Module VII – Aggregate Reports

Contents

1. Significance of Aggregate Reports

At the time of marketing Authorization (MA), a medicinal product is authorized on the basis that in the specified indication (s) and the benefit-risk balance is judged to be positive for the target population.

Generally, a medicinal product will be associated with adverse reactions and these will vary in terms of severity, likelihood of occurrence, effect on individual patients and public health impact. However, not all actual or potential adverse reactions will have been identified at the time when an initial MA is granted, and some will only be discovered and characterized in the post-authorization phase.

During the clinical development of an investigational drug (experimental product under study or development), periodic analysis of safety information is crucial to the ongoing assessment of risk to trial subjects[1].

It is also important to inform regulators and other interested parties (e.g., ethics committees) at regular intervals about the results of such analyses and the evolving safety profile of an investigational drug and apprise them of actions proposed or being taken to address safety concerns.

[1] The Development Safety Update Report (DSUR): Harmonizing the Format and Content for Periodic Safety Reporting During Clinical Trials: Report of CIOMS Working Group VII, Geneva 2007.

2. Overview of Aggregate Reports

Aggregate safety report is a review of cumulative safety data obtained from a wide range of sources, including clinical study studies (i.e., reports and study results), spontaneous reports, preclinical studies, epidemiology sources and literature reports on a periodic basis and these are submitted to the regulators worldwide.

Aggregate safety reporting involves compilations and analyses of safety data from a group of patients exposed to a drug or sometimes more than one drug, (e.g. combination products), including adverse events (AEs) and other safety issues such as medication errors or lack of effect (efficacy) for over a defined period (e.g., months or years according to regulatory guidelines).

Aggregate safety reports play a key role in the safety assessment of medicinal products

The exact type of report that it is required varies by country and with the approval status of the medicinal product.

2.1 Purpose of Aggregate Safety Reports

The purpose of Aggregate safety reports is:

- To update and evaluate the worldwide safety experience with a medicinal product at defined time points before and after approval
- To provide a concise summary of safety information, and an evaluation of the benefit-risk profile of the medicinal product to identify safety information that would require:
- Further investigation of the product,
- Changes to the approved medicinal product label to provide up-to-date information the patient, health care professionals (HCPs), and the health authorities worldwide
- To comply with the regulatory guidelines

2.2 Type of aggregate reports:

Pre-marketing Aggregate Safety Reports (ASRs):

a) Development Safety Update Report (DSUR)

b) United States (US) Investigational New Drug (IND) Reports

c) European Union (EU) Annual Safety Reports

Post Marketing Aggregate Safety Reports:

a) DSUR (if clinical trials are ongoing in post-marketing reports)

b) Periodic Benefit Risk Evaluation Reports (PBRER)\Periodic Safety Update Reports (PSUR)

c) Periodic Adverse Drug Experience Report (PADER)/ Periodic Adverse Experience Report (PAER)

3. Formats of Aggregate Reports

3.1 DSUR

Development Safety Update Report

3.1.1. Introduction to the DSUR

Regular analysis of safety is crucial for the assessment of risk to trial subjects and to understand the risk benefit of a medical product.

Council for International Organization for Medical Sciences (CIOMS) working group VI (Managing Safety information from clinical trial) provides recommendations regarding the general principles behind a DSUR, as well as an example of a model DSUR.

CIOMS working group VII (Development Safety Update Report: Harmonizing the format and content for periodic safety reports during clinical trials) proposals on the creation of a DSUR and its content and format will be endorsed and universally implemented by all stakeholders. The CIOMS VII Working Group also envisions a further, more ambitious objective, whereby the DSUR and PSUR are integrated into a single harmonized safety report that would cover a product throughout its lifecycle. Proposals are made for future development of such a document and process.

The format and content of a DSUR is described in International Conference on Harmonization (ICH) guideline E2F (dated September 2011). The DSUR proposed in this guideline is intended to be a common standard for periodic reporting on drugs under development (including marketed drugs that are under further study) among the ICH regions. United States (US) and European Union (EU) regulators consider that the DSUR, submitted annually, would meet national and regional requirements currently met by the US Investigational New Drug (IND) Annual Report and the EU Annual Safety Report, respectively, and can therefore take the place of these existing reports.

The DSUR is intended to serve as an annual report to regulatory authorities. Where national or regional laws or regulations require submission of an annual safety report on an investigational drug to ethics committees/institutional review boards, the DSUR Executive Summary might be appropriate, supplemented with line listings of serious adverse reactions (SARs) as warranted.

Note: Serious adverse reaction," "serious adverse event" and "adverse drug reaction" are defined in ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting. October 1994[2].

The DSUR should provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period including:

- Clinical trials using an investigational drug (i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials [Phase I – III]);
- Clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase IV));
- Therapeutic use of an investigational drug (e.g., expanded access programs, compassionate use programs, patient use, single patient INDs, and treatment INDs); and
- Clinical trials conducted to support changes in the manufacturing process of medicinal products.

The DSUR should also include significant other findings pertinent to the safety of the investigational drug, including findings from:

- Observational or epidemiological studies;
- Non-clinical studies (toxicological and in vitro studies);
- Related DSURs, if applicable to the investigational drug;
- Manufacturing or microbiological changes;
- Studies recently published in the literature;
- Clinical trials with results indicating lack of efficacy that could have a direct impact on subject safety (e.g., worsening of the underlying condition if the indication is serious or life-threatening);
- Any other source of relevant safety findings for products in the same therapeutic class;
- Clinical trials conducted by a co-development partner, if permitted by the contractual agreement

[2] http://www.ich.org/LOB/media/MEDIA436.pdf

3.1.2 General Principles for DSURs:

a). A sponsor should prepare a single DSUR with data pertinent to all dosage forms and strengths, all indications, and all patient populations under study with the investigational drug, wherever feasible. If this is not possible (e.g., when the data are not available to the sponsor), an explanation should be provided in the introduction section of the DSUR. If more than one sponsor is involved in drug development, particularly in a co-development or other contractual agreement, a single DSUR can be submitted.

b). The "Development International Birth Date" * (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.

Where clinical trials are ongoing in one country and are later initiated in another country, the original DIBD should be maintained and used for all countries in preparing the DSUR.

The data lock point (DLP) of the DSUR should be the last day of the one-year reporting period.

When clinical development of a drug continues following a marketing approval in any country worldwide, both a PSUR and a DSUR should be submitted as specified by national or regional laws or regulations. If desired by the sponsor, a DSUR can be prepared based on the PSUR International Birth Date (IBD) so that the DSUR and the PSUR can be synchronized. In synchronizing the DLPs for the DSUR and PSUR, the period covered by the next DSUR should be no longer than one year.

c). The DSUR should be submitted to all concerned regulatory authorities no later than 60 calendar days after the DSUR DLP.

d). Till when a sponsor should submit a DSUR: DSURs should continue to be submitted for as long as indicated by national or regional laws or regulations.8 When submission of an annual report is no longer required in an individual country or region, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug in that country or region. The sponsor should also indicate whether clinical trials are continuing elsewhere.

e). Reference Safety Information for a DSUR: The Investigator's Brochure (IB) in effect at the start of the reporting period should serve as the reference safety information to determine whether the information received during the reporting period remains consistent with previous knowledge of the safety profile of the investigational drug.

3.1.3 Format and Presentation of a DSUR:

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

A). Title page

The title page of the DSUR should include the following information: DSUR report number; Investigational drug(s); Reporting period covered by the DSUR; Date of the report; Sponsor(s) name(s) and address(es); Statement on the confidentiality of the information included in the DSUR; A cautionary statement that the DSUR includes unblinded information, if applicable.

B). Executive Summary

This section should provide a concise summary of the important information contained in the report. Together with the title page, it can serve as a "stand-alone" document suitable for submission to ethics committees and other stakeholders, if required by national or regional laws or regulations.

C). Table of Contents

1. Introduction

This section should include information regarding DIBD or IBD (as applicable); reporting period and sequential number of the report; information regarding mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, and formulation(s) of the investigational drug; a brief description of the indication(s) and population(s) being studied; a short summary of the scope of the clinical trials covered by the report (e.g., all trials with the investigational drug, indication-specific trials, trials with combination products); a brief description and explanation of any information that has not been included in the DSUR (e.g., when written agreements with a partner company do not provide for exchange of all safety data).

2. Worldwide Marketing Approval Status

This section should provide a brief overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable.

3. Actions Taken in the Reporting Period for Safety Reasons

This section should include a description of significant actions related to safety that have been taken during the reporting period by the sponsor, regulators, data monitoring committees (DMC) or ethics committees that had an impact on the conduct of a specific clinical trial(s) or on the overall clinical development program. The reason(s) for each action should be provided if known.

4. Changes to Reference Safety Information

This section should summarize any significant safety-related changes to the IB or other reference safety information (RSI) within the reporting period. Such changes might include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest (AESI), interactions, and any important findings from non-clinical studies (e.g., carcinogenicity studies). Specific information relevant to these changes should be provided in the appropriate sections of the DSUR.

5. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

This section should provide a brief overview of the clinical trials ongoing and completed by the sponsor in the reporting period, with detailed information presented in a table as an appendix.

6. Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Programme

6.2 Patient Exposure from Marketing Experience

Sections 6.1 and 6.2 of the DSUR should provide information on cumulative exposure in clinical trials and the marketed setting, respectively.

An estimation of cumulative subject exposure can help provide context for the cumulative summary tabulations of serious adverse events (SAEs), and the overall assessment of safety.

7. Data in Line Listings and Summary Tabulations

7.1 Reference Information

7.2 Line Listings of Serious Adverse Reactions during the Reporting Period

7.3 Cumulative Summary Tabulations of Serious Adverse Events

Sections 7.1-7.3 of the DSUR should present important clinical safety information through:

- Interval line listings of the SARs that were reported to the sponsor during the period covered by the DSUR; and
- Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.

Therefore, the summary tabulations in a DSUR should include all SAEs and not just SARs for the investigational drug and comparators.

The line listings and tabulations should include blinded and unblinded clinical trial data.

Unblinded data might originate from completed trials and individual cases that have been unblinded for safety-related reasons (e.g., expedited reporting), if applicable. Sponsors should not unblind data for the specific purpose of preparing the DSUR.

At the sponsor's discretion, graphical displays can be used to illustrate specific aspects of the data when useful to enhance understanding.

If the Medical Dictionary for Regulatory Activities (MedDRA) terminology is used for coding the adverse event/reaction terms, the Preferred Term level should be presented in the line listings and summary tabulations.

In general, the tabulation(s) of SAEs should include only those terms that were used in defining the case as serious; they should not include non-serious events. Certain adverse events can be excluded from the line listings and 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, and those that are integral to efficacy 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).

8. Significant Findings from Clinical Trials during the Reporting Period

8.1 Completed Clinical Trials

8.2 Ongoing Clinical Trials

8.3 Long-term Follow-up

8.4 Other Therapeutic Use of Investigational Drug

8.5 New Safety Data Related to Combination Therapies

This section of the DSUR should provide a summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed section 8.1)/ongoing (section 8.2) during the reporting period. This information can be presented in narrative format or as a synopsis.

In section 8.3, information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g., gene therapy, cell therapy products and tissue engineered products) should be summarized. When the development program is completed, and long-term follow-up is the only ongoing activity generating data for the DSUR, this could be the only section where new information is presented.

In section 8.4 of the DSUR, clinically important safety information from other programs conducted by the sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (e.g., expanded access program, compassionate use program, patient use, single patient INDs and treatment INDs) should be provided.

In section 8.5 of the DSUR, important safety findings from the combination therapy DSUR (if investigational drug is under development as a combination of fixed dose combination) should be summarized.

Conversely, if this DSUR is for a multi-drug therapy or fixed combination product, this section should summarize important safety information arising from trials on the individual components.

9. Safety Findings from Non-Interventional Studies

This section should summarize relevant safety information from non-interventional studies that became available to the sponsor during the reporting period (e.g., observational studies, epidemiological studies, registries* and active surveillance programs).

10. Other Clinical Trial/Study Safety Information

This section should summarize relevant safety information from any other clinical trial/study sources that became available to the sponsor during the reporting period (e.g., results from pooled analyses or meta-analyses of randomized clinical trials, safety information provided by co-development partners or from investigator-initiated trials).

11. Safety Findings from Marketing Experience

If the investigational drug has been approved for marketing in any country, this section should include a concise summary of key safety findings that have arisen from marketing experience during the reporting period, particularly if the findings resulted in changes to the product labelling, IB, informed consent document or amendments to the product's risk management plan.

This section should also include safety findings relating from off-label use, administration to special populations (e.g., pregnant women), medication errors, overdose and abuse.

12. Non-clinical Data

This section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immune-toxicity studies) ongoing or completed during the reporting period.

13. Literature

This section should summarise new and significant safety findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug that the sponsor became aware of during the reporting period. This section should include information from non-clinical and clinical studies and, if relevant and applicable, information on drugs of the same class.

14. Other DSURs

- A sponsor should prepare a single DSUR for a single investigational drug.

- However, if a sponsor prepares multiple DSURs for a single investigational drug (e.g., covering different indications, development programmes, or formulations), this section should summarise significant findings from the other DSURs if they are not presented elsewhere within this report.
- When available, the sponsor should summarise significant findings from DSURs provided by other sponsors conducting clinical trials with the same investigational drug during the reporting period.

15. Lack of Efficacy

This section included data indicating lack of efficacy, or lack of efficacy relative to established therapy (ies), for Investigational drugs intended to treat serious or life-threatening illnesses.

16. Region-Specific Information

- The information in this section can be used to comply with national or regional requirements and can be provided in appendices to the DSUR.
- Sponsors should refer to national or regional requirements to determine which of the following sections should be included, as well as the scope of clinical trials that should be covered by these sections.

Examples include:

- Cumulative summary tabulation of serious adverse reactions
- List of subjects who died during the reporting period
- List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period
- Significant Phase I protocol modifications
- Significant manufacturing changes
- Description of the general investigation plan for the coming year

17. Late-Breaking Information

This section should summarise information on potentially important safety findings that arise after the DLP but while the DSUR is in preparation.

18. Overall Safety Assessment

The overall safety assessment should be a concise, integrated evaluation of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug.

This assessment should consider cumulative experience, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant post-marketing data.

It should not summarise or repeat information presented in previous sections of the DSUR; but provide an interpretation of the information and its implications for the clinical trial population and the development programme.

18.1. Evaluation of the Risks

This section includes:

- Newly identified safety issues (detailed description of adverse events or reactions; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions);
- Meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);
- Symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities;
- Deaths that are an outcome of an adverse event
- Study drug discontinuations because of adverse events;
- Drug–drug and other interactions;
- Important non-clinical safety findings;
- Manufacturing issues that could affect risk;
- LOE where this would place trial participants at risk;
- Any specific safety issues related to special populations;
- Pregnancy and lactation exposure and outcomes;
- Safety findings arising from experience with long-term treatment;

- Evidence of clinically significant medication errors/ lack of patient compliance/experience with overdose and its treatment;
- Drug misuse and abuse;
- Any safety issues resulting from procedures required by the protocol or associated with the conduct or design of a study (e.g., inadequate subject monitoring schedule, excessive period without active treatment); and
- Potential impact of significant new safety issues identified with another drug in the same class

18.2 Benefit-risk Considerations

This section should provide:

- A succinct statement on the perceived balance between risks that have been identified from cumulative safety data and anticipated efficacy/benefits
- Whether there have been any changes in this balance since the previous DSUR. This section is not intended to be a full benefit-risk assessment of the investigational drug.

19. Summary of Important Risks

- This section should provide a concise, cumulative, list of important identified and potential risks.
- Each risk should be re-evaluated annually and re-summarised as appropriate, based on the current state of knowledge. New information should be highlighted.
- The appropriate level of detail is likely to be dependent on the stage of drug development. For example, summaries covering drugs in early development might include information on individual cases, whereas in later development, as more knowledge and perspective are gained, the information on each risk might be less detailed.
- Risks that have been fully addressed or resolved should remain in the summary and be briefly described, e.g., findings from toxicology studies or early clinical trials that were not borne out by later clinical data.
- The information can be provided in either narrative or tabular format.

20. Conclusions Appendices to the DSUR

- The conclusion should briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR.
- The conclusion should outline actions that have been or will be taken to address emerging safety issues in the clinical development programme.

Appendices to DSUR

a) Investigator's Brochure (if required by national or regional laws or requirements);
b) Cumulative Table of Important Regulatory Requests;
c) Status of Ongoing and Completed Clinical Trials;
d) Cumulative Summary Tabulations of Demographic Data;
e) Line Listings of Serious Adverse Reactions;
f) Cumulative Summary Tabulation of Serious Adverse Events;
g) Scientific abstracts (if relevant).
h) Regional Appendices

3.2 Comparison of DSUR, EU Annual safety report, US IND annual report

Report Type	DSUR	IND AR	ASR
Scope	Molecule	Indication (IND)	Molecule
Time Period Covered	Cumulatively (mostly)	Annual (mostly)	Annual
Data Lock Point	DIBD (or IBD)	IND anniversary date	DIBD (or IBD)
AE Summaries	Serious	Serious and non-serious	Serious
Serious AE Listings	Yes	Yes	Yes
Death Listings	Yes	Yes	No
AE Dropout Listings	Yes	Yes	No
PK-PD, Manufacturing, Microbiology, Investigation Plan, Phase I Protocol Changes	No	Yes	No
Investigator Brochure	No	Yes	Yes
Non-Clinical Results	Yes	Yes	Yes
Literature, Marketing Developments	Yes	Yes	No
Summary of Important Risks	Yes	No	Yes
Regulatory Limitations	Yes	No	No
Specifications	ICH E2F	21 CFR 312.33	EU Directive 2001/20/EC, ENTR/CT3

3.3 PBRERs and PSURs

Periodic Benefit Risk Evaluation Report (PBRER) and Periodic Safety Update Reports (PSUR)

The PBRER provides an update of the worldwide safety experience and an evaluation of the benefit-risk of a medicinal product to regulatory authorities at defined time points post authorization.

3.3.1 Introduction to PBRER and PSUR

Objectives of a PBRER:

A comprehensive and critical analysis of the Benefit-risk (BR) balance of the medicinal product

- New or emerging information (safety, efficacy and effectiveness)
- In context of cumulative information
- The PBRER is therefore a tool for post-authorization evaluation of benefit-risk at defined time points in the lifecycle of the product

Within the EU, the name PSUR is the legal name and therefore PSUR and PBRER are synonymous.

Regulations:

A detailed description of specific PBRER regulatory requirements and guidance is available in:

- **International Conference on Harmonization (ICH) E2C(R2) Guideline – Periodic Benefit-Risk Evaluation Report (PBRER)**
- **Guideline on Good Pharmacovigilance Practices (GVP) Module VII – Periodic Safety Update Report**

Legislation:

The requirements for PSURs have been significantly amended i.e.

- For many generic and traditional herbal medicinal products, PSURs will no longer be required. However, competent authorities can request PSURs for these products on the basis of pharmacovigilance concerns.
- MAHs shall submit to EMA (after the repository has been established) PSURs containing:

Summaries of data relevant to the benefits and risks of the product (line listings will no longer be routinely required).

3.3.2 PBRER versus PSUR

	PSUR	PBRER
Guidelines	ICH E2C R1	ICH E2C R2 and GVP Module VII
Focused on	Safety of drugs	Benefit Risk Evaluation
Analysis of	Interval data	Interval and cumulative data
Sections	10	19
Modular Approach	No	Yes
	Clinical trial SARs	Clinical trial SAEs
Detailed assessment of ICSRs	Yes	No [Concise, scientific summary only (only index/noteworthy cases to present)]
Signal table	No	Yes
Time lines for submission	DLP + 60 days	DLP + 70 days (if PBRER covers ≤ 12 months period) or DLP + 90 days (if PBRER covers > 12 months period)

3.3.3 Key Considerations for the PBRER

Main Objectives of a PBRER:

- Present a comprehensive, concise and critical analysis of the risk-benefit balance of the medicinal product
- Consider new or emerging information in the context of cumulative information on risks and benefits
- A tool for post-authorization evaluation at defined time points in the lifecycle of a product
- Should *not be used to provide initial notification of* significant new safety information or, as a rule, provide the means by which new safety issues are detected, or new efficacy data are submitted

General Principles for preparing a PBRER:

- A single PSUR for all medicinal products containing the same active substance with information covering all the authorized indications, route of administration, dosage forms and dosing regiments, irrespective of whether authorized under different names and through separate procedures.
- Where relevant, data relating to a indication, dosage form, route of administration or dosing regimen, presented in a separate section of the PSUR and any safety concerns addressed accordingly
- Exception – separate PSURs in the event of different formulations for entirely different indications – in agreement with authorities

European Union Reference date (EURD) List:

- EMA published EURD list (frequency of PSUR submission)
- A comprehensive list of active substances/combinations with corresponding Union reference dates, frequencies for submission of PSURs and related DLPs
    - EURD corresponds to the date of 1st MA in EU (or earliest known date of MA)
    - PSUR frequency for active substance take effect 6 months after EURD list published
- Amendments to EURD list can be requested by the MAH for following reasons:
    - public health
    - to avoid a duplication of the assessment
    - to achieve international harmonization
- Active substance
- EU reference dates
- Frequencies of submission of PSURs
- Data lock points of the next submissions of PSURs
- Date of publication on the European Medicines web-portal) of the frequency for PSUR submission and data lock point for each active substance and combination of active substances.
- Changes to dates & frequency of PSURs will take place 6 months after publication

- Changes to EURD list are approved by CHMP (Committee for Medicinal Products for Human Use) and CMD-h (Co-ordination group for Mutual recognition and Decentralised procedures – human) following consultation with PRAC and changes take effect 6 months after publication amended list

3.3.4 Format and Content of a PBRER

PBRER/PSUR has three parts:

- Part I: Title page
- Part II: Executive summary
- Part III: Table of contents (core report)

Part I: Title page should include name of medicinal product/substance, IBD, reporting period covered by PBRER, MAH details, statement of confidentiality and signature (For PSURs submission in the EU, it is at the discretion of the Qualified Person for Pharmacovigilance (QPPV) to determine the most appropriate person to sign the document according to the MAH structure and responsibilities), a statement confirming the designation by the QPPV should be included.

Part II: Executive Summary

Executive summary is a brief overview providing the most important safety information covering:

- Short description of product
- Worldwide marketing authorization status
- Other relevant regulatory information related to the period covered by the PSUR (e.g. any urgent safety restriction should be highlighted)
- Patient exposure data
- Number of case reports received and the cumulative numbers
- Safety concerns observed
- Overall findings
- Conclusion

Sections of a PBRER:

1. Introduction: In this section, following information should be summarized:

- Brief introduction about product
    - Product name & class
    - Indication
    - Contraindications
    - Use in special populations
    - Use during pregnancy & lactation
    - Main adverse events
    - Dependency risk if applicable

State the possibility of data duplication with PSURs of other marketing authorization holders (MAHs).

2. Worldwide marketing approval status

This Section contain a brief narrative overview including: date of first authorization worldwide, indication (s), authorization dose (s) and where authorized.

3. Actions taken in the reporting interval for safety reasons

This section should include a description of significant actions related to safety that have been taken worldwide during the reporting interval, related to either investigational uses or marketing experience by the MAH, sponsors of clinical trial(s), data monitoring committees, ethics committees or competent authorities that had either:

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

4. Changes to reference safety information

- This section includes any significant changes made to the reference safety information within the reporting interval. Such changes might include information relating to contraindications, warnings, precautions, serious adverse drug reactions, interactions, important findings from ongoing or completed clinical trials and significant non-clinical findings (e.g. carcinogenicity studies).

- Which RSI has been used for listed-ness assessment in the PSUR?
- Summarize changes made to this RSI during the review period of PBRER/PSUR.

5. Estimated exposure and use patterns

5.1. Cumulative subject exposure in clinical trials

5.2. Cumulative and interval patient exposure from marketing experience

This section provides number of patients exposed to medicinal product in clinical trials (section 5a) and number of patients exposed in post-marketing period (cumulative and interval period: section 5.2).

6. Data in summary tabulations

- The objective of this section is to present safety data through summary tabulations of serious adverse events from clinical trials (section 6.2), spontaneous serious and non-serious reactions from marketing experience and serious reactions from non-interventional studies and other non-interventional solicited source (section 6.3).
- MedDRA terminology is used for coding the adverse event/reaction terms (the PT and SOC) to present in the summary tabulations.
- The seriousness of the adverse events/reactions in the summary tabulations should correspond to the seriousness assigned to events/reactions included in the ICSRs using the criteria established in ICH-E2A.

6.1. Reference information

This sub-section of the PSUR should specify the version(s) of the coding dictionary used for presentation of adverse events/reactions (i.e. MedDRA version)

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

- A summary tabulation of serious adverse events reported in the marketing authorisation holder's clinical trials, from the DIBD to the data lock point of the current PSUR.
- This sub-section should not serve to provide analyses or conclusions based on the serious adverse events.

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

- Cumulative (from the IBD to the DLP of and interval (reporting period) summary tabulations of adverse drug reactions from post-marketing sources are provided in Appendix 2b.
- Including post-authorization safety studies, and reports from other solicited sources.

- Analysis or conclusions based on the summary tabulations should not be provided in this PSUR sub- section.

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

This section provides a summary of the clinically important efficacy and safety findings during the reporting interval. Section 7 deals with interventional studies.

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

The MAH should include an appendix listing (appendix 4a) of the MAH sponsored interventional trials with the primary aim of identifying, characterizing, or quantifying a safety hazard or confirming the safety profile of the medicinal product that were completed or ongoing during the reporting interval.

7.1. Completed clinical trials

This section provides a summary of clinically important emerging safety findings obtained from clinical trials completed during the reporting interval.

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 a result of unblinding of subjects with adverse events), this section should briefly summarize the concern(s).

7.3. Long-term follow-up

This section provides 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 PBRER should include clinically important safety information from other programs conducted by the MAH that follow a specific protocol, with solicited reporting as per ICH Guideline E2D (e.g., expanded access programs, compassionate use programs, patient use, single-patient Investigational New Drug applications [INDs], treatment INDs, and other organized data collection).

7.5. New safety data related to fixed combination therapies

This section is applicable if medicinal product is a fixed dose combination.

8. Findings from non-interventional studies

This section should also summarize relevant safety information or information with potential impact in the benefit-risk assessment from marketing authorization holder-sponsored non-interventional studies that became available during the reporting interval

9. Information from other clinical trials and sources

9.1 Other clinical trials

This section should summarize information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources, including patient support programs, which are accessible by the marketing authorization holder during the reporting interval

9.2 Medication errors

10. Non-clinical data

This section should summarize major safety findings from non-clinical *in vivo* and *in vitro* studies ongoing or completed during the reporting interval

This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorization holder became aware of during the reporting interval, when relevant to the medicinal product

11. Literature

This PSUR section should include a summary of new and significant safety findings, either published in the peer-reviewed scientific literature or made available as unpublished manuscripts that the marketing authorization holder became aware of during the reporting interval, when relevant to the medicinal product.

12. Other periodic reports

This section will only apply in certain circumstances concerning fixed combination products or products with multiple indications and/or formulations where multiple PSURs are prepared in agreement with the competent authority.

13. Lack of efficacy in controlled clinical trials

This section should highlight results of clinical trials indicating lack of efficacy that could have a direct impact on subject safety (e.g., worsening of the underlying condition if the indication is serious or life-threatening).

14. Late-breaking information

The MAH should summarize the potentially important safety, efficacy and effectiveness findings that arise after the data lock point but during the period of preparation of the PSUR. Examples include clinically significant new publications, important follow-up data, clinically relevant toxicological findings etc.

15. Overview of signals: new, ongoing or closed

This section provides an overview of signals detected, under review, and evaluated during the reporting interval. The scope includes signals detected from any source (for example from spontaneous reports, published literature, clinical trials, epidemiological study findings) using quantitative and/or qualitative methods.

- A newly identified signal refers to a signal that has been identified during the reporting interval.
- An ongoing signal refers to a signal that was still under evaluation at the data lock point.
- A closed signal refers to a signal for which an evaluation was completed during the reporting interval.

16. Signal and risk evaluation

This section comprises of five sub-sections.

16.1. Summary of safety concerns

The purpose of this sub-section is to provide a summary of important safety concerns at the beginning of the reporting interval, against which new information and evaluations can be made

16.2. Signal evaluation

This sub-section of the PSUR should summarize the results of evaluations of all safety signals that were closed during the reporting interval

16.3. Evaluation of risks and new information

This sub-section should provide a critical appraisal of new information relevant to previously recognized potential and identified risks, together with an update on important missing information.

16.4. Characterization of risks

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

16.5. Effectiveness of risk minimization (if applicable)

Risk minimization activities are public health interventions intended to prevent the occurrence of an adverse drug reaction(s) associated with the exposure to a medicinal product or to reduce its severity should it occur

In this risk, information regarding effectiveness of risk minimization activities should be summarized (if applicable).

17. Benefit evaluation

17.1. Important baseline efficacy/effectiveness information

This sub-section of the PSUR summarizes information on both efficacy and effectiveness of the medicinal product at the beginning of the reporting interval

17.2. Newly identified information on efficacy/effectiveness

For some products, additional information on efficacy or effectiveness in authorized indications may have become available during the reporting interval. Such information should be presented in this sub-section.

17.3. Characterization of benefits

This sub-section provides an integration of the baseline benefit information and the new benefit information that has become available during the reporting interval, for authorized indications.

18. Integrated benefit-risk analysis for approved Indications

The MAH should provide in this PSUR section an overall appraisal of the benefit and risk of the medicinal product as used in clinical practice. This section should provide an analysis and integration of the information in the previous sections with respect to benefit and risk

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

This sub-section of the PSUR should provide a brief description of the medical need for the medicinal product in the authorized indications and summarized alternatives (medical, surgical or other; including no treatment)

18.2. Benefit-risk analysis evaluation

- A benefit-risk profile is generally specific to an indication and population. Therefore, for products authorized for more than one indication, benefit-risk profile should usually be evaluated and presented by each indication individually
- There may be some circumstances for products authorized for multiple indications (e.g. antibiotics) where it would be appropriate to assess the benefit-risk profile across

more than one indication or population. If there are important differences in the benefit-risk profile among populations within an indication, the benefit-risk evaluation should be presented by population, if possible.

19. Conclusions and actions

- A PSUR/PBRER should conclude with the implications of any new information that arose during the reporting interval in terms of the overall evaluation of benefit-risk for each authorized indication, as well as for relevant subgroups, if appropriate
- The conclusions should include preliminary proposal(s) to optimize or further evaluate the risk-benefit balance

A PBRER/ PSUR should contain the following appendices as appropriate, numbered as follows:

1. Reference information (CCDS)

2. Cumulative summary tabulations of serious adverse events from clinical trials (2a); and cumulative and interval summary tabulations of serious and non-serious adverse reactions from post-marketing data sources (2b).

3. Tabular summary/overview of safety signals (if not included in the body of the report)

4. Listing of all the marketing authorisation holder-sponsored interventional and non-interventional studies with the primary aim of identifying, characterising, or quantifying a safety hazard or confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures, in case of non-interventional studies.

5. List of the sources of information used to prepare the PSUR (when desired by the marketing authorisation holder):

5a: list of PBRERs/PSUR since IBD

5b: List of countries with marketing authorization status

6. Regional appendix

3.4 Periodic Adverse Drug Experience Report (PADER)/ Periodic Adverse Experience Report (PAER):

As per the US FDA guidelines regarding post-marketing reporting of adverse drug experience (Sec. 314.80 under CFR 21, dated April 2015), following are the requirements:

Periodic adverse drug experience reports.

It is the responsibility of the applicant to report each adverse drug experience not reported as a 15-day "Alert reports" at quarterly intervals, for 3 years from the date of approval of the application, and then at annual intervals.

The applicant is required to submit each quarterly report within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and each annual report within 60 days of the anniversary date of approval of the application. Upon written notice, FDA may extend or re-establish the requirement that an applicant submit quarterly reports or require that the applicant submit reports under this section at different times than those stated. For example, the agency may re-establish a quarterly reporting requirement following the approval of a major supplement. Follow-up information to adverse drug experiences submitted in a periodic report may be submitted in the next periodic report.

Each periodic report is required to contain:

(A) ***Descriptive information.***

(*1*) A narrative summary and analysis of the information in the report;

(*2*) An analysis of the 15-day Alert reports submitted during the reporting interval (all 15-day Alert reports being appropriately referenced by the applicant's patient identification code, adverse reaction term(s), and date of submission to FDA);

(*3*) A history of actions taken since the last report because of adverse drug experiences (for example, labeling changes or studies initiated); and

(*4*) An index consisting of a line listing of the applicant's patient identification code, and adverse reaction term(s) for all ICSRs.

(B) ***ICSRs for serious, expected, and non-serious adverse drug experiences.***

An ICSR for each adverse drug experience not reported (all serious, expected and non-serious adverse drug experiences).

(C) ***Information reported on ICSRs.***

ICSRs data should include the following information:

(1) ***Patient information.***

(i) Patient identification code;

(ii) Patient age at the time of adverse drug experience, or date of birth;

(iii) Patient gender; and

(iv) Patient weight.

(2) ***Adverse drug experience.***

(i) Outcome attributed to adverse drug experience;

(ii) Date of adverse drug experience;

(iii) Date of ICSR submission;

(iv) Description of adverse drug experience (including a concise medical narrative);

(v) Adverse drug experience term(s);

(vi) Description of relevant tests, including dates and laboratory data; and

(vii) Other relevant patient history, including pre-existing medical conditions.

(3) ***Suspect medical product(s).***

(i) Name;

(ii) Dose, frequency, and route of administration used;

(iii) Therapy dates;

(iv) Diagnosis for use (indication);

(v) Whether the product is a prescription or non-prescription product;

(vi) Whether the product is a combination product as defined in 3.2(e) of this chapter;

(vii) Whether adverse drug experience abated after drug use stopped or dose reduced;

(viii) Whether adverse drug experience reappeared after reintroduction of drug;

(ix) Lot number;

(x) Expiration date;

(xi) National Drug Code (NDC) number; and

(xii) Concomitant medical products and therapy dates.

(4) ***Initial reporter information.***

(i) Name, address, and telephone number;

(ii) Whether the initial reporter is a health care professional; and

(iii) Occupation, if a health care professional.

(5) ***Applicant information.***

(i) Applicant name and contact office address;

(ii) Telephone number;

(iii) Report source, such as spontaneous, literature, or study;

(iv) Date the report was received by applicant;

(v) Application number and type;

(vi) Whether the ICSR is a 15-day "Alert report";

(vii) Whether the ICSR is an initial report or follow up report; and

(viii) Unique case identification number, which must be the same in the initial report and any subsequent follow up report(s).

Electronic format for submissions.

(1) Safety report submissions, including ICSRs, ICSR attachments, and the descriptive information in periodic reports, must be in an electronic format that FDA can process, review, and archive. FDA will issue guidance on how to provide the electronic submission (e.g., method of transmission, media, file formats, preparation and organization of files).

(2) An applicant or nonapplicant may request, in writing, a temporary waiver of the requirements in paragraph (g)(1) of this section. These waivers will be granted on a limited basis for good cause shown. FDA will issue guidance on requesting a waiver of the requirements in paragraph (g)(1) of this section.

Multiple reports.

An applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved.

If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

(i) ***Patient privacy****.* An applicant should not include in reports under this section the names and addresses of individual patients; instead, the applicant should assign a unique code for identification of the patient. The applicant should include the name of the reporter from whom the information was received as part of the initial reporter information, even when the reporter is the patient. The names of patients, health care professionals, hospitals, and geographical identifiers in adverse drug experience reports are not releasable to the public under FDA's public information regulations in part 20 of this chapter.

(j) ***Recordkeeping****.* The applicant must maintain for a period of 10 years records of all adverse drug experiences known to the applicant, including raw data and any correspondence relating to adverse drug experiences.

(k) ***Withdrawal of approval****.* If an applicant fails to establish and maintain records and make reports required under this section, FDA may withdraw approval of the application and, thus, prohibit continued marketing of the drug product that is the subject of the application.

4. Authoring of Aggregate Reports

A generic process of authoring of a periodic safety reports is presented below:

	Period	Activity
Pre-DLP	DLP – 8 to 10 weeks	Kick –off meeting between various stakeholders to plan regarding preparation of the PSUR/PBRER
	DLP – 7 to 8 weeks	Follow-up meeting to retrieve the data from various stakeholders and to request information pertaining to ongoing clinical studies, MAH regulatory updates (RSI/RMP update in current review period, health authority (HA) assessment reports/ HA request) and sales units.
DLP	DLP + 0 day	Generate line listings/ CIOMS forms from safety database, retrieve other sources of data (literature, pre-clinical, clinical trials, epidemiology)
Post-DLP	DLP + 0 day to DLP +69/89 days	Report writing, quality review (both medical and technical), QPPV signature, publishing of the report
	DLP +70/90 days	Submission to concerned regulatory authorities

5. Sources for Aggregate Safety Reports

Safety data is generally received from a variety of sources and depending on the aggregate safety report, the information is determined by guidelines on each aggregate safety report. The sources included are:

- Clinical Studies
- Spontaneous notifications from Health Care Professionals (HCP's) and non-HCP's
- Literature
- ADR reporting systems of a Regulatory Health Authority
- Other sources of safety data are:
    - ADRs exchanged between business partners (e.g., licensors, licensees),
    - Special registries (e.g., pregnancy, HIV, organ toxicity monitoring centers),
    - Poison control centers and epidemiologic databases