Safety Writing –Aggregate reports, Package inserts

Aggregate study reports (ASR)

- DSUR
- RMP
- PSUR
- PBRER
- PADER
- SmPC

Aggregate Safety Reports

Aggregate Reports refers to those safety reports that focus not so much on individual cases, but rather on overview, assessment of the safety profile and benefit-risk-evaluation. They comprise e.g.

- Periodic Safety Update Reports (PSURs) / Periodic Benefit Risk Evaluation Reports (PBRERs),
- Periodic Adverse (Drug) Experience Reports (US),
- Development Safety Update Reports (DSURs),
- Integrated Summaries of Safety (US), or
- Clinical Summaries of Safety (EU)

These reports need special diligence and attention to detail on the one hand, overview and a sense of what is essential on the other hand.

Development Safety Update Report (DSUR)

- Objective of DSUR is to present a comprehensive, thoughtful annual review and evaluation of pertinent safety information related to a drug under investigation, whether or not it is marketed.
- DSUR provides safety information from all ongoing clinical trials or completed trails.
- DSUR provides safety information from all Clinical trials conducted using marketed drugs in approved indication which requires additional monitoring.
- Other therapeutic use of an investigational drug and comparability trials.
- The DSUR is always submitted on a yearly basis

What Is a Risk Management Plan (RMP)?

- A Risk Management Plan (RMP) is the document submitted as part of the Marketing Authorization Application that describes the activities and interventions designed to identify, characterize, prevent or minimize risks relating to a medicinal product, including the assessment of the effectiveness of those interventions and document post-authorization obligations that have been imposed as a condition of the marketing authorization updated throughout the lifetime of the medicine as new information becomes available.

What are the objectives of a Safety RMP?

The specific objectives of RMPs are three-fold:

- To specify what is and is not known about safety of a drug at the time of submission drug (Safety Specification)
- To further characterize the safety risks post authorization (Pharmacovigilance Plan)
- Where necessary, to define appropriate measures to minimize known risks to patients and to monitor the success of those measures (Risk Minimization Plan and Evaluation of Effectiveness)

Risk Evaluation and Mitigation Strategy (REMS)

- In the USA, a REMS will be required if the Food and Drug Administration (FDA) determines that a REMS is necessary to ensure the benefits of the drug or biological product outweigh its risks.
- A Risk Evaluation and Mitigation Strategy (REMS) is a strategy to manage a known or potential serious risk associated with a drug or biological product and can be comprised of: Medication Guide, Patient Package Insert, including a communication plan elements to assure safe use, and an implementation system.

WHAT IS A PERIODIC SAFETY REPORT (PSUR)

- Periodic safety update reports (PSURs) are 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.

OBJECTIVES OF THE PSUR

To contain an evaluation of new relevant information that became available to the MAH during the reporting interval, in the context of cumulative information:

1. Examine whether new information is in accord with previous knowledge of the benefit risk profile
2. Summarises relevant new safety information that may impact the benefit risk profile
3. Summarises any important new efficacy and effectiveness information
4. Conduct an integrated Benefit/Risk evaluation (where new important safety information has emerged)

PERIODICITY OF PSUR

PSUR must be prepared at the following intervals:

1. Immediately upon request
2. Every six months from authorisation until product placed on the market
3. Every six months for first two years on the market
4. Annually for the next two years
5. Thereafter every 3 years Exception – frequency and dates of submission are laid down as a condition of the MA or determined otherwise in the list of Union Reference Dates (EURD List).
6. Submit: • By day 70 for intervals up to 12 months • By day 90 for intervals in excess of 12 months

PSUR Vs PADER

- Approved worldwide.
- Adverse events occurring around the world .
- Overall safety evaluations with specific highlighting.
- Cumulative data is analyzed for assessing benefit risk balance.

- Approved by US FDA
- Adverse events occurring in the U.S. (especially 15 day report).
- Non-Serious Adverse Events can be exempted.
- Specific periodic data is analyzed for assessing benefit risk balance.

PADER-Periodic Adverse Drug Experience Report

Periodic Benefit Risk Evaluation Report (PBRER)

- Periodic Benefit Risk Evaluation Report (PBRER) is an analysis of the safety, efficacy, and efficiency of a drug, once it is already in the market.
- The PBRER submission is intended to present a periodic, comprehensive, brief and critical evaluation of new or emerging information on the risks of the health product and the product's overall benefit-risk profile.
- Compared to PSUR, a PBRER concentrates more on the risk benefit.
- A Market Authorization Holder (MAH) is required to make the PBRER submission:
  - every 6 months for the first 2 years after the product is marketed
  - once a year for the following 2 years

Prescribing Information

- Summary of Product Characteristics
- Prescribing Information
- Package insert
- Package leaflet

What is the summary of product characteristics (SmPC)?

- The SmPC is a legal document approved as part of the marketing authorisation of each medicine
- The SmPC is the basis of information for healthcare professional on how to use the medicine
- Its information is updated throughout the life-cycle of the product as new data emerge

Which information can be found in the SmPC?

- Essential information for the use of a medicine
- Qualitative and quantitative information on the benefits and the risks
- Information for individualised care
  - Paediatric and elderly population
  - Organ impairment, concomitant disease
  - Interaction with other medicines
  - Genomic factors
  - Pregnancy, lactation and fertility
  - Composition of the medicine: prevention of hypersensitivity and excipients with known effects
  - Information on specific situations
- Pharmaceutical information

What is not included in the SmPC?

- Detailed information on the scientific development which is available in the public assessment report
- Information in non-approved indication
  - Because the MAH has not claimed the indication
  - An indication has been claimed but data did not demonstrate a positive benefit risk of the medicine; withdrawal or refusal AR provide available data.
  - Exception in the paediatric group; the Paediatric Regulation aims to improve the information regarding this subgroup by providing all information on clinically relevant trials
- Specific issue for which data is lacking
- General advice on the treatment of particular medical conditions