

REGULATORY ASPECTS OF SAFETY REPORT IN PHARMACEUTICALS

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ABSTRACT

In pharmaceutical industry it is essential to evaluate safety profile of pharmaceutical products during drug development and after marketing authorization. Regulatory agencies are very stringent to give marketing authorization of investigational drug for public health. That's why regulatory agencies implement new rules for safety report. Safety report provides concise information on safety of drug. In pharmaceutical industry there are two types of safety report, Expedited safety report and aggregated safety reports. ICH provides a harmonized format for safety report to regulatory agencies that includes Expedited safety report for preclinical and post marketing safety studies, Periodic benefit and risk evaluation report (PBRER) aggregated report for

marketing authorized drug and development safety update report (DSUR) aggregated report for drugs under clinical trial.

KEYWORDS: Safety Report, Expedited, Aggregated, DSUR, PBRER.

INTRODUCTION^[1-7]

In 2008 U.S. Food and Drug Administration sentinel initiate define safety as “Using medical product brings benefit and risks. Although marketed medical product are required by federal law to be safe for their intended use”.

Safety report presents a concise, comprehensive and critical analysis of emerging new safety information on risk and efficacy of medicinal products. Numerous steps involve in safety

report formation includes intake of adverse drug reaction, case processing, data retrieval, data analysis and medical review and risk assessment. Clinical trial safety report aim is to detect subject safety information. There is clinical trial protocol which describes the method for detecting adverse drug reaction and responsibility to investigator and sponsor report adverse drug reaction. Post marketing safety report includes information from postmarketing study. It is part of promoting and ensuring safety in patient from untoward adverse drug reactions. Main aim of post marketing study is ensure newly launched medicine product achieves higher standard of safety. Pre marketing clinical trial have limitation as short duration of exposure, restricted data from limited number of group and narrow indication so limited information available for predicting safety profile of drug. Post marketing safety study includes Pharmacoepidemiology Study, Registries and Survey to gather information for Safety report formation.

OBJECTIVES OF SAFETY REPORT

- Summarizing relevant new safety information that could have an impact on the benefit-risk profile of the medicinal product
- Examine whether the information obtained by MAH during the reporting interval is accordance with previous knowledge of the medicinal product's benefit and risk profile.
- Where important new safety information has emerged, conducted an integrated benefit-risk evaluation for approved indication
- To improve public health and safety
- In clinical trial detect subject safety issues
- Provides update on status of Clinical trial
- Examine change in product safety profile
- Describes new safety issues which have impact on safety profile of drug.

Events reported in Safety Report

- Serious Adverse Drug Reaction: It includes
 - Death
 - Significant or persistent disability/incapacity
 - Congenital anomaly/birth defect
- Unexpected Adverse Drug Reaction
- Lack of Efficacy

- Over Dose
- Minimum Data Elements Required

Minimum criteria for safety reporting are as:

It is recommended that as much as information possible is collected at the time of initial reporting.

However minimum data required for reporting are as

- Identification of reporter
- Identification of patient
- Adverse drug experience
- Suspected product

Safety Report Submitted By

- Manufacturer.
- Applicant who hold NDA or ANDA.
- Any person whose name written on label as packer or distributor.
- Health professional.
- Patient

In Pharmaceutical industry there are two type of safety report

- a) Expedited Safety Report
- b) Aggregated Safety Report.

2. Expedited Safety Report^[8-9]

In expedited report a single cases of serious and unexpected adverse reaction are reported. Expedited report also called as alert report, it is submitted within a 15 day of adverse event occurrences.

The sources of information always are specified. Information obtained by a sponsor or manufacture on serious and unexpected reaction from any source should be submitted on expedited basis to appropriate regulatory authorities.

There are two type of expedited safety report Clinical trial safety report and post marketing expedited safety report.

Events Reported in Expedited Safety Report

Add all type of adverse event of drug which is serious and unexpected from any type of clinical trial study and any other unsolicited sources.

Any types of information on drug which affect benefit-risk profile of drug are submitted as expedited safety report to agency.

Report Responsibility

In clinical trial sponsor and manufacturer responsibility to submit safety report and for licensed marketed product manufacturer responsible for reporting.

Reporting Time

For clinical trial and post marketing safety report adverse event should be reported within 15 calendar days. Time frames for other types of serious reports vary among countries, depending on source, expectedness and outcome.

For clinical trial fatal adverse event or life-threatening event should be reported as soon as possible but not later than 7 calendar days.

Information Submitted with Expedited Safety Report.**Patient Details**

- Initials
- Other relevant identifier (patient number, for example)
- Gender
- Age
- Category (e.g., adolescent, adult, elderly)
- Date of birth
- Concomitant conditions
- Medical history
- Relevant family history

Suspected Medicinal Product

- Brand name as reported
- International Non-Proprietary Name (INN)
- Batch/lot number

- Indication(s) for which suspect medicinal product was prescribed or tested
- Dosage form and strength.
- Daily dose (specify units - e.g., mg, ml, mg/kg) and regimen
- Route of administration
- Starting date and time
- Stopping date and time, or duration of treatment

Other Treatments: The same information as in item 2 should be provided for the following:

- Concomitant medicinal products
- Relevant medical devices

Details (all available) of Adverse Drug Reaction

- Full description of reaction(s), including body site and severity
- The criterion (or criteria) for regarding the report as serious
- Description of the reported signs and symptoms
- Specific diagnosis for the reaction
- Onset date (and time) of reaction
- Stop date (and time) or duration of reaction
- Relevant diagnostic test results and laboratory data
- Setting (e.g., hospital, out-patient clinic, home, nursing home)
- Outcome (recovery and any sequel)
- For a fatal outcome, stated cause of death
- Relevant autopsy or post-mortem findings
- Relatedness of product to reaction(s)/event(s)

Details on Reporter of an ADR

- Name
- Mailing address
- Electronic mail address
- Telephone and/or facsimile number
- Reporter type (consumer, healthcare professional, etc.)
- Profession (specialty)

Administrative and MAH Details

- Source of report (spontaneous, epidemiological study, patient survey, literature, etc.)
- Date the event report was first received by manufacturer/company Country in which the event occurred.
- Type (initial or follow-up) and sequence (first, second, etc.) of case information reported to authorities.
- Name and address of MAH
- Name, address, electronic mail address, telephone number, and facsimile
- Number of contact person of MAH
- Identifying regulatory code or number for marketing authorization dossier
- Company/manufacturer's identification number for the case (the same number should be used for the initial and follow-up reports on the same case).

Aggregated Safety Update Reports^[4-5]

It is also known as periodic report. It involves a compilation of safety data for drug over a prolong period of time. It provides broader view of the safety profile of drug.

Type of Safety aggregated safety update report includes

- Clinical trial aggregated safety update report
- Post marketing aggregated safety report.

Clinical Trial Aggregated Safety Report

Every investigational drug undergoes clinical trial for prove safety and efficacy. Researcher is required to submit safety information of drug periodically to agency. However, because different countries' regulatory authorities require different content and use different formats and schedules, the International Conference on Harmonization (ICH) has developed guidelines for the E2F Development Safety Update Report (DSUR).

Rational for DSUR

- Current clinical trial aggregated Safety report is not comprehensive
- Give Benefit of Harmonization.

SCOPE of DSUR

- Clinical trials using an investigational drug (both ongoing and completed)

- Clinical trials conducted using marketed drugs in approved indications (i.e., therapeutic use trials (Phase 4).
- Therapeutic use of an investigational drug
- Clinical trials conducted to support changes in the manufacturing process of medicinal products
- Summarize current understanding and management of known and potential safety risk to expose patient.

Periodicity and data lock point

Development International Birth Date (DIBD) is used to determine the start of annual safety report. DIBD is first date of authorization of clinical trial in any countries. DSUR is submitted as specified by national and regional law. DSUR submitted to all regulatory agencies no later than 60 calendar days the DSUR data lock point.

Recipient of DSUR

- Regulatory authority
- IEC or IRB

Format and content of DSUR

- A. Title page
- B. Executive Summary
- C. Worldwide Marketing Approval Statu
- D. Actions Taken in the Reporting Period for Safety Reasons
- E. Changes to Reference Safety Information
- F. Inventory of Clinical Trials Ongoing and Completed during the Reporting Period
- G. Estimated Cumulative Exposure
- H. Data in Line Listings and Summary Tabulations
- I. Significant Findings from Clinical Trials during the Reporting Period
- J. Safety Findings from Non-Interventional Studies
- K. Other Clinical Trial/Study Safety Information
- L. Safety Findings from Marketing Experience
- M. Non-clinical Data
- N. Literature
- O. Other DSUR

- P. Lack of Efficacy
- Q. Region-Specific Information
- R. Late-Breaking Information
- S. Overall Safety Assessment
- T. Summary of Important Risks
- U. Conclusions
- V. Appendices of DSUR

Post Marketing Aggregated Safety Report

Post marketing aggregated safety report is also known as Periodic safety update report is document that allows comprehensive assessment of safety profile of marketed drug during reporting periods. It important source of safety signal that provides information on benefit risk profile evaluation of drug. ICH provide a common format for periodic safety report in “Periodic- Benefit Risk Evaluation Report” E2C (R2) in December 2012. Objective of guideline is to provide harmonized format for post marketing periodic safety report in different regions.

Rational for PBRER

Harmonize the periodic safety report regulation

Scope of PBRER

PBRER provided for marketing drug products

Periodicity and Data lock point

Periodic safety report submitted at following interval

Immediately upon request

Every six months for new product up to 2 year

Annually for marketed after 2 year

There after every 3 year

The report submission period is decided based on international birth date and data lock point. The date of first marketing authorization is international birth date and data lock point is cutoff date to include data in periodic safety report.

Responsibility of periodic safety report submission

Marketing authorization holder is responsible for periodic safety report submission.

Format and Content of PBRER

- A. Title Page
- B. Executive Summary
- C. Introduction
- D. Worldwide Marketing Approval Status
- E. Actions Taken in the Reporting Interval for Safety Reasons
- F. Changes to Reference Safety Information
- G. Estimated Exposure and Use Patterns
- H. Data in Summary Tabulations
- I. Summaries of Significant Safety Findings from Clinical Trials during the Reporting Interval
- J. Finding from Non-Interventional Study
- K. Information from Other Clinical Trials and Sources
- L. Non-Clinical Data
- M. Literature
- N. Other Periodic Reports
- O. Lack of Efficacy in Controlled Clinical Trials
- P. Late-Breaking Information
- Q. Overview of Signals: New, Ongoing, or Closed
- R. Signal and Risk Evaluation
- S. Benefit Evaluation
- T. Integrated Benefit-Risk Analysis for Approved Indications
- U. Conclusions and Actions
- V. Appendices to the PBRER

Modular Approach Of Dsur And Pbrer^[4]

Aim of guideline is to develop flexibility in use of one section of safety report in other safety report. For example, content of DSUR section is used to PBRER report section for same drug if data lock point is same for both reports.

Advantage

- Maximize the utility of module in different regulatory authority
- Promote consistency
- Decrease unnecessary duplication
- Facilitate utilization of existing module

Table 1: List of PBER Sections that may be shared with other documents.

Section	Shared with other document
Introduction	
Worldwide Marketing Approval Status	DSUR
Actions Taken in the Reporting Interval for Safety Reasons	Common in PBRER and DSUR
Cumulative Subject Exposure in Clinical Trials	PBRER and DSUR
Cumulative and Interval Patient Exposure from Marketing Experience	Only cumulative used in DSUR and PBERE
Cumulative Summary Tabulations of Serious Adverse Events from Clinical Trials	DSUR
Completed Clinical Trials	DSUR
Ongoing Clinical Trials	DSUR
Long-Term Follow-up	DSUR
Other Therapeutic Use of Medicinal Product	DSUR
New Safety Data Related to Combination Therapies	DSUR
Findings from Non-Interventional Studies	DSUR
information from Other Clinical Trials and Sources	DSUR
Non-Clinical Data	DSUR
Literature	DSUR
Lack of Efficacy in Controlled Clinical Trials	DSUR
Late-Breaking Information	DSUR if report cover same submission date
Conclusions and Actions	DSUR

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REFERENCES

1. J. Rick *et al.*, "Clinical Trial in New Drug Development", the journal of Clinical Hypertension, 2013; 15(5): 306-309.

- <http://onlinelibrary.wiley.com/doi/10.1111/jch.12085/full>.
2. European Medicines Agency, “Guideline on good Pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1)”, 2013.
 3. European Medicines Agency, “Post authorization safety study”,
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000377.jsp&mid=WC0b01ac058066e979.
 4. International Conference on Harmonisation, “Periodic Benefit– Risk Evaluation Report (PBRER) E2C (R2)”, December 2012.
 5. International Conference on Harmonisation, “Development Safety Update Report E2F”, August 2010.
 6. Aron Shapiro, “The Importance of Adverse Event Reporting”,
http://retinatoday.com/pdfs/1013RT_Clinical%20trials.pdf.
 7. Drug Safety Research Unit, “Why are post marketing study important?”,
<http://www.dsru.org/news/post-marketing-studies-important/>.
 8. International Conference on Harmonisation, “Clinical Trial Safety Data Management: Definition and Standard for Expedited Reporting E2A” October, 1994.
 9. International Conference on Harmonisation, “Post Approval Safety Data Management: definitions and Standard for Expedited Reporting E2D”, October 1994.