; • a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or • a congenital anomaly or birth defect.
Signal	[1]	Information that arises from one or multiple sources that suggests a new potentially causal association or a new aspect of unknown 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 actions to verify.
Solicited reports	[3]	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	[3]	An unsolicited communication to a company, regulatory authority or other organization that describes an ADR in a patient given one or more medical products and which does not derive from a study or any organized data collection scheme.

6.0 References

[1] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Harmonised Tripartite Guideline; Periodic Benefit-Risk Evaluation Report (PBRER) E2C(R2), Current *Step 4* Version dated 17, December 2012, available under https://database.ich.org/sites/default/files/E2C_R2_Guideline.pdf

[2] Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1); European Medicines Agency (EMA), EMA/816292/2011, 9 December 2013, available under https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf

[3] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH E2D(R1) Guideline on post-approval safety data: definitions and standards for management and reporting of individual case safety reports, Current *Step 2b* Version dated 5 February 2024, available under https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e2dr1-guideline-post-approval-safety-data-step-2b-revision-1_en.pdf

[4] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Topic E 3 Structure and Content of Clinical Study Reports, Note for Guidance on Structure and content of clinical study reports, CPMP/ICH/137/95, Current *Step 5* Version dated July 1996, available under https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-3-structure-and-content-clinical-study-reports-step-5_en.pdf

[5] The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials Report of CIOMS Working Group VII, Council for International Organizations of Medical Sciences (CIOMS), ISBN 92 9036 080 1, Geneva 2006, available under

https://cioms.ch/sd7fdh93gewd882ds/sdf3dmv09dsn23ld2-dsur/WEB_WG%20VII_DSUR_.pdf

[6] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; Development Safety Update Report E2F, Current *Step 5* Version dated September 2011, available under https://www.ema.europa.eu/en/documents/scientific-guideline/ich-guideline-e2f-development-safety-update-report-step-5_en.pdf

[7] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; ICH Topic E 2 E Pharmacovigilance Planning (Pvp), Note for Guidance on Planning Pharmacovigilance Activities, CPMP/ICH/57167/03, Current *Step 5* Version dated June 2005, available under https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-topic-e-2-e-pharmacovigilance-planning-step-5_en.pdf

[8] EU Individual Case Safety Report (ICSR) Implementation Guide; European Medicines Agency (EMA), EMA/51938/2013 Rev 2*, March 2021, available under https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/european-union-individual-case-safety-report-icsr-implementation-guide_en.pdf

[9] List of the European Union reference dates and frequency of submission of periodic safety update reports (PSURs); European Medicines Agency (EMA), EMA/630645/2012 Rev. 136, first published 01/10/2012, last updated 26/03/2024, available under https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/periodic-safety-update-reports-psurs.

	Title: Guideline for Periodic Benefit-Risk Evaluation Reports (PBRERs)	
Rev No: 00	**Doc No: PBSL/GL/057**	Version no. 02
Issue date: 25th Nov. 2025	**Effective date: 28 Nov 2025**	Approved by: Registrar

Prepared by	**Reviewed by**	**Approved by**
Signature	**Signature**	**Signature**
Head, Pharmacovigilance & Clinical trials	**Head, Quality Assurance**	**Registrar**
Name: Dr. Onome Abiri	**Name**	**Name**