Aggregate reporting- Periodic Safety Udate Report

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

Why?

- report all the relevant new safety information from appropriate sources;
- relate these data to patient exposure;
- summarise the market authorisation status in different countries and any significant variations related to safety;
- create periodically the opportunity for an overall safety re-evaluation;
- indicate whether changes should be made to product information in order to optimise the use of the product.

PSUR?

- Its a formal, structured update of the worldwide safety experience for a registered medicinal product (per ICH E2C standards), prepared for submission to regulatory authorities at defined times post-authorisation.

NDCTR 2019 says.....

- The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant.
- For subsequent two years – the PSURs need to be submitted annually.
- Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health.
- PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period.

ICH region says….

- The US regulations require quarterly reports during the first 3 years, then annual reports.
- In the EU, Council Directive 93/39/EEC and Council Regulation 2309/93 require reports with a periodicity of 6 months for two years, annually for the three following years and then every five years, at time of renewal of registration.
- In Japan, the authorities require a survey on a cohort of a few thousand patients established by a certain number of identified institutions during the 6 years following authorisation. Systematic information on this cohort, taking into account a precise denominator, must be reported annually.

Glossary Of Special Terms

- **Company Core Data Sheet (CCDS)** – A document prepared by the MAH containing, in addition to safety information, material relating to indications, dosing, pharmacology and other information concerning the product.
- **Company Core Safety Information (CCSI)** – All relevant safety information contained in the Company Core Data Sheet prepared by the MAH and which the MAH requires to be listed in all countries where the company markets the medicinal product, except when the local regulatory authority specifically requires a modification. It is the reference information by which **listed** and **unlisted** are determined for the purpose of periodic reporting for marketed products, but not by which expected and unexpected are determined for expedited reporting.

Glossary Of Special Terms

- **Data Lock-Point (Data Cut-off Date)** – The date designated as the cut-off date for data to be included in a PSUR. It is based on the International Birth Date (IBD) and should usually be in six-monthly increments.
- **International Birth Date (IBD)** – The date of the first marketing authorisation for a new medicinal product granted to any company in any country in the world.
- **Listed Adverse Drug Reaction** - An ADR whose nature, severity, specificity, and outcome are consistent with the information in the CCSI.
- **Spontaneous Report** or **Spontaneous Notification** – An unsolicited communication to a company, regulatory authority or other organisation that describes an adverse drug reaction in a patient given one or more medicinal products and which does not derive from a study or any organised data collection scheme

Model For A Periodic Safety Update Report

SAMPLE TITLE PAGE

PERIODIC SAFETY UPDATE REPORT FOR: *(PRODUCT)*

MAH's NAME AND ADDRESS *(Corporate headquarters or other company entity responsible for report preparation)*

PERIOD COVERED BY THIS REPORT: *(dates)*

INTERNATIONAL BIRTH DATE: Date *(Country of IBD)*

DATE OF REPORT

(Other identifying information at the option of MAH, such as report number)

Table of contents…

- Introduction
- Worldwide market authorisation status
- Update of regulatory authority or MAH actions taken for safety reasons
- Changes to reference safety information
- Patient exposure
- Presentation of individual case histories
- Studies
- Other information
- Overall safety evaluation
- Conclusion
- APPENDIX: COMPANY CORE DATA SHEET

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	• Benefit-risk evaluation
• Analysis of Interval data	• Interval & cumulative data
• 10 sections (non-modular)	• 19 sections (modular)
• No link to DSUR & RMP	• Linked to DSUR & RMP
• Primarily safety data	• Also clinical, non clinical, epidemiology
• Clinical trial SARs	• Clinical trial SAEs (new)
• Detailed assessment of ICSR	• Concise, scientific summary only (only index/note worthy case to present)
• No signal tabulation	• Signal tabulation – new, ongoing closed
• Submission timelines – 60 days post data lock	• 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

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.