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Review Article

Overview of post marketing aggregate reports and global regulatory requirements

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ABSTRACT

Pharmacovigilance is the science that deals with the activities related to the detection, assessment, understanding, and prevention of ADRs. The scope of pharmacovigilance has evolved over time. We now recognize the importance of a systematic approach for monitoring and improving the safe use of medicines. At the level of individual case safety reports, it is not possible for marketing authorization holders (MAH) to evaluate benefit/risk ratio profile and understand the detailed safety feature of a medicinal product. In addition to submission of individual case safety reports MAH also review periodically, cumulative safety information attained from various sources and submit the findings as aggregate reports to drug regulators. Aggregate reporting is a vital tool to study benefit/risk balance of a medicinal product throughout the product's life cycle. The timelines, frequency and exact type of aggregate report required to be submitted for the approved product varies globally amongst various drug regulatory agencies. In this review the significance, background, objectives, scope, structural components, timelines for regulatory submissions of post marketing aggregate reports viz. PSUR, PBRER, and PADER have been discussed.

Keywords: Pharmacovigilance, Aggregate reporting, PSUR, PBRER, PADER, ADCO

INTRODUCTION

Disease management and strategies to prevent disease the occurrence have changed tremendously after the introduction of modern medicines. However adverse reactions to medicines are a common, yet often preventable, cause of illness, disability and even death. Adverse drug reactions (ADRs) are among the top 10 leading cause of death in some countries.[1] World Health Organization defines ADRs as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function".[2] Pharmacovigilance is a vital tool in patient care and it identifies the benefit/risk factors associated with the drug and helps in avoiding or minimizing the harm from adverse reactions. WHO defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems".[2]

Pharmacovigilance activities commence with receiving safety information from various sources namely clinical trials, spontaneous reports, regulatory agencies, published literature articles etc. Each of these reports needs to be triaged, evaluated for its causal association with the product before entering in to drug safety data base. This is followed by the storage of each safety report in a drug safety data base. Further, each of these reports needs to be communicated to the appropriate regulatory agencies/ stake holders as either as an individual case report or as part of aggregate reports with in the specified timelines. Depending on the significance of benefit/risk factors

identified with the medicinal product appropriate action needs to be taken. In addition, throughout the product's life cycle, safety data for medicinal products are systematically analyzed for safety issues and assessed for benefit versus risk. Accordingly, aggregate safety reports are submitted to the regulatory authorities.[3]

The primary focus of aggregate reports is to evaluate the world wide safety experience of medicinal product in a periodical manner and to update the medicinal product's label. Pre-approval aggregate reports includes annual safety reports (ASRs) in Europe and IND annual reports in United States. Lately development safety update report (DSUR) a well harmonized document has replaced ASRs and IND annual reports. In most parts of the globe post-approval aggregate reports include periodic safety update reports (PSURs)/ periodic benefit risk evaluation reports (PBRER)/ addendum to clinical overview (ADCO) in many regions including in Europe and periodic adverse drug experience reports (PADERs) in United States.

The aim of the current review emphases on reviewing the significance and structural components of post-approval aggregate reports (PSUR, PBRER, ADCO, PADER) and various regulatory agencies submission requirements for post-approval aggregate reports.

SIGNIFICANCE AND STRUCTURAL COMPONENTS OF POST APPROVAL AGGREGATE REPORTS

Periodic safety update reports (PSURs):[4]

During the developmental period, the efficacy and safety of the active substance has been evaluated based on the limited number of patients included in the trails. Hence marketing authorization holders (MAH) required monitoring the product consistently after launching the product especially during the initial years in market to understand the safety net of active substance. Regulatory authorities and MAH are sharing responsibilities in surveillance of marketed drugs. Detailed analysis and evaluation of benefit/risk ratio of a drug is not possible at the level of individual case reports. Therefore periodically reviewing safety reports received cumulatively worldwide, becomes highly significant to analyze the benefit/risk balance of the product. For each active substance, one periodic safety report is required regardless of its market approval for different formulations/ dosage forms or for different indications. For fixed dose combination, safety information for the active substances may be reported either in separate PSUR or may include in the same document under different sections as appropriate. The focus of PSUR should be on adverse drug reactions (ADRs) and to identify whether changes needs to make in the reference safety information of the product in order to optimize the use of the product. Although there are no specific methodologies recommended to present specific ADR trends, attention should be given to present such increase in frequency of ADRs and its implication on over all safety of the product. All relevant clinical, non-clinical safety data received during the reporting interval needs to be presented in PSUR, global marketing authorization status along with the approval/ withdrawal/ launch status of the product and data on serious, unlisted ADRs needs to be presented cumulative. When companies are involved in contractual relationships (e.g., licensor-licensee), arrangements for sharing safety information and responsibilities of safety reporting should be clearly mentioned on safety data exchange agreement. Data lock point (DLP) and reporting cycle should be derived from the International Birth Date (IBD) of the product, the date of the first marketing authorization for the product granted to any company in any country in the world.

ICH E2C (R1) guidelines states main objectives of the PSUR are as mentioned below:

- To report all the relevant safety data received during the reporting interval as appropriately
- To establish the relation between patient exposure data and safety data
- To summarize the marketing authorization status globally and any changes in approvals due to safety reasons
- To establish the overall safety evaluation periodically
- To specify whether changes should be made to product information in order to optimize the use of the product.

The structure and specifications of the PSUR is presented on the Table 1.

Periodic benefit risk evaluation reports (PBRER):[5]

The main objective of the PSUR is to provide an overview of the safety of the marketed medicinal products periodically. Major advances in the field of pharmacovigilance include automated data mining techniques, electronic submission of Individual Case Safety Reports (ICSRs) to regulatory authorities, changes in regulatory requirement includes more attention towards benefit-risk evaluation rather than focusing only on safety of the product and increasing prominence towards documenting risk management plans. All these changes in the field of pharmacovigilance has led to revision and refocus of the existing guidelines for periodic report submission.

The main focus of the PBRER is assessment of relevant new safety information (from the available data sources) to study the overall safety evaluation and integrated benefit-risk evaluation of the medicinal product. The PBRER has been developed in such a way that the content of several sections may be used for sections of other documents such as DSUR as a basis for a modular approach. Similar to PSUR, one report is required for each active substance regardless of its market approval for different formulations/ dosage forms or for different

indications. In exceptional cases such as an active substance being used in two different formulations with entirely different indications, separate reports need to be submitted by getting prior approval from regulatory authorities. For a fixed dose combination, safety information for the active substances may be reported either in a separate report or may be included in the same document under different sections as appropriate. When companies are involved in contractual relationships (e.g., licensor-licensee) arrangements for sharing safety information, responsibilities of submitting PBRER should be clearly mentioned in safety data exchange agreement as appropriate.

Table 1: Structure and specifications of the PSUR.

S No.	Component	Significance
	Title page	Includes title of the medicinal product, report number (varies from each MAH based on their policies), MAH's name and address, period covered by this report, International Birth Date (IBD) along with the country name and date of report.
	Executive summary	An overview of each section of the PSUR along with the safety issues identified and proposed actions to be taken
	Table of contents	
1	Introduction	Includes brief introduction of the product, mechanism of action and approved therapeutic indications. It is also placed in perspective relative to previous reports and circumstances.
2	Worldwide market authorisation status	Includes cumulative information of all countries in which a regulatory decision about marketing has been made related to dates of marketing authorisation, trade name, launch date, approved therapeutic indications (including status in special population), withdrawal date and explanation in comments section for the same if it is withdrawn for safety/efficacy reasons.
3	Update of regulatory authority or MAH actions taken for safety reasons	Includes worldwide actions taken during the reporting interval or between data lock point and submission such as marketing authorisation withdrawal/ suspension and failure to obtain approval due to safety reasons, product recall details from the market, dosage modification/formulation changes due to safety reasons, regulatory authorities communications and proposed actions.
4	Changes to Reference Safety Information (RSI)	Changes such as new contraindications, precautions, warnings, ADRs, or interactions, made during the period covered by the report in company core data sheet CCDS/ RSI should be mentioned along with the version number and date of modification.
5	Patient Exposure	Includes estimation of the number of patients exposed along with the method used to derive the estimate usually in patient treatment years (PTY), patient treatment month (PTM) or patient treatment days (PTD). Data broken down by sex and age (especially pediatric vs adult) can be included when required.
6	Presentation of individual case studies	
6.1	General Considerations	An overview of number of cases/ events reported during the reporting interval with the breakdown of serious, non serious, medically confirmed and non confirmed cases/ events. A cumulative detail of serious and non serious cases also needs to be included. Significant new information from follow up of the same case presented in previous PSUR should be included.
6.2	Cases present as line listing	The following types of cases should be included in the line listings: • all serious and non-serious unlisted reactions, from spontaneous notifications • all serious reactions (attributable to drug by either investigator or sponsor), available from studies or compassionate use; • all serious and non-serious unlisted reactions, from the literature • all serious reactions from regulatory authorities
6.3	Presentation of the line listing	Includes all the cases organised by body system (standard organ system classification scheme). Necessary steps needs to be taken to avoid the duplication of the report.
6.4	Summary tabulaions	Includes aggregate summary of the each of the line listing generated. Data includes in tabular format with breakdown of serious and non serious cases along with the status of listedness.
6.5	MAH's Analysis of Individual Case Histories	An analysis of selected individual case reports discussion can be presented on particular serious or unanticipated findings along with the causal association details.

S No.	Component	Significance
7	Studies	An overview of completed/ ongoing studies (non-clinical, clinical, epidemiological) and relevant published literature articles.
7.1	Newly analysed company-sponsored studies	Includes all the relevant studies containing important safety information. Study design, abstract of findings, number of subjects, safety outcome with supporting details and date of completion needs to be presented as applicable.
7.2	Targeted new safety studies	Includes new studies planned during the reporting interval. Study design, expected number of subjects to be enrolled, projected completion data and interim analysis data if available needs to be presented.
7.3	Published safety studies	Includes relevant published literature articles with references and comments.
8	Other Information	
8.1	Efficacy related information	An overview of lack of efficacy cases reported during the reporting interval along with the individual case explanation if required.
8.2	Late Breaking Information	Any important, new information received after the data lock point and before the submission of PSUR.
9	Overall safety evaluation	Includes analysis of safety information discussed in all the above sections including late breaking information with respect to change in characteristics of listed events if any and any recommendations for update in CCDS/RSI. Further, this section includes any new safety issues on drug interactions experience with overdose, drug abuse or misuse exposure during pregnancy or lactation, exposure in special patient groups (e.g., children, elderly, organ impaired) and effects of long-term treatment.
10	Conclusion	Includes status of all the significant safety data with respect to CCDS/RSI. Specification and justification for action recommended or initiated.
	Appendices	Including CCDS/RSI, detailed line listings and summary tabulations.

Table 2: Structure and specifications of the PBRER.

S No.	Component	Significance
	Title page	Includes title of the medicinal product, report number (varies from each MAH based on their policies), MAH's name and address, period covered by this report, International Birth Date (IBD) along with the country name, date of report, signature of the responsible person and statement on the confidentiality of the information included in the document.
	Executive summary	An overview of each section of the PBRER along with the safety issues identified and proposed actions to be taken
	Table of contents	
1	Introduction	Includes brief introduction of the product, IBD with reporting interval, approved therapeutic indications, mechanism of action, dosage and route of administration, special population studied. It is also placed in perspective relative to previous reports and circumstances.
2	Worldwide marketing approval status	Includes cumulative information of all countries in which a regulatory decision about marketing has been made related to dates of first approval, indication(s), approved dose(s) and where approved.
3	Actions taken in the reporting interval for safety reasons	Includes description of significant actions related to safety that have been taken during the reporting interval, related to either investigational uses or marketing experience by the MAH. In addition, regulatory authorities communications and proposed actions.
4	Changes to reference safety information	Changes such as new contraindications, precautions, warnings, ADRs, or interactions, made during the period covered by the report in company core data sheet CCDS/ RSI should be mentioned along with the version number and date of modification. The reference safety information needs to be attached in the appendices.
5	Estimated exposure and use patterns	Includes the estimation of the size and nature of the population exposed to the medicinal product.
5.1	Cumulative subject exposure in clinical trials	Includes Cumulative numbers of subjects from ongoing and completed clinical trials exposed to the investigational medicinal product, placebo, and/or active comparator(s) since the DIBD, break down of subjects under gender, race, age, special population and SAEs reported if any along with the details.

S No.	Component	Significance
5.2	Cumulative and interval patient exposure from marketing experience	Includes overall patient exposure during the interval period and cumulative data separately under three categories viz. post-approval (non-clinical trial) exposure, post-approval use in special populations and other post approval use.
6	Data in summary tabulations	An overview of cumulative summary tabulation of SAEs from clinical trials and post marketing data sources
6.1	Reference information	Provides the information on version number of coding dictionary used for analysis of events
6.2	Cumulative summary tabulations of Serious adverse events from clinical trials	An overview of cumulative summary tabulation of SAEs, those have been reported from interventional clinical trials that have been reported. Tabular format may include in appendices separately.
6.3	Cumulative and interval summary tabulations from post-marketing data sources	An overview of cumulative summary tabulation of SAEs from interventional clinical trials that have been reported. Tabular format may include in appendices separately.
7	Summaries of significant findings from clinical trials during the reporting period	A brief summary of clinically important emerging efficacy/effectiveness and safety findings obtained from the MAH's sponsored clinical trials that became available during the reporting interval of the report.
7.1	Completed clinical trials	Includes important efficacy/effectiveness and safety findings from the completed clinical trials during the reporting interval along with the synopsis of findings.
7.2	Ongoing clinical trials	Includes significant safety information from ongoing clinical trials like interim safety analyses if any.
7.3	Long-term follow-up	An overview of long-term follow-up of subjects obtained during the reporting period
7.4	Other therapeutic use of medicinal product	Include clinically important safety information from other solicited reporting programmes conducted by the MAH viz. expanded access programmes, compassionate use programmes, particular patient use, and other organized data collection
7.5	New safety data related to fixed combination therapies	Includes significant safety data from fixed dose combination or multidrug regimen if available for the active substance. In case, if the active substance itself a fixed dose combination then significant safety data from its individual components needs to be incorporated if available.
8	Findings from non-Interventional studies	Includes relevant safety information obtained during the reporting interval from MAH sponsored non-interventional studies for the active substance.
9	Information from other clinical trials and sources	Includes information relevant to the benefit-risk assessment of the medicinal product from other clinical trial/study sources. Further includes relevant information on patterns of medication errors and potential medication errors, even when not associated with adverse outcomes.
10	Non-clinical data	Includes the significant safety findings from in vivo, in vitro non-clinical studies completed or ongoing during the reporting interval with the product.
11	Literature	Includes relevant literature articles published during the reporting interval under categories viz. pregnancy outcomes (including termination) with no adverse outcomes; use in paediatric populations; compassionate supply, named patient use; lack of efficacy; asymptomatic overdose, abuse or misuse; medication error where no adverse events occurred; important non-clinical safety results and other studies which cannot be defined under above mentioned categories.
12	Other periodic reports	Includes significant findings from other periodic reports submitted during the reporting interval if MAH prepares multiple reports for a single active substance due to covering different indications, or formulations.
13	Lack of efficacy in controlled clinical trials	Includes the significant risk due to lack of efficacy in approved indication(s) of the active substance reported in controlled clinical trials during the reporting interval.
14	Late-breaking information	An overview of potentially important safety and efficacy/effectiveness data reported after the DLP of the reporting period and before the due date for submission.
15	Overview of signals: new, ongoing, or closed	A high-level overview of new safety signals identified, details of ongoing signals and closed signal during the reporting interval have to be presented. New signals may be classified as closed or ongoing, depending on the status of signal evaluation at the DLP of the report.

S No.	Component	Significance
16	Signal and risk evaluation	
16.1	Summary of safety concerns	Includes a summary of safety concerns at the beginning of the reporting interval under important identified risks, important potential risks and missing information, against which new information and evaluations can be made.
16.2	Signal evaluation	Summarize the results of evaluations of all safety signals (whether or not classified as important) that were closed during the reporting interval. It can be organized under topics viz. closed and refuted signals; closed signals that are categorised as important potential risks; closed signals that are categorised as important identified risks; closed signals that are potential risks not categorised as important and closed signals that are identified risks not categorised as important.
16.3	Evaluation of risks and new information	Includes new information relevant to previously recognised risks that is not already included in Section 16.2 of the PBRER, Signal Evaluation. It can be organized under topics viz. new information on important potential risks; new information on important identified risks; new information on other potential risks not categorised as important; new information on other identified risks not categorised as important; update on missing information and update on important missing information.
16.4	Characterisation of risks	Includes characterisation of important potential risk, important identified risk and missing information based on the cumulative data received till the DLP of the report. The characterisation can be presented in the tabular format constitutes details majorly with its frequency, seriousness/outcomes, severity and nature of the risk, background incidence/prevalence, risk groups or risk factors, potential mechanisms, preventability, impact on individual patients, potential public health impact of safety concern and evidence source.
16.5	Effectiveness of risk minimization (if applicable)	Includes relevant information available during the reporting interval on the effectiveness and/or limitations of specific risk minimization activities for important identified risks. Regional/country wise information can be presented as applicable.
17	Benefit evaluation	
17.1	Important baseline efficacy/effectiveness information	Includes information as of in beginning of the reporting interval on the efficacy/effectiveness of the medicinal product for the approved indications and provides the basis for the benefit evaluation. Information can be categorized individually if the medicinal product has been approved for multiple indications, populations and/or routes of administration. Information should be sufficient to support the characterisation of benefit in Section 17.3 and the benefit-risk assessment in Section 18.
17.2	Newly identified information on efficacy/effectiveness	Includes new information on efficacy/effectiveness in approved indications available during the reporting interval. Information should be sufficient to support the characterisation of benefit in Section 17.3 and the benefit-risk assessment in Section 18.
17.3	Characterisation of benefits	Provides the integration of the baseline benefit information (Section17.1) and any relevant new benefit information (Section17.2). In addition, critical evaluation of the strengths and limitations of the evidence on efficacy/effectiveness needs to be presented. Information should be sufficient to support the analysis of benefit-risk in Section 18.
18	Integrated benefit-risk analysis for approved indications	Provides an integration and critical analysis of the key information in section 16.4 and 17.3.
18.1	Benefit-risk context - medical need and important alternatives	Includes the medical need for the medicinal product in the approved indications, and summarize alternatives (medical, surgical, or other; including no treatment).
18.2	Benefit-risk analysis evaluation	Includes benefit-risk profile specific to approved indication and population for the medicinal product. If approved for more than one indication, analysis needs to be presented individually and also if there are important differences in the benefit-risk profiles among populations within an indication the analysis needs to be presented appropriately. It can be organized under topics viz. context of use of the medicinal product; With respect to key benefit(s); With respect to key risk(s); strengths, weaknesses, and uncertainties of the evidence and methodology and reasoning used to develop the benefit-risk evaluation.

S No.	Component	Significance
19	Conclusions and actions	An overview of conclusion regarding new information arouse during the reporting interval and its implications on overall risk-benefit balance of the product. In addition based on the evaluation of safety data any changes to reference safety information if required needs to be mentioned. These proposals should also be considered for incorporation into the risk management plan as appropriate. Information on any final, ongoing, or proposed changes to the national or local authorized product information needs to be appended under regional appendix section.
20	Appendices	Includes reference safety information, detailed summary tabulations, tabular summary of safety signals, listing of post authorization interventional, non-interventional studies and regional appendices as appropriate.

Table 3: Structure and specifications of the PADER.

Component	Significance
Title page	Includes molecule name along with strength, formulation, reporting interval along with NDA/ANDA number. Title page may include signature of report writer, reviewer and Responsible Person for Pharmacovigilance.
Cover letter	An overview of cases in particular number of serious unexpected cases submitted during the reporting interval and number of serious expected, non serious un expected and non serious expected cases received during the current reporting interval, MedDRA version number and details of recent prescription information (PI) signed by Responsible Person for Pharmacovigilance.
Introduction	Includes brief introduction of the product, reporting interval, authorization details, recent PI and effective PI details. It is also placed in perspective relative to previous reports and circumstances.
Summary and analysis of the information contained in the report	Includes analysis of the 15-day reports submitted during the reporting period. Details of safety issues identified in current reporting interval and an overview of safety issues under monitoring from previous report.
Discussion of action taken for safety reasons since last report	Includes details of labeling changes, studies initiated/completed, drug safety recommendations from FDA, "Dear Health Care Professional" letter issued by MAH during the reporting interval
Appendices	Including recent PI/ effective PI, Med Watch forms for each adverse event not previously submitted as a 15-day report and Tables of frequency of occurrence of adverse events from the reporting period, organized by body system.

The main objective of a PBRER is to present a critical review of risks of the medicinal product which emerged during the reporting interval along with cumulative data and benefits of the medicinal product for the approved indications, to assist in evaluation of product's overall benefit-risk profile. The PBRER should contain an evaluation of new information received during the reporting interval relevant to the medicinal product, in the context of cumulative information, by reviewing the new relevant safety information received during the reporting interval along with its impact on over all benefit-risk profile of the product, reviewing the important efficacy/ effectiveness information received during the current reporting interval for the product, relating the safety and efficacy related information availed during the reporting interval is in line with previous knowledge of the medicinal product's benefit and risk profile, integrated benefit-risk evaluation needs to be presented for approved indications based on the relevant new safety information received during the reporting interval and PBRER also should include proposed actions to optimize the benefit risk profile as needed.

The structure and specifications of the PBRER is presented on the Table 2.

In addition, in the EU as a part of the renewal procedure, a report on the re-evaluation of the benefit/risk balance of the medicinal product needs to be included within the renewal application form. As a part of the renewal application, benefit/risk balance of the medicinal product based on the clinical data has to be presented in the addendum to clinical overview (ADCO). The structure and specifications of the ADCO are same as that of PBRER, however the data is discussed with greater emphasis on the information 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.[6,7]

Periodic adverse drug experience reports (PADERs)[8]

Periodic adverse drug experience report is a form of aggregate report that needs to be submitted to US FDA for the products approved for marketing in United States of America. Based on FDA guidelines, MAH needs to review all adverse drug experience information received from any source, foreign or domestic, including information derived from commercial marketing experience, post marketing clinical investigations, post marketing epidemiological/surveillance studies, reports in the scientific literature, unpublished scientific papers and communicate with FDA. As a part of routine pharmacovigilance activities, MAH needs to submit a post marketing adverse experience report on individual case safety reports which are serious and unexpected, which were received from either domestic or foreign source within 15 calendar days of receipt of that information. Hence the scope of PADER is mainly limited to reports other than serious and not expected i.e. serious expected, non-serious expected, non-serious unexpected received from domestic market. The report mainly includes the narrative and summary analysis of the 15-day Alert reports submitted during the reporting interval, history of actions taken since the last report because of safety reasons, labelling changes during the reporting period, studies initiated and completed during the reporting period along with the relevant safety outcomes.

The structure and specifications of the PADER is presented on the Table 3.

REPORTING SPECIFICATIONS FROM VARIOUS REGULATORY AUTHORITIES

Food and drug administration – United States

Post marketing adverse drug reports for FDA needs to be presented as per the format prescribed under 21CFR314.80. MAH needs to submit the PADER initially at quarterly intervals for 3 years from the date of approval of the application and then at annual intervals till the approval of the product withdrawn. The first quarterly reporting interval begins from date of approval of the product and all the twelve quarterly reports needs to be submitted within 30 calendar days from the date lock point. Similarly annual reports needs to be submitted within 60 calendar days from the date lock point. Follow-up information received for adverse drug experiences in the submitted PADER needs to be included in the next report. Further, FDA may request MAH to extend or restore quarterly reports or in different cycles other than standard cycles. For example, the agency may reestablish a quarterly reporting requirement following the approval of a major supplement.[8]

FDA has granted waivers to marketing authorization holders under 314.90(b) and 600.90(b) to allow applicants to substitute the PSUR for the PADER.[9,10] In addition, waiver allows MAH to change the date of DLP from approval date in US to a different date for harmonizing the reporting interval. FDA has also permitted applicants to produce same safety report for multiple products constituting same active ingredient/moiety. In general FDA has not waived reporting frequencies i.e. if the PSUR reporting cycle for a particular product is three years then MAH may submit annual PADERs for first two years and may submit PSUR in third year. In addition, if MAH holds PSUR waiver for an approved application, it permits MAH to submit PBRER instead of PSUR. When switching from PSUR to PBRER if there are no changes with reporting frequency/ DLP, MAH can continue the same without submitting any new waiver request. However, if there are changes with either frequency or DLP then MAH needs to submit new waiver request and one time PADER to cover the gap if required.[11]

European medicines agency – European Union

The list of Union reference dates (EU reference date) and frequency of submission of PSURS comprises of list of active substances along with combination products as applicable in alphabetical order for which PSURs are required along with the required frequency. The same has been determined by the Committee for Medicinal Products for Human Use (CHMP) and the Coordination Group for Mutual Recognition and Decentralized Procedures - Human (CMDh) after consultation with the Pharmacovigilance risk assessment committee (PRAC) [DIR Art 107c(4) and (6)]. The main objectives of list of EU reference dates are as follows: [12]

- Harmonization of DLP and frequency of submission of PSURs for the same active substance and combination of active substances for different MAHs
- Optimization of the management of PSURs and PSURs assessments within the EU
- Single EU assessment and reassessment of the risk-benefit balance of an active substance based on all available safety data.

General requirement for submitting PSURs has been described in Figure 1:

As per the standard submission schedule of PSURs for products authorized before 02 July 2012 (centrally authorized products), 21 July 2012 (nationally authorized products) and for which the frequency and dates of submission of PSURs are not informed to MAH as a condition or determined otherwise in the list of Union reference dates, shall submit PSURs according to the following submission schedule [REG 28(2), DIR Art 107c (2)]: [12]

- After receiving authorization for the product (even it is not marketed) – at six months interval.
- After the launch of product in market – 6 monthly PSUR needs to be continued initially for 2 years. After that once in a year for the next 2 years and thereafter at 3 years intervals.

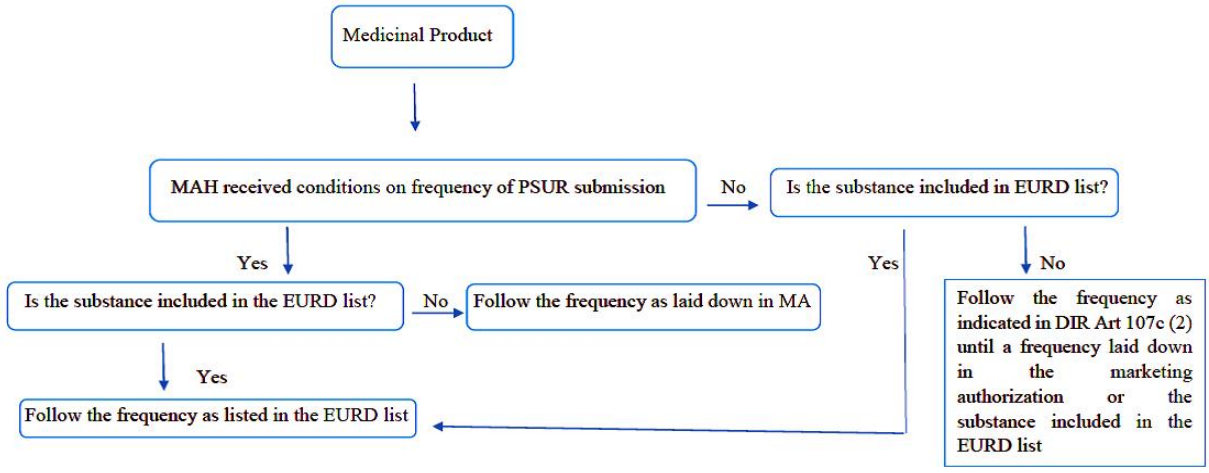

Figure 1: Requirement for submitting PSURs in EU.

Marketing authorization holders shall be responsible for submitting PSURs based on the list of union reference dates and frequency of submission for their own approved products as per the following timelines:[12]

- PSURs covering intervals up to 12 months – within 70 calendar days from data lock point DLP (day 0)
- PSURs covering intervals in excess of 12 months – within 90 calendar days from DLP (day 0)
- Ad hoc PSURs – within 90 calendar days from DLP (day 0) unless or otherwise specified in the request.

Health Canada-Canada

As per Health Canada guidance, MAHs are expected to prepare annual summary reports for all their health products, with an active DIN, including generic drugs. Annual summary reports shall be prepared in either PSUR or PBRER format, are only required to be submitted if agency requested or any significant change identified in the known risk/benefit of the product. For PBRER format agency requested MAH to follow ICH E2C (R2) guidance and the time interval for submitting PBRERs are as given below:

- PBRERs covering intervals of 6 or 12 months - within 70 calendar days from DLP;
- PBRERs covering intervals in excess of 12 months - within 90 calendar days from DLP
- Ad hoc PBRERs: 90 calendar days, unless otherwise specified.

When significant information identified, the notification to the agency should include the most recent complete annual summary report, which may be provided in either PSUR or PBRER format along with the cover letter. All annual summary report submissions will be processed and tracked using the Drug Submissions Tracking System (DSTS) managed by the Office of Submissions and Intellectual Property (OSIP) in Ontario.[13]

TGA-Australia

As per the guidance of Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines released by Therapeutic Goods Administration, Australia Periodic Safety Update Reports are required for certain registered products. PSURs are not required for all medicines, only those to which this specific condition is imposed during registration of that product. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good Pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII. The frequencies of periodic reports are as follows:

- PSURs can be submitted annually for at least 3 years from the date of registration, alternatively can submit separately every 6 months or two together at the end of the year that they cover.
- The first DLP is either 6 months or one year from date of approval.

PSURs need to be submitted within 90 calendar days from the data lock point. After the final PSUR i.e. third PSUR, no need to submit PSUR unless there have been further PSUR requirements placed as conditions of registration.[14,15]

HSA-Singapore

As per Guidance for Industry – Post-marketing Vigilance Requirements for Medicinal Products released by Health

Sciences Authority (HAS, Singapore) routine submissions of PBRERs may requested for selected medicinal products as required to monitor closely. The format of PBRER should be as per the guidance of ICH E2C R2 guidelines. Each safety update report should cover the period of time since the last update report. When requested, PBRERs shall be submitted as follows:

- Initially at intervals of 6 months from international birth date (IBD) or from approval date locally for a period of 2 years.
- Thereafter annually for the next 3 years unless or otherwise specified.
- Agency may request MAH to submit PBRER after 5 years of marketing approval as required.

PBRERs need to be submitted within 70 calendar days from the DLP for reporting interval not exceeding 12 months or within 90 calendar days from the DLP for reporting interval covering more than 12 months.[16]

DCGI-India

In India as per the requirements of clause 4 of schedule "Y" Drugs and Cosmetics Rules, Periodic safety Update Reports (PSURs) of new drugs are required to be submitted to office of Drugs Controller General India. The PSUR cycles immediately after the approval of the product are as follows:

- After approval of the drug granted to the applicant – six monthly for the first 2 years
- For subsequent two years – annual PSURs needs to be submitted
- After that, licensing authority may extend the total duration of submissions of PSURs if required based on the interest of public health.

PSUR needs to be submitted within 30 calendar days from the data lock of point. Single PSUR shall submit for different formulations, dosage forms and indications of the same medicinal product. Within the PSUR data needs to be presented separately for different formulations, dosage forms and indications as applicable.[17]

CONCLUSION

Aggregate reporting is a significant tool to understand the benefit/risk ratio of any medicinal product. Although it is marketing authorization holder's responsibility to submit aggregate reports it is important for healthcare professionals all over the globe need to understand the significance of aggregate reporting and their regulatory requirements. This review may thus be an initiative for the same.

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