Authoring a periodic adverse drug experience report...here’s what you need to know!

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Abstract

Aggregate reporting involves preparation and submission of safety reports for a given medicinal product to worldwide regulatory agencies and constitutes an essential part of safety monitoring of a medicinal product. There are specific aggregate safety reports required for a molecule in development called development safety update reports while Periodic Adverse Drug Experience Reports (PADERs) and Periodic Safety Update Reports/Periodic Benefit-risk Evaluation Reports (PBRERs) are submitted for products with marketing authorization. Based on the periodic analysis of worldwide safety reports, product label is updated to optimize safe use of a medicinal product. PADERs are aggregate safety reports to be submitted to the Food and Drug Administration (FDA) for products approved for marketing in the United States (US). PADER submission starts once marketing authorization approval is received for a medicinal product by the sponsor. Quarterly and annual PADERs should be submitted within 30 and 60 days of data lock point, respectively. PADERs mainly involve presentation of case reports with serious unlisted events (15-day alert reports) in the form of narratives or in a tabular format. The present article focuses on the background, scope, structure of a PADER, and its submission timelines; lists differences between PADER and PBRER; and describes the knowledge, skills, and attitudes required for a PADER writer.

Keywords: Periodic Adverse Drug Experience Report, Periodic Benefit-risk Evaluation Report, Periodic Safety Update Report, pharmacovigilance

INTRODUCTION

Aggregate safety reports are an important tool in the safety evaluation throughout the life cycle of a medicinal product. Individual case safety reports provide information on adverse events associated with a medicinal product in an individual patient; however, analysis of cumulative safety information (reported worldwide) is necessary to not only understand the safety profile but also to monitor the benefit-risk profile of a medicinal product. During clinical development of a medicinal product, the Development Safety Update Reports (reports submitted as the Investigational New Drug Annual Reports in the United States (US) and Annual Safety Reports in the European Union) are submitted to the regulatory agencies. After obtaining marketing authorization approval for a medicinal product, a Periodic Adverse Drug Experience Report (PADER), Periodic Safety Update Report (PSUR)/Periodic Benefit-risk Evaluation Report (PBRER), or Addendum to Clinical Overview (ACO) is submitted periodically to regulatory agencies depending on the country for submission and/or stage of development of a medicinal product.

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A PADER is a type of aggregate safety report required to be submitted by a sponsor or marketing authorization holder (MAH) to the US Food and Drug Administration (FDA) after obtaining marketing authorization approval. It means that submission of a PADER starts following completion of Phase 3 trials and with approval of a new drug application ([NDA] for innovator products), abbreviated NDA ([ANDA] for generic products), and biologic license application ([BLA] for biological products) by the US FDA. Hence, for each NDA/ANDA/BLA, MAH should submit a separate PADER. With the recognition that assessment of the risk of a medicinal product is more meaningful when evaluated in context of its benefits, the guidelines were revised with change in the report format from PSUR to PBRER, in 2012. The PSUR/PBRER is an aggregate safety report that is accepted worldwide including the European Union, Japan, and Canada. Although as per 21 Code of Federal Regulations (CFR) 314.80 US FDA recommends periodic submission of a PADER, MAH can submit PSUR/PBRER along with NDA listings (also called US Supplement/FDA PSUR) in place of PADER after obtaining a waiver per 314.90 (b) and 600.90 (b). Important differences between PADER and PBRER are provided below in Table 1. The ACO is a kind of aggregate safety report submitted for renewal of marketing authorization license of a medicinal product.

A team consisting of safety physician, person responsible for pharmacovigilance, pharmacovigilance data management team, regulatory team, and medical writers is involved in preparation of a PADER. Once the first marketing authorization approval (international birth date) is obtained by a MAH, a reporting cycle starts and first quarterly PADER needs to be submitted within 30 days.

Source documents for drafting a PADER include:

- Line listings: It includes all the 15-day alerts (serious unlisted domestic and foreign cases) and non-15-day alerts (serious listed, nonserious unlisted, and nonserious listed domestic cases) reported during the reporting interval. It also includes summary tabulation for all the adverse events (preferred terms as per the latest Medical Dictionary for Regulatory Activities; MedDRA) by System Organ Class for all the cases submitted to FDA for the NDA number. It covers cases where the medicinal product is reported as a co-suspect medication as well. Council for International Organizations of Medical Science (CIOMS) forms are also received as a part of input data which contains narratives for the serious unlisted cases.
- Regulatory input: It includes information on actions taken for safety reasons (e.g., dear doctor letters or safety recommendations from regulatory agency), safety-related labeling changes, and update on clinical trials initiated, ongoing, or completed during the reporting interval.

A PADER includes introductory paragraph, which is followed by summary of tabulation (providing bifurcation on number of serious/nonserious and domestic/foreign cases), description of 15-day alert cases, regulatory section, conclusion, and lastly appendices (package insert and line listings). An overview of steps involved in preparation and submission of a PADER is provided in Figure 1.

### Table 1: Important differences between Periodic Adverse Drug Experience Report and Periodic Benefit-Risk Evaluation Report

| PADER | PBRER |
|-------|-------|
| It consists of individual case narratives for cases with fatal outcome and/or events of special interest. It is prepared per US 21 CFR 314.80 and is submitted to US FDA. | It consists of detailed analysis on the benefit-risk evaluation of the given medicinal product. It is prepared per ICH E2C R2 and European Medicines Agency Module VII guidelines and is submitted to the European Union and rest of the world. |
| It consists of around 5 sections and is relatively less complex document. It includes case presentation of serious unlisted events and regulatory updates. | It consists of 20 sections and is a more complex document. It mainly includes sections on regulatory updates, cumulative and interval exposure, interventional and noninterventional clinical trials, overview of signals, and benefit-risk assessment. |
| A separate PADER is to be submitted with each NDA approval (for different indications and/or formulations of an investigational medicinal product) though sometimes MAH can prepare one PADER for different NDAs for different strengths of a formulation with appropriate justification. The frequency of submission is quarterly for first 3 years followed by annually. Quarterly and annual PADERs are submitted within 30 and 60 calendar days of DLP, respectively. | Usually, one PBRER is prepared for an investigational product with different formulations, dosage forms, or indications. In exceptional cases with provision of appropriate justification, for example, entirely different indications, submission of separate PBRERs might be acceptable. For newly approved products, PBRERs are submitted 6 months for first 2 years followed by annually (with exception of ad hoc requests). Annual or multiyear PBRERs are submitted within 70 or 90 calendar days of DLP, respectively. |

DLP = Data lock point, FDA = Food and Drug Administration, ICH = International Council for Harmonization, MAH = Marketing authorization holder, NDAs = New drug applications, PADERs = Periodic Adverse Drug Experience Reports, PBRERs = Periodic Benefit-Risk Evaluation Reports, US = United States, CFR = Code of Federal Regulation.
At the start of the month, a PADER schedule is shared with the pharmacovigilance data management team, so that case processing of the medicinal product can be completed by the data lock point (DLP) of the PADER.

Five to seven days before DLP, an introductory email with timelines for various activities of a PADER is circulated with the stakeholders, so that they can confirm their availability for the action items. By the DLP, a request for regulatory input in a template-specific format is sent to the regulatory team.

Drafting of a PADER starts with the introductory paragraph, wherein information on indication and therapeutic class of a medicinal product, reporting interval, and NDA/ANDA/BLA number is provided.

Once the line listings are received, a meeting with safety physician and qualified pharmacovigilance personnel is conducted for case selection for presenting them in a draft of PADER. The focus of the PADER is to present concise narratives for 15-day alerts. If many cases are selected for presentation, they can also be presented in a tabular format. In general, cases with fatal outcome or with events of special interest are selected for presentation and line-listing and MedWatch forms are appended to the draft. Events of special interest are serious or nonserious events (e.g., hair loss, loss of taste, and impotence) which are thought to be potential precursors (prodromes) of more serious medical conditions in susceptible individuals.\[8\] If there are no cases reported for a medicinal product during the reporting interval, only a cover letter (null report) with relevant appendices (listing [showing no reported cases] and US Package Insert) is prepared.

Regulatory input is usually received by days 3–5 of the DLP. The drug label in effect during the reporting interval is appended to the draft.

PADER also covers a statement on number of cases reported where the medicinal product is reported as a co-suspect medication.

Once all the relevant information is entered into the PADER template, the draft PADER undergoes stakeholders’ review, and contents are finalized by day 25 or 55 (for quarterly or annual PADER, respectively) for providing it to the publication team. Final submission package usually includes cover letter, PADER draft, NDA line listings, package insert, and form FDA 356 h (application to market a new or abbreviated new drug or biologic for human use).

Now that we have some understanding about the process of preparing PADERs, let’s look at the knowledge, skills, and attitude required to be a competent PADER writer.

**Knowledge**

The writer should be well aware of the following:

- The standard pharmacovigilance guidelines and regulations including 21 CFR part 314.80 and 600.80
- Data protection/privacy regulations as applicable
- Basics of clinical development of a drug\[9\]
- Understanding and experience of individual case safety report processing\[10\] are an added advantage
- Good therapeutic area knowledge and understanding across varied products and study indications.
Skills
The three key skills for a PADER writer are:

- Project management skills: Each report represents a unit project by itself to be completed within the defined timelines and per desired quality for regulatory submission. Hence, a writer should be able to work under stringent timelines and with multiple stakeholders who may have differing opinions (writing being a subjective entity) to arrive at a suitable consensus in a timely fashion
- Proficient in using Microsoft Word and Excel: This skill helps the author to spend less time in formatting and allows him/her to concentrate on the content of a report. The ability to use Excel proficiently helps author to analyze the line listings swiftly, which is required to gather insight from the data
- Effective communication skills: The writer needs to represent the data clearly and concisely without changing the meaning yet covering all significant points of the case, without any grammatical errors; to do so, the writer needs to have excellent written communication skills. Furthermore, in order to communicate with multiple stakeholders, the writer should be good listener and should be able to communicate effectively to deliver a high-quality report.

Attitude
A writer should develop following attitude/traits:

- Proactivity: Aggregate reports have timelines for submission, and hence, the author needs to be proactive in considering all the possible risks which may delay report and act accordingly. Procrastination may have serious implications
- Positive attitude: Since timelines for submission are defined and irrespective how much one plans in advance few things may come up at the last moment, in such case, the author needs to have a positive attitude and should focus on delivering in timeline rather than focusing on the reason for the unexpected delays (which could be investigated later)
- Emotional intelligence: Working under pressure of timelines and with multiple stakeholders (reviewers and approvers) may lead to situations which may test person’s ability to manage self in high-pressure situations. Hence, emotional intelligence is required to effectively manage difficult situations.

The performance of an aggregate report writer is measured based on the following parameters:

- Timelines: Adherence to the expected turnaround time for each step in the aggregate reporting workflow and eventually compliance to regulatory submission timeline
- Quality/error percentage: Nature and number of errors versus the available error opportunities in a given report at various review stages.

Today, pharmacovigilance has become more complex and regulated, leading to an increased demand for competent medical writers who are familiar with safety documents and have the skill set necessary to deal with multidisciplinary teams, complicated data, and challenging deadlines.

Periodic safety aggregate reports are vehicle to regulatory dialog and facilitate the monitoring of adverse events in an organized manner. PADER is a concise safety aggregate report and an effective means of risk analysis and safety communication to the regulatory authority. Preparation and submission of these reports helps ascertain whether further investigations are necessary and whether changes should be made to the approval or to the product labeling at predetermined time points.

It is of utmost importance that the presentation of patient safety, the drug’s benefit/risk profile, and the MAH’s risk management assessments to regulatory authorities is compliant with the requirements, clear and consistent across the whole suite of pharmacovigilance documents, and that these documents are produced in a timely and efficient manner. Involving an experienced pharmacovigilance medical writer in a scientific writing team ensures this and enables the pharmacovigilance and medical experts to focus on their core task of ensuring patient safety.

In the era where every organization, every company wants to go digital, the pharmacovigilance industry is also doing its bit. The current efforts are mainly to automate individual case safety reports processing which includes:

- Robotic Process Automation for process steps automation, where-in manual repetitive steps can be automated where human intervention or decision making is not required. Eg, distribution of case reports, seriousness and labelling assessment, or literature screening
- Artificial Intelligence, where the system can interpret and analyze the source, select the appropriate content, and perform end to end case processing (by machine learning).

Referring to a PADER writing, the steps which can be automated can include generation of NDA listings and writing of sections other than narrative writing, which could
be the most challenging step considering medical judgment in summarizing the case. Presently more and more companies are heading towards automation and only time will tell us the role of automation in aggregate safety reports writing.

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