Aggregate reporting

Aggregate reporting is the process that reviews the cumulative safety information from a wide range of sources, on a periodic basis and submits the findings to regulators worldwide

Introduction:

The periodical reporting of aggregate safety reports to regulatory health authorities includes comprehensive overview of the safety profile of the medicinal product based on cumulative safety information accumulated by Marketing Authorization Holder (MAH). They also provide assurance that the MAH is continuously monitoring and also critically assessing the benefit-risk profile of the product and taking appropriate risk minimizing actions where new safety concerns or changes to the existing safety issues are identified. The international standard for periodic reports follows reporting guidelines set by the International Conference on Harmonization (ICH).
In addition to the submission of Individual case safety reports (ICSRs), MAH is obliged to report the cumulative safety exposure data in periodical intervals to respective health authorities within specified timelines which in turn depends on age of the medicinal product in the market and type of aggregate report. This continued monitoring on aggregate safety data facilitates regulators and MAH to maintain positive benefit risk balance and implementing the early risk minimization plans for safety concerns reported.

Types of Aggregate reports:

Based on marketing authorisation status, different types of reports are prepared by MAH, which include the pre-approval aggregate safety reports and post-approval aggregate safety reports.

1. Pre-approval aggregate reports:
   It includes the cumulative summary of safety information for molecules under clinical development. It usually includes safety information from non-clinical studies and safety data for the subjects participated in clinical trial.
   A. Annual safety reports (ASRs) in Europe
   B. IND annual reports in United States

However, these two documents were replaced by a well harmonized document, development safety update report (DSUR), in which health regulators in the three ICH regions can receive same information at the same time, thereby reducing the total number of reports generated.

2. Post-approval aggregate reports:

They provide the cumulative summary of safety information for the medicinal products from the marketing exposure. The sources of safety data include Non-clinical, clinical studies and Non international studies, literature articles and spontaneous cases.
The following types of reports are submitted for medicinal products post marketing authorisation.

1. PADER (Periodic adverse drug experience report)
2. Periodic Benefit Risk Evaluation Report (PBRER)/ Periodic safety update report (PSUR)
3. Addendum to clinical overviews (ACO)
4. Risk management plan (RMP)

Timelines and Regulatory requirements:

DSUR: Marketing authorisation holders are obliged to report the evolving safety profile of investigational medicinal product and actions taken or proposed for the new safety concerns identified during the development to the respective health authority and local regulatory bodies (eg., Institutional review board and local ethics committee). The significant safety findings, serious adverse reactions in line listings, and significant safety information of investigational product and of drugs of similar therapeutic class from published literature are included in corresponding sections of DSUR.

It should be submitted no later than 60 calendar days from the DSUR data lock point (DLP). The DLP for DSUR is stop date of reporting interval for a molecule from the date of authorisation for conducting a clinical trial which is called as developmental International birth date (DIBD).

PBRER/PSUR: The Benefit-risk evaluation should be carried out throughout the lifecycle of the medicinal product to promote and protect public health and to enhance patient safety through effective risk minimization plans and implementations. After a marketing authorization is granted, it is necessary to continue evaluating the benefits and risks of medicinal products in actual use and/or long term use, to confirm that the benefit-risk profile remains favourable.
The date when sponsor received authorisation for marketing a drug is considered as International birth date (IBD) of the medicinal product. Data lock point is the cut-off date for completion of reporting interval. PBRER is a complex report with 20 sections including appendices compared to DSUR and PADER. The timeline for these post approval aggregate reports varies based on the age of medicinal product in the market which included the following kinds of reporting intervals and their respective regulatory timelines.

Timeline for PBRER/PSUR

Reporting Interval category	Criteria for medicinal products	Regulatory timeline
6 month reporting interval	Newly approved and marketed for 1 year period	70 calendar days
Annual reporting interval	In market for more than 1 year	90 calendar days
Multilayer reporting Interval	In market for more than 5 years	90 calendar days

The comprehensive list of active substances and combinations of active substances contained in medicinal products subject to different marketing authorisation, together with the corresponding EU reference dates, frequencies for submission of periodic safety update reports and related data lock points could be obtained from the European Union reference dates (EURD) list. European Medicines Agency (EMA) updates the EURD list on monthly basis.
A brief overview of primary author responsibilities in preparation of PBRER is depicted here.

- A kick off meeting schedule with multiple stakeholders for contributing information into various sections of report. (Regulatory, clinical, finance/sales, medical and signal management teams)
- Discussing action items with respective due timelines
- Retrieval/reconciliation of line listings (ICSR cases from safety database)
- Compilation of safety information received from different stakeholders into a draft PBRER report.
- Internal quality & medial review
- Amendments of draft report, if required per reviewer comments
- Approval of final report
- Submission of PBRER to regulatory authority (70th or 90th calendar day)

MAH can get relief in submitting PBRER/PSUR for the products which are well established, generic products in the market for longer time, homeopathic medicines and for traditional herbal medicines.

PADER: Periodic Adverse Drug experience report is a post-marketing safety report submitted to the United States Food and Drug Administration (USFDA). The main objective is to provide summary data with an assessment of an approved drug product's benefit risk profile from the post marketing exposure. The scope of PADER is limited to serious and unlisted cases which include concise narratives and summary analysis of 15-day ICSR reports. It also includes the regulatory actions taken for safety reasons during the reporting interval since last submitted PADER. The US FDA timeline for submission of PADER is presented in the table-2.

Table: 2- Timeline for PADER submissions

Reporting Interval category	Criteria for medicinal products	Regulatory timeline
Quarterly	For First three years, after marketing authorization	30 calendar days
Annual	In market for more than 2 years	60 calendar days

ACO: Addendum to clinical overviews are aggregate safety reports which are submitted to respective regulatory authorities for renewal of marketing authorization license of a medicinal product. They include the benefit-risk balance of the medicinal product based on the clinical data. The structure and specifications of the ACO and PBRER are similar. But the information presented with greater emphasis on the data received since the last renewal/approval rather than discussing cumulatively. In addition, the history of Pharmacovigilance system inspections (date, inspecting authority, site inspected, type of inspection and if the inspection is product specific, the list of products concerned) with the details of findings and its impact if any on the benefit-risk profile of the product has to be included in the document.
Timeline: The MAH should submit the renewal application by the recommended submission dates published on the EMA website and, in any case, no later than 9 months before the marketing authorisation ceases to be valid.

Risk Management Plan (RMP): The main objective of RMP is to document the risk management system considered necessary to identify, characterize and minimize a medicinal product's important risks. The three major sections of this document include the following

1. Safety specification: It describes the significant information on important identified and important potential risks and missing information and also on safety concerns which are need to be managed proactively.
2. Pharmacovigilance Plan: It provides the planning of pharmacovigilance activities to characterize and quantify clinically relevant risks and to identify new adverse reactions.
3. Risk minimization plan: It includes the planning and implementation of risk minimization measures (RMM), including the evaluation of the effectiveness of RMM activities.

MAH is responsible to maintain a proper risk management system and to monitor continuous influx of safety data from multiple sources for the identification of any new risks and changes to the risk benefit balance of the product. In general, RMP is warranted to prepare with the first 5-year renewal and in the time period when the first PSUR following the first 5 year renewal is due for submission, to review the list of safety concerns and the planned and ongoing Pharmacovigilance and risk minimization activities.