Module 7: Aggregate Safety Reports

What is Aggregate Reporting?

- 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 in order to provide up-to-date information the patient, health care professionals (HCPs), and the health authorities worldwide
- To comply with the regulatory guidelines

Sources for Aggregate Reporting

- 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
- 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:
    - 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

Type of Aggregate Safety Reports (ASRs)

Pre-marketing ASR

- Development safety update report (DSUR) – currently meets
- The U.S. investigational new drug application (IND) annual report DSUR is accepted by the Food and Drug Administration (FDA) in place of the INDA annual report
- The EU annual safety report (ASR), respectively

Post-marketing ASRs

- Development Safety Update Report (DSUR) – also includes studies conducted after product is approved
- Periodic Adverse Drug Experiences Reports (PADER) - USA
- Periodic Safety Update Report (PSUR) – Global document

Development safety update report (DSUR)

Pre approval Periodic Safety Reports

- US IND Annual Report (US IND AR)
  - 21 CFR 312.33
- EU Annual Safety Report (EU ASR)
  - Directive 2001/20/EC and ENTR/CT3
- Japan - Japan Investigational Product Serious / Infection Case Periodical Report' – 6 monthly [PFSB 0229011 Feb 08 and 1001005 Oct 08]
  - In December 2012, the PMDA* implemented a new annual safety reporting guideline. Currently, there is a transition period from 6 monthly safety reporting to annual reporting.

DSUR

- A DSUR is similar to the US's IND-AR and the EU's ASR in that its purpose is to provide a brief overview of safety for a project on an annual basis so health authorities can better make decisions to protect the safety of patients.

Objective of the DSUR

The DSUR presents an annual review & evaluation of safety information:

- Reported during the current review period and analysis based on previous knowledge of the product's safety;
- Description of new safety issues that may impact the overall program or specific clinical trials;
- Summarization of current understanding and management of known and potential safety risks to exposed patients;
- Examine changes in the product's safety profile; and
- Provide an update on the status of the clinical development program.

Scope of the DSUR

- **A DSUR focuses on**:

✓ Interventional clinical trials of drugs,vaccines and biologics, whether or not they have a marketing approval

✓ Other findings that impact the safety and welfare of clinical trial subjects (e.g., non-clinical studies, observational studies)

- **A DSUR should**:

✓ focus on the investigational drug, providing information on comparators where relevant to the safety of trial participants;

✓ provide safety information from all ongoing clinical trials and other studies that the sponsor is conducting or has completed during the review period

Content of DSUR

Title Page

Executive Summary

Table of Contents

1. Introduction
2. Worldwide Marketing Approval Status
3. Actions Taken in the Reporting Period for Safety Reasons
4. Changes to Reference Safety Information
5. Inventory of Clinical Trials Ongoing and Completed During the Reporting Period
6. Estimated Cumulative Exposure
    - 6.1: Cumulative Subject Exposure in the Development Programme
    - 6.2: Patient Exposure from Marketing Experience

Content of DSUR

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
8. Significant Findings from Clinical Trials
    - 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
9. Safety Findings from Non-interventional Studies
10. Other Clinical Trial/Study Safety Information

Content of DSUR

11. Safety Findings from Marketing Experience
12. Non-clinical Data
13. Literature
14. Other DSURs
15. Lack of Efficacy
16. Region-Specific Information
17. Late-Breaking Information
18. Overall Safety Assessment
    - 18.1. Evaluation of the Risks
    - 18.2 Benefit-risk Considerations
19. Summary of Important Risks
20. Conclusions

Appendices to the DSUR

Periodic safety update report (PSUR)

History of PSUR - PBRER

- 1992 CIOMS II Guideline on PSURs published
- 1996 – ICH Guideline published: *Clinical Safety Data Management – PSURs for Marketed Drugs*
- 2003 – Addendum to ICH E2C (R1) published
- 2010 European Pharmacovigilance Legislation – *Regulation (EU) No 1235/2010 of the European Parliament and of the Council; Directive 2010/84/EU of the European Parliament and of the Council of 15 Dec 2010*
- 2012 June GVP Module VII
- 2012 – ICH E2C (R2) November; Published on ICH website December – *Periodic Benefit Risk Evaluation Report*
- 2013 Dec GVP Module VII R1

PSUR - PBRER Key Differences

PSUR (Vol. 9A, E2C R1)	PBRER (GVP VII, E2CR2)
• Focused on safety of drugs • Analysis of Interval data • 10 sections (non-modular) • No link to DSUR & RMP • Primarily safety data • Clinical trial SARs • Detailed assessment of ICSR • No signal tabulation • Submission timelines – 60 days post data lock	• Benefit-risk evaluation • Interval & cumulative data • 19 sections (modular) • Linked to DSUR & RMP • Also clinical, non clinical, epidemiology • Clinical trial SAEs (new) • Concise, scientific summary only (only index/note worthy case to present) • Signal tabulation – new, ongoing closed • 70/90 days post data lock in EU, 70 days in USA

PBRER: Main Objectives

- 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 general rule, provide the means by which new safety issues are detected, or new efficacy data are submitted

PBRER – Format & Content

- Modular structure
- No routine requirement for line listings
- Data presentation sections –exposure and analysis of use patterns, summary tabulations, CT findings, findings from non-interventional studies etc.
- Risk evaluation sections - including signals and effectiveness of risk minimisation
- Benefit evaluation sections
- Integrated benefit-risk analysis
- Information is similar to DSUR, layout may be different

Appendices

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

An Overview of PADERs

PADERs*/PAERs: Why needed?

- Most countries usually require the submission of Periodic Safety Reports for aggregate post marketing safety reporting.
- In addition to the 15-day alert reports, the US FDA requires the submission of New Drug Application (NDA), Abbreviated NDA, and Biologic License Application (BLA) periodic reports.
- The regulations covering this are found in 21CFR314.80(c)(2)(I,II).
- The NDA Periodic Reports, also called Periodic Adverse Drug Experience Reports (PADERs), are still required according to the regulations.
- The United State (US) Food and Drug Administration (FDA) accepts PSURs (PBRER format), though this must be agreed on with the agency in writing beforehand.

Section 4: FDA Form 3500As or VAERS Forms

- FDA Form 3500As or VAERS forms must be provided for the following spontaneously reported adverse experiences that occurred in the United States during the reporting period:
  - Serious and expected
  - Nonserious and unexpected
  - Nonserious and expected

- If no adverse experiences were identified for the human drug or biologic product for the time period involved and no regulatory actions concerning safety were taken anywhere in the world where the product is marketed,
  - The periodic report should simply state this and be submitted to the FDA along with a copy of the current U.S. labeling.

Other Reports

The FDA requires other reports for “NDA maintenance”:

- **Distribution reports (21CFR600.810):** This is a 6-month report requiring the submission of all information about the quantity of product distributed under licensing agreements. It does not touch drug safety.
- **Annual reports (21CFR314.81(b)(2)):** This is a yearly report requiring the submission of information from the previous year
  - That might affect safety, efficacy, or labeling as well as
  - Information on labelling changes, distribution, chemistry, manufacturing and controls changes, nonclinical laboratory studies, clinical trial data, and pediatric data.