

Introduction to PSUR/PBRER

Periodic Safety Update Reports/Periodic Benefit Risk Evaluation Report in Pharmacovigilance

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Aggregate Reporting Requirements
Periodic reporting to regulatory authorities

- Pre-licensure from clinical trials:
 - ICH E2F Development Safety Update Report DSUR
- Post-licensure from authorized products:**
 - ICH E2C (R1) Periodic Safety Update report (Nov 1996, Nov 2005)
 - ICH E2C (R2) Periodic Benefit-Risk Evaluation Report PBRER (Nov 2012), or
 - National Requirements

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Periodic safety update reports (PSURs)/ Periodic Benefit Risk Evaluation Report

'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'

Guideline on good pharmacovigilance practices (GVP) Module VII. EMA/816292/2011 Rev 1* .

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Objective of a PSUR/PBRER

- ✓ Presentation of a **comprehensive** and **critical analysis** of **new or emerging** information on the **risks** of medicinal product and on its **benefit** in approved indications **to enable an appraisal** of product's overall benefit-risk profile.

How does a PBRER facilitates:

- Summarizes relevant new safety information that may impact the benefit risk profile
- Summarizes important new efficacy / effectiveness information
- Examines if new information is in accord with previous knowledge of the benefit risk profile
- Integrates Benefit / Risk Evaluation where new important safety information has emerged.

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Contents – High Level

Contents

- The emerging information - new signals, any identified/ potential risks etc.
- The summary of safety and efficacy information of the medicine.
- An integrated benefit-risk analysis for all authorized indications.
- The summary of any Risk minimization measures.
- The outline plans for signals or risk evaluations.

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Sources of Information

- Non-clinical studies;
- Clinical trials, including research in unapproved indications or populations;
- Spontaneous reports (for example, on the MAH's safety database);
- MAH-sponsored websites;
- Observational studies such as registries;
- Product usage data and drug utilization information;
- Published scientific literature or reports from abstracts;
- Unpublished manuscripts;
- Active surveillance systems (for example, sentinel sites);
- Systematic reviews and meta-analyses;
- Information arising from licensing partners, other sponsors or academic institutions/research networks;
- Patient support programmes;
- Investigations of product quality; and
- Information from regulatory authorities.

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Format: Periodic Benefit Risk Evaluation Report (PBRER)

ICH PBRER requirements:
ICH HARMONISED TRIPARTITE GUIDELINE
Current Step 4 version
dated 17 December 2012

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The Recommended Table of Contents

Title Page
Executive Summary
Table of Contents
1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Interval for Safety Reasons
4. Changes to Reference Safety Information
5. Estimated Exposure and Use Patterns
 5.1 Cumulative Subject Exposure in Clinical Trials
 5.2 Cumulative and Interval Patient Exposure from Marketing Experience

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The Recommended Table of Contents (contd.)

- 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

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The Recommended Table of Contents (contd.)

- 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)

New in PBRER

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The Recommended Table of Contents (contd.)

17. Benefit Evaluation

17.1 Important Baseline Efficacy/Effectiveness Information

17.2 Newly Identified information on Efficacy/Effectiveness

17.3 Characterization of Benefits

New in PBRER

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

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Guidance on Contents of the PBRER

Title Page

- Basic information (e.g., MAH info, International birthday, reporting interval)

Executive Summary :

Concise summary of the most important information contained in the report:

- Introduction
- Reporting interval
- Medicinal product(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s)
- Estimated cumulative exposure of clinical trial subjects
- Number of countries in which the medicinal product is approved
- Summary of overall benefit-risk evaluation
- Actions taken or proposed for safety reasons
- Conclusions.

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Section 1: Introduction

- International Birth Date (IBD)
- Reporting interval;
- Medicinal product(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);
- A brief description of the approved indication(s) and population(s);
- A brief description and explanation of any information that has not been included in the PBRER; and
- The rationale for submission of multiple PBRERs for the medicinal product, if applicable.

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Section 2: Worldwide Marketing Approval Status

Brief narrative overview including following:

- Date of first approval
- Indication (s)
- Approved dose(s)
- Where approved (if applicable)

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Section 3: Actions Taken in the Reporting Interval for Safety Reasons

Description of significant actions related to safety:

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

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Section 3: Actions Taken in the Reporting Interval for Safety Reasons (contd.)

Examples related to **investigational** drugs:

- Refusal to authorize a clinical trial for ethical or safety reasons
- Partial or complete suspension, or early termination due to safety/efficacy
- Protocol modifications due to safety/ efficacy
- Plans for new studies to address safety concerns
- Restrictions in study population or indications

Examples related to **marketed** drugs:

- Failure to obtain or apply for a marketing approval renewal
- Withdrawal or suspension of a marketing approval
- Suspension of supply by MAH
- Significant restrictions on distribution
- New post-marketing study requirement(s) imposed by regulator(s)

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Section 4: Changes to Reference Safety Information (RSI)

- RSI should include core safety and approved indication information.
- RSI may be Company Core Data Sheet (Company Core Safety Information)
- If CCDS/CCSI is not available, then Pack Insert can be used
- Document applicable at the end of reporting period should be used

Any significant changes to the RSI within the reporting interval.

- Information relating to contraindications, warnings, precautions, ADRs, overdose, and interactions
- Important findings from ongoing and completed clinical trials
- Significant non-clinical findings (e.g., carcinogenicity studies)

Latest RSI at DLP should be provided in Appendix. Track-change version is not required.

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Section 5: Estimated Exposure and Use Patterns

Section 5 is subdivided into two sections:

- **5.1 Cumulative Subject Exposure in Clinical Trials**
 - ✓ ongoing and completed
 - ✓ As detailed as possible – age, sex, racial/ethnic group, special population (e.g. pregnant, renal/hepatic impairment)
- **5.2 Cumulative and Interval Patient Exposure from Marketing Experience**
 - 1) Post-approval (non-clinical trial) exposure
 - 1) Presented by indication, age, sex, region, number of vaccination courses, etc. where applicable
 - 2) Post-approval use in special populations (e.g., pediatric, elderly, pregnant, Patients with hepatic and/or renal impairment, racial/ethnic origin, etc.). May be from post approval non-interventional studies
 - 3) Other post-approval use (Anything patterns which MAH becomes aware- e.g., overdose, drug abuse, off label use)

Include brief descriptions of the method(s) used to estimate the subject/patient exposure

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Section 6: Data in Summary Tabulations

Cumulative summary tabulations of SAEs from clinical trials and post-marketing sources that have been reported to the MAH since the beginning (DIBD).

Graphical displays can be used

Section 6 is subdivided into three sections:

- 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

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Section: 6.1 Reference Information

Should specify the MedDRA version(s) of the coding dictionary used for analyses of adverse reactions

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Section: 6.2 Cumulative Summary Tabulations of Serious Adverse Events (SAEs) from Clinical Trials

- Provide background for the appendix on cumulative summary tabulation of SAEs from clinical trials
- from the DIBD to DLP
- Explain any omission of data (e.g., no data for old CT)
- Include only serious AE terms. SOC and PT MedDRA terms.

Table – Cumulative Tabulations of Serious Adverse Events from Clinical Trials

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

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Section 6.3: Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources

- Provide background for the appendix on cumulative and interval summary tabulation of adverse reactions from IBD to DLP
- *Spontaneously reported AE usually imply a suspicion of causality by reporter. Hence considered adverse reactions for regulatory reporting purposes (ICH E2D)*

The tabulation should include:

- Serious and non-serious ADRs from spontaneous ICSRs, including reports from healthcare professionals, consumers, scientific literature, and regulatory authorities
- Serious adverse reactions from non-interventional studies
- Solicited reports of ADRs.

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Section 6.3: Cumulative and Interval Summary Tabulations from Post-Marketing Data Sources (contd.)

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

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

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Section 7: Summaries of Significant Safety Findings from Clinical Trials during the Reporting Interval

Brief summary of clinically important emerging efficacy/effectiveness and safety findings that became available during the reporting interval.

Section	Content
7.1 Completed Clinical Trials	Brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting interval.
7.2 Ongoing Clinical Trials	Clinically important information that has arisen in trials. (e.g., interim safety analyses or as a result of unblinding of subjects with adverse events)
7.3 Long-Term Follow-up	Long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products. (when applicable)

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Section 7: Summaries of Significant Safety Findings from Clinical Trials during the Reporting Interval (contd.)

Section	Content
7.4 Other Therapeutic Use of Medicinal Product	Clinically important safety information from other programmes conducted by the MAH (e.g., expanded access/compassionate use programmes)
7.5 New Safety Data Related to Fixed Combination Therapies	Safety info summarized from constituent/combo product PBRERs, if applicable; or incorporate info specific to combo into applicable sections of PBRER for one/all of the constituents

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Section 8: Findings from Non-Interventional Studies

Summaries relevant safety information or information with potential impact on the benefit or risk evaluations from MAH sponsored non-interventional studies that become available during the reporting period.

- e.g., observational studies, epidemiological studies, registries,
- A listing of any MAH-sponsored post-marketing non-interventional study(ies) completed or ongoing during the reporting interval should be included in appendix

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Section 9: Information from Other Clinical Trials and Sources

9.1 Other Clinical Trials

- e.g. pooled analyses or meta-analyses of randomized clinical trials, and safety information provided by co-development partners or from investigator-initiated trials.

9.2 Medication Errors

- Summaries relevant information on patterns of medication errors and potential medication errors even when not associated with adverse outcomes
- May be received from spontaneous reporting systems, medical information queries, customer complaints, screening of digital media, patient support programmes, or other sources

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Section 10: Non-Clinical Data

Summary of 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.

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Section 11: Literature

Summarize new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts

- Literature searches should be wider than those for individual adverse reaction cases
- If relevant, information on active substances of same class should be considered

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Section 12: Other Periodic Reports

Unless otherwise specified by national or regional regulatory requirements, a single PBRER should be prepared for a single active substance.

However, if multiple PBRERs are prepared for a single active substance (e.g., covering different indications, or formulations), important findings should be summarized here.

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Section 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)

should be summarized in this section.

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Section 14: Late-Breaking Information

Any potentially important safety and efficacy/effectiveness findings that arise **after the DLP** but while the PBRER is in preparation.

Examples include:

- Clinically significant new publications
- Important follow-up data
- Clinically relevant toxicological findings
- 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 important index case or signal

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

The WHO defines a signal as reported information on a **possible causal association between an adverse event and a drug**, the **relationship being unclear or incompletely documented previously**.

Definition of New, Ongoing or Closed Signals by ICH Guideline E2C (R2)

- ❑ **Newly identified signals:** A signal first identified during the reporting interval, prompting further actions or evaluation.
- ❑ **Ongoing signals:** A signal that remains under evaluation at the data lock point.
- ❑ **Closed signals:** A signal for which an evaluation was completed during the reporting interval.

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Section 15: Overview of Signals: New, Ongoing, or Closed (contd.)

Provide a high-level overview of:

- safety signals that were closed (i.e., evaluation completed) during the reporting interval as well as
- ongoing signals that were undergoing evaluation, at the end of reporting interval.

The methods of signal evaluation, source and actions should be included in this section

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Section 15: Overview of Signals: New, Ongoing, or Closed (contd.)

Example of a Tabular Summary of Safety Signals that Were Ongoing or Closed during the

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

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Section 16: Signal and Risk Evaluation

The purpose of Section 16 is to provide :

- ✓ A summary of what is known about important identified and potential risks and important missing information (16.1);
- ✓ An evaluation of all signals closed during the reporting interval (16.2);
- ✓ An evaluation of new information with respect to previously recognized identified and potential risks (16.3);
- ✓ An updated characterization of important potential and identified risks ,where applicable (16.4); and
- ✓ A summary of the effectiveness of risk minimization (16.5)

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Potential Risk, Identified Risk and Missing Information

Identified risk: An untoward occurrence for which there is adequate evidence of an association with the medicinal product.

- e.g.: an adverse reaction adequately demonstrated in non-clinical studies and confirmed by clinical data;

Potential risk: 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.

- E.g.: toxicological findings seen in non-clinical safety studies which have not been observed in clinical studies

Missing information

Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations,

which could be clinically significant.

- E.g.: populations not studied (e.g. pregnant women)

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Section 16.1: Summary of Safety Concerns

Provide a summary of safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made. These comprise:

Important identified risks, Important potential risks and Important missing information.

- What constitutes an important risk will depend upon several factors, including the impact on the individual, the seriousness of the risk, frequency, predictability, reversibility, and the impact on public health.

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Section 16.2: Signal Evaluation (1/2)

Summarize the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval.

Two main categories to be included in this section are:

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

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Section 16.2: Signal Evaluation (2/2)

Include description of signal evaluations with the following information:

- Source of the signal;
- Background relevant to the evaluation;
- Method(s) of evaluation, including data sources, search criteria (where applicable, the specific MedDRA terms [e.g., PTs, HLTs, SOCs, etc.] or Standardised MedDRA Queries [SMQs] that were reviewed), and analytical approaches;
- Results – a summary and critical analysis of the data considered in the signal evaluation;
- Discussion; and
- Conclusion.

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Section 16.3: Evaluation of Risks and New Information

- Provide a critical appraisal of **new information** relevant to previously recognized risks that is not already included in Section 16.2 of the PBRER (Signal Evaluation).
- Updated information on a previously recognized 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 characterization of a previously recognized risk.

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Section 16.3: Evaluation of Risks and New Information (contd.)

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

- Source of the new information;
- Background relevant to the evaluation;
- Method(s) of evaluation, including data sources, search criteria, and analytical approaches;
- Results – a summary and critical analysis of the data considered in the risk evaluation;
- Discussion; and
- Conclusion

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Section 16.4: Characterization of Risks

This section characterizes important identified and important potential risks based on cumulative data and describes important missing information.

Characterization may include:

- 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

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Section 16.5: Effectiveness of Risk Minimization (if applicable)

Summarize:

Relevant information on the effectiveness and/or limitations of specific risk minimization activities for important identified risks that has become available during the reporting interval.

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Section 17: Benefit Evaluation

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

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Section 17.1: Important Baseline Efficacy/Effectiveness Information

Summarizes information on the efficacy/effectiveness of the medicinal product as of the beginning of the reporting interval,

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Section 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
- Also include changes in the therapeutic environment that could impact efficacy/effectiveness over time, e.g., vaccines

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Section 18: Integrated Benefit-Risk Analysis for Approved Indications

- Whereas PBRER Sub sections 16 and 17 present the risks and benefits, respectively, Section 18 should provide an integration and critical analysis of the key information.
- Section 18 provides the benefit-risk analysis and should not simply duplicate the benefit and risk characterization presented earlier.

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18.1: Benefit-Risk Context - Medical Need and Important Alternatives

Provide a brief description of the medical need for the medicinal product in the approved indications, and summarize alternatives (medical, surgical, or other; including no treatment).

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18.2: Benefit-Risk Analysis Evaluation

- A benefit-risk profile is specific to an indication and population
- The evaluation should be presented and discussed in a way that facilitates the comparison of benefits and risks
- Few considerations for evaluation:
 - Context of use of the product: the condition to be treated, prevented, or diagnosed; its severity and seriousness; and the population to be treated
 - Nature, clinical importance, duration, and generalizability, as well as evidence of efficacy in non-responders to other therapies and alternative treatments.
 - Clinical importance of risk, 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.
 - Strengths, weaknesses, and uncertainties of the evidence
- Provide a clear explanation of the methodology and reasoning used to develop the benefit-risk evaluation

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Section 19: Conclusions and Actions

- ❖ Provide a conclusion about the implications of any new information that arose during the reporting interval, in terms of overall benefit-risk evaluation, as well as for relevant subgroups.
- ❖ Assess the need for further changes to the reference product information and propose changes as appropriate.
- ❖ Include preliminary proposal(s) to optimize or further evaluate the benefit-risk balance, for further discussion with the relevant regulatory authorities. This may include proposals for additional risk minimization activities.

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Section 20: Appendices to the PBRER

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

1. Reference Information;
2. Cumulative Summary Tabulation of Serious Adverse Events from Clinical Trials and Interval/Cumulative Summary Tabulations from Marketed Experience;
3. Tabular Summary of Safety Signals (if not included in the body of the report);
4. Listing of Interventional and Non-Interventional Studies with a Primary Objective of Post-Authorization Safety Monitoring; and
5. List of the Sources of Information Used to Prepare the PBRER (when desired by the MAH).

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

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Additional Requirements for PSURs for Vaccines: EU GVP

- Consideration to any potential impact on safety of changes in the manufacturing process
- Batch and age-related adverse reactions must be evaluated
- Analysis of adverse reactions for different doses and across different vaccination schedules
- Reports on vaccine failure , lack of efficacy / effectiveness
- Vaccination errors
- Vaccination-anxiety-related reactions such as syncope
- Literature data relevant to similar vaccine / vaccine components (e.g., stabilizers, preservatives, adjuvants)

Reference: Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases

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Periodicity / Submission

PSUR are generally prepared at the following intervals:

- Immediately upon request
- Every 6 months from authorization until vaccine is placed on the market
- Every 6 months for the first 2 years on the market
- Annually for the next 2 years
- Thereafter every 3 years

Submission of PSUR:

- By day 70 after data lock point (DLP) for intervals up to 12 months
- By day 90 after DLP for intervals > 12 months

Differences in periodicity / submission schedules, regional content requirements and even format according to national legislation.

- Please check local regulatory requirements to confirm.

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Periodic Safety Update Report PSUR Vs. Periodic Benefit Risk Evaluation Report PBRER

ICH E2C (R2) Periodic Benefit Risk Evaluation Report (PBRER)

- introduced new concepts linked to the evolution of the traditional PSUR from an interval safety report to a cumulative benefit-risk report.
- Changed the focus from individual case safety reports to aggregate data evaluation.



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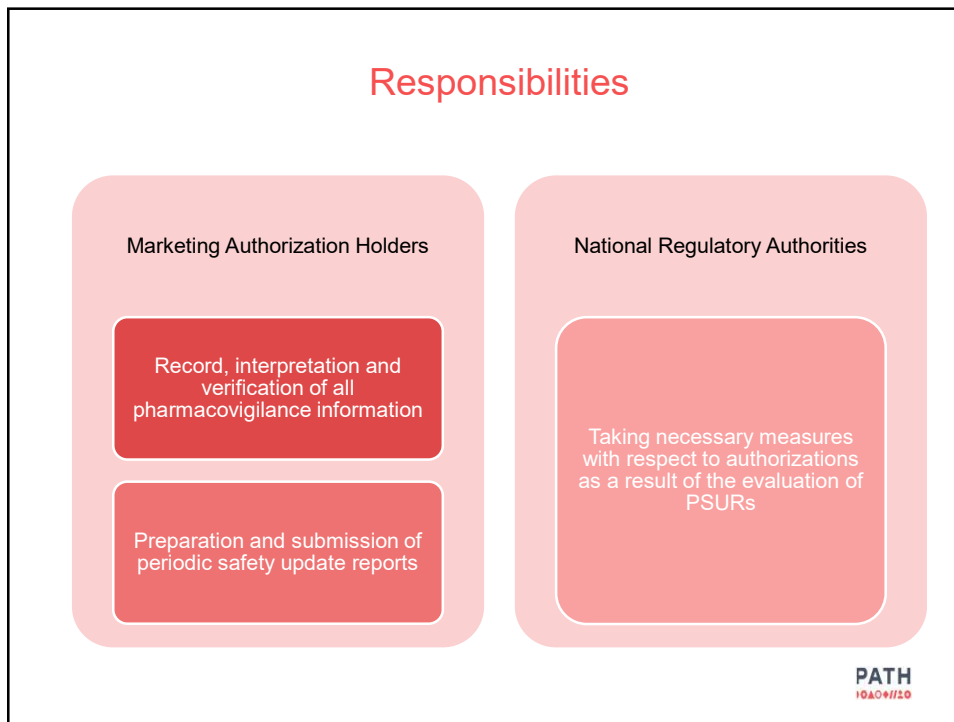
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Major Changes in the new PBRER format

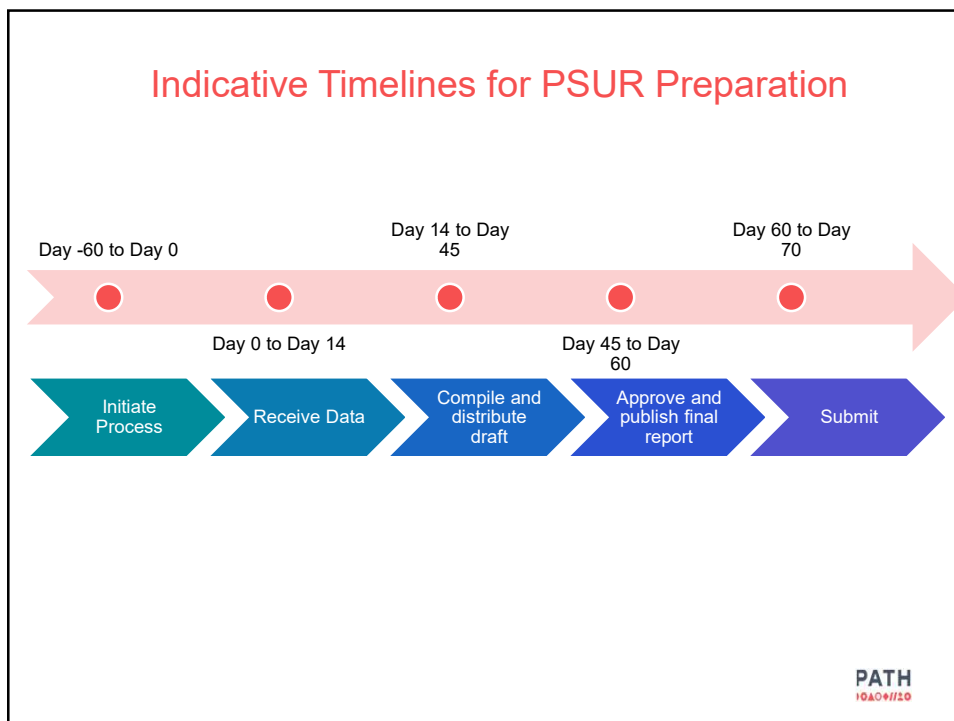
- No detailed (ADR) line listings, however, may be requested during the assessment
- More concise cumulative summary tabulation of SAEs from CT and cumulative and interval summary tabulations of ADRs.
- Case narratives to be provided where relevant to the scientific analysis of a signal or safety concern
- Multiple six monthly, Bridging and Addendum reports will not be accepted.

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Effective PSUR Development Process

Written SOP for PSUR preparation, quality control, review and submission

Involve and train all stakeholders (other departments)

PSUR **document template** could be developed to ensure completeness of data

Review by an experienced person with knowledge of the vaccine and drug safety concepts

Quality assurance – frequent audits

Comply with all promises and commitments made to the NRAs

Access to appropriate data, e.g., pack inserts, sales information, etc.

Careful review of all sections including SAEs/ADRs: **Create PSUR Review Checklist**

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Outcome of PSUR Assessment by NRA

- Legally binding decision or position in case of any action to vary, suspend, revoke the marketing authorizations of the medicinal products containing the concerned active substance or combination of active substances

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Common PSUR inspection findings

- Non-submission - Complete non-submission of PSUR
- Submission, but time frame not correct
- Poor quality reports, Incorrect format of the document
- New safety signals not or poorly assessed
- Medication errors not highlighted
- Absence of use of standardized medical terminology (MedDRA)
- Published literature not properly reviewed
- Omission of required information e.g., Update of Regulatory or MAH Actions taken for Safety Reasons, Changes to Reference Safety Information
- Subject exposure poorly calculated, explanation of calculation missing
- Previous requests from Regulatory Agencies not addressed, E.g., close monitoring of specific safety issues

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