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Preparation and Submission of Periodic Adverse Drug Experience Report (PADER).

Dimpal Jain [a], Riya Patel [b], Mohit Soni [c], Dr. Maitreyi Zaveri [d]

[a] *Student, K.B. Institute of Pharmacertical Education and Research (Gandhinagar), India*
[b] *Head of Department, Pharmazone (Ahmedabad), India*
[c] *Manager- PV operator, Pharmazone (Ahmedabad)India*
[d] *HOD-RA K.B. Institute of Pharmacertical Education and Research (Gandhinagar), India*

A B S T R A C T

For pharmaceutical products, the creation and filing of Periodic Adverse Drug Experience Reports (PADERs) are essential elements of post-marketing surveillance. These reports, which are mandated by regulatory body like the FDA, offer a continuous evaluation of a medication's efficacy and safety after it has been approved for use on the market. Adverse drug reactions (ADRs) are systematically gathered, examined, and reported through the PADER process from a variety of sources, including as patient registries, clinical trials, spontaneous reports, and healthcare practitioners. In addition to an assessment of any new safety issues, PADER usually include a thorough examination of the frequency, seriousness, and consequences of adverse events that have been recorded. To guarantee the drug's safe usage, this data aids in updating the risk profile of the medication, improving clinical recommendations, and changing labelling information. Additionally, based on fresh post-marketing data, the PADER process incorporates a benefit-risk evaluation to determine whether the drug's safe usage, this data aids in updating the risk profile of the medication, improving clinical recommendations, and changing labeling information. The PADER submission includes information on any ongoing trials or new clinical research, drug interactions, and any identified changes in drug effectiveness across various patient populations in addition to ADR analysis. Submitting PADERs on time and accurately guarantees regulatory compliance, improves patient safety, and offers vital information that helps assure the best possible administration of medications in practical situations. To safeguard the public's health, this paper emphasizes the significance of ongoing medication monitoring, open communication with regulatory agencies, and evidence-based decision-making.

Keywords: Pharmacovigilance, Risk-benefit, Safety, Adverse drug Reaction, Drug Interaction, Submission, Compliance.

1. Introduction

1.1 Periodic Adverse Drug Experience Report (PADER):

To ensure the safety and effectiveness of pharmaceuticals, pharmacovigilance relies heavily on Periodic Adverse Drug Experience Reports (PADERs). Pharmaceutical companies must submit PADERs, which include information on adverse drug experiences and lack-of-efficacy reports, to regulatory bodies regularly after receiving clearance for their marketing authorization.

The US Food and Drug Administration (FDA) mandates PADERs to guarantee ongoing monitoring of a drug's safety and effectiveness throughout of its life cycle. Finding, assessing, and managing possible safety signals and adverse drug experiences related to a certain medication is the main goal of PADER. For the FDA to take the proper action—such as revising labelling information, issuing safety warnings, and, in certain situations, removing the product from the market—these reports are designed to monitor both known and emerging safety problems.

1.2 Development of PADER:

The PADER system was codified in the 1990s as part of the FDA's continuous efforts to improve medication safety. It provided a methodical approach to tracking long-term medication safety by requiring pharmaceutical companies to produce reports regularly that summarized adverse events linked to their medicines.

1.3 Purpose of PADER:

Drug Safety Surveillance: - A Periodic Adverse Drug Experience Report's (PADER) main goal is to guarantee drug safety by gathering, assessing, and disseminating pertinent data about adverse drug experiences. pharmaceutical product is constantly checked for possible safety issues throughout its whole lifecycle after it has been authorized for sale. This post-marketing surveillance procedure is essential for spotting hazards that were previously unknown

or any changes to the drug's benefit-risk balance. Pharmaceutical firms and regulatory bodies obtain vital information on a drug's safety through the filing of PADERs, which may lead to additional research or modifications to prescribing practices to reduce any risks

Regulatory Compliance: - Regulatory agencies like the U.S. Food and Drug Administration (FDA) mandate that businesses submit PADERs regularly. These reports are used as a tool to guarantee ongoing adherence to the FDA's post-marketing regulations in addition to validating the data gathered during clinical studies. The foremost common symptoms are:

PADER contributions include several components, such as:

- A list of all adverse medication experiences that happened during the reporting period; modifications to the product's label or indications;
- An assessment of the medication's benefit-risk ratio given fresh safety data

2. Material and Methods

2.1 Component of PADER

The primary elements of a PADER—quantitative data, a narrative summary and analysis, and individual case reports.

Quantitative Data –

It shows the type and frequency of these occurrences, broken down by the unpleasant reaction term or terms. The reader can more easily understand the drug's overall safety profile during the reporting interval thanks to this part. To facilitate simple comprehension, the data in the tables should be arranged methodically and presented in an understandable manner. To guarantee proper evaluation of the data collected during the reporting period, the endpoint for the data collecting process—also known as the Data Lock Point—must be established.

Narrative Summary and Analysis

The material provided throughout the reporting period has to be analysed and narratively summarized.

A. The number of first bad experience reports that were not within 15 days, the number of follow-up reports that were not within 15 days, and the duration of the periodic report.

B. A list of the 15-day reports that were turned in during the reporting period, listed in line. The manufacturer report number, adverse experience term or terms, and the date the 15-day report was delivered or submitted to the FDA should all be included in this line-listing.

C. A summary tabulation of all adverse experience terms and counts of occurrences submitted during the reporting period, broken down by bodily system (e.g., cardiovascular, central nervous system, endocrine, renal). The data ought to be extracted from.

D. A summary of adverse experience reports that included the medication or biological product as one of the suspect products but were filed under another applicant-held NDA, ANDA, or BLA.

E. A detailed account of the clinical importance of the for reports that are submitted within 15 days of the reporting period.

Narrative discussion of actions taken:

Any labeling modifications and studies started since the last periodic report must be included in a narrative overview of the measures taken. This section ought to contain:

- A copy of the most recent product labeling in the US.
- A summary of all labeling modifications made over the reporting period.
- A list of studies that have been started.
- A synopsis of significant international regulatory actions (e.g., new warnings, limitations in the product's indications and use).
- Any notification of new safety information (such as a letter addressed to the doctor)
- FDA Form 3500As, VAERS forms, E2B forms, and SRP Acknowledgment forms must be listed in an index line. Each FDA Form 3500A, VAERS, or SRP Acknowledgment form that is submitted should have the following line listing:
- Manufacturer report number;
- Adverse experience term or terms;
- FDA Form 3500A, VAERS, or SRP Acknowledgment page number as included in the periodic report. When a product contact is reported as an unfavorable experience, the interacting products are identified.

- Only domestic spontaneous cases require the provision of FDA Form 3500As, VAERS forms, or SRP Acknowledgment forms.
- Expected and serious Unexpected and nonserious Expected and not serious
- This section should cover adverse experiences resulting from a lack of impact, or a failure to generate the anticipated pharmacologic activity.

Individual Case Reports:

Individual Case Safety Reports (ICSRs), which are comprehensive accounts of specific adverse drug experiences, are included in the final PADER subsection. These case reports provide a thorough examination of every incident, including pertinent details on adverse reactions, drug exposure, patient demographics, and medical histories. The case reports are a useful tool for comprehending the hazards associated with drugs and for spotting any warning signs of new safety issues. A PADER offers a comprehensive understanding of a drug's safety profile throughout its post-marketing lifecycle by combining these three essential elements: quantitative data, narrative summary and analysis, and individual case reports. This aids in the continuous monitoring and management of pharmaceutical products.

- Requirements for a valid ICSR According to ICH E2B, the bare minimum of data required for a legitimate report is:
- One response or incident, one identifying patient, one identifiable reporter, and one suspected drug

2.2 Timeline of PADER Submission

- PADER: Within 30 days following the end of the quarter, each quarterly report must be sent to the PV authority. The first quarter starts on the day the application is approved. Annual reports must be submitted to the PV authority within 60 days of the end of the year.
- In case of Annual reports and subsequent reports, submission to PV Authority shall be done within 60 days to close of that period.

2.3 Format of PADER

Authoring PADER shall involve drafting two different documents:

- Cover Letter
- PADER

Cover Letter of PADER

The PADER report accompanies a cover letter which includes essential information about a PADER. Following information shall be covered under a PADER cover letter:

- Product details along with ANDA/NDA number
- MAH details
- Reporting period: MMM DD, YYYY to MMM DD, YYYY
- Revision date of up-to-date prescribing information
- Summary of submissions during reporting period of current PADER.

PADER Submission Number	Reporting period	Number of 15- Day Reports	Number of non15-Day Repor
Xth Quarterly/Annual	MMM DDD, YYYY to MMM DD, YYYY	Number of cases	Number of cases

Contents of PADER

Each page of the periodic report shall be numbered and shall include the name of the product, ANDA/NDA number and reporting period in header.

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15-Day alert reports

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Narrative summary and clinical significance

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Appendix 5: Index listing of serious labeled and non-serious reports

Appendix 6: U.S. Labeling

3. SUBMISSION OF PADER

Reporting to the US-FDA electronically

For the purpose of receiving electronic regulatory submissions, the FDA has an agency-wide solution called the Electronic Submissions Gateway (ESG). The FDA ESG makes it possible to submit premarket and post-market regulatory data securely for evaluation. Information sent electronically to the USFDA is transmitted mostly through the FDA ESG. The FDA ESG serves as a channel for submissions to reach the appropriate FDA Center or Office in that regard, as described below (though not exclusively):

- Center for Biologics Evaluation and Research (CBER)
- Center for Drug Evaluation and Research (CDER)
- Center for Devices and Radiological Health (CDRH)
- Adverse Event Reporting System (AERS)
- Center for Veterinary Medicine (CVM)
- Office of the Commissioner (OC)
- Center for Tobacco Products
- The overall purpose of the FDA ESG is to provide a centralized, agency-wide communications point for securely receiving electronic regulatory submissions.

Registration with US-FDA ESG

•Before gaining access to the system, each user must register with the US-FDA ESG.

•Registration instructions are available on the US-FDA website.

• The Line Manager must notify US-FDA ESG that the account of a designated user must be retired from the US-FDA ESG system with a justification in order to remove the user's access rights. The user's access role will thereafter be removed by US-FDA ESG. Communications pertaining to the deactivation of a user account must be kept on the shared drive.

PADER submission using FDA ESG

• The PADER's author, the aggregate report group leader or designee, will create an eCTD file from Knowledge Net and send it to the submission team for submission to the US FDA.

• The submission person or online trader user must take the steps listed below. PADER's submission to the US FDA.

Login onto FDA ESG webpag

⇓

Click on send document menu item.

⇓

On the send document page, select the appropriate FDA centre.

⇓

As per the selected FDA centre, the submission type drop-down box Shall be populated with correct submission types.

⇓

User shall select the signing certificate for submission and enter password

⇓

After clicking the “send” button, PADER Shall be sent to US-FDA

Acknowledgement of submitted PADER

• The US-FDA's official center will acknowledge receipt of the submission document, and all acknowledgements will be kept electronically. The user who submitted the PADER should check their acknowledgement on the same day or the following business day after the PADER submission date. The submitting user will share the acknowledgement with the Aggregate Report Team after receiving acknowledgements for the submitted PADER., Generation of Periodic Adverse Drug Experience Reports, must be followed for ongoing tracking of submitted PADERs and recognition.
• Should the authority provide a negative acknowledgement or any feedback, the submission team will resubmit the PADER and take the appropriate steps.

Actions to take in the event of an electronic transmission error in FDA ESG

If PADERs cannot be electronically transmitted to the US-FDA, the data must be reported to the US-FDA in physical format (CD burned) and sent by courier to the FDA at the address below. The aggregate report team or designee is responsible for tracking the data. Generation of Periodic Adverse Drug Experience Reports, the submitted PADER will be tracked further.

Central Document room (CDR)

FDA/Center for Drug Evaluation and Research (CDER)

5901-B Ammendale Road

Beltsville, MD 20705-1266.

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