WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 7, 441-457. Review Article ISSN 2277– 7105

STUDY ON REGULATORY REQUIREMENTS OF SAFETY REPORT IN US, EUROPE, JAPAN AND INDIA

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Article Received on
03 February 2018,

Revised on 24 Feb. 2018,
Accepted on 16 March 2018,

DOI: 10.20959/wjpr20187-11558

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ABSTRACT

It is essential to evaluate the safety profile of pharmaceutical products during drug development and after marketing authorization. That's why regulatory agencies implement new rules to submit safety reports. Safety report provides concise information on safety profile of drug. In pharmaceutical industry there are two type of safety report expedited safety report and aggregated safety repots. US, Europe, Japan and India required both type safety reports. US required safety report submission through electronic format by use of FAERs and VAERs reporting system. EMA required electronic report by use of Eudravigilance system. Japan requires safety report by use adverse event reporting system and data store in PMDA data base. India requires electronic report submitted by Pharmacovigilance programme of India. US, Europe and Japan required both type safety reports as per ICH harmonized safety report format. India required harmonized ICH format only for Post Marketing Aggregated Safety Report.

KEYWORDS: Safety, Expedited, Aggregated, Adverse.

1. INTRODUCTION[1-5]

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.

Safety report submitted for

- Death
- Life threatening adverse event
- Initial inpatient hospitalization and prolongation of hospitalization
- Birth defect

There are two type safety reports

a) Expedited Safety Report
b) Aggregated Safety Report

Expedited Safety Report

It is called as so alert report; this type report is submitted within a 15 days of incidence.

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

Aggregated Safety Report

It is also called as periodic safety report. This type report is submitted periodically. Periodicity is depending upon a regional rule. Two type aggregated safety report clinical trial aggregated safety report and post marketing aggregated safety report.

ICH guideline for safety report

ICH E2A: Clinical safety data management: definitions and standards for expedited reporting.

ICH E2D: Post approval safety data management: definitions and standards for expedited reporting.

ICH E2F: Development safety update report.

ICH E2C (R2): Periodic Benefit and Risk Evaluation Report.

2. Safety Report Regulation in US[6]

In US pharmaceutical products are regulated by USFDA (United States Food and Drug Administration). FDA's Center for Drug Evaluation and Research (CDER) and Center for Biological Evaluation and Research (CBER) regulate safety report I FDA.

2.1 Provision of Safety Report Regulation in US[6]

Table No. 1: FDA Codes for Safety Reports.

Code	Regulation
21 CFR 312.32	Require Pre marketing expedited safety report for investigational human drug and biological
21 CFR 312.64 (b)	Describes requirement for safety report to sponsor by investigator
21 CFR 320.31 (d) (3)	Describes Bioavailability and bioequivalence requirement for IND safety report.
21 CFR 310.305	Describes the reporting requirement for prescription marketing drug without marketing approval.
21 CFR 314.80	Post marketing safety report requirements for human drug with marketing approval
21 CFR 314.98	Describes regulation for post marketing safety report for approved ANDA
21 CFR 600.80	Safety report regulation for biological products.
21 CFR 803.21	Medical Device Safety Reporting

2.2 Types of Safety Report in USFDA[6]

In FDA there are two type safety reports

- Expedited Safety Report: Expedited safety reports are also called as so alert report.
  - ➢ Clinical trial expedited safety reports
  - ➢ Post marketing expedited safety reports
- Aggregated Safety Reports: Submitted periodically.
  - ➢ Clinical trial aggregated safety report
  - ➢ Post marketing aggregated safety report

2.3 Time Period for Expedited Safety Report[6]

Table No.2: Time Period for Expedited Safety Report.

Type of Safety Report	Time Period
Suspected and unexpected Adverse drug reaction	Within 15 Calendar days
Unexpected adverse drug reaction from unknown outcome	Within 45 Calendar days
Unexpected fatal or life threatening adverse drug reaction	Within 7 Calendar days

2.4 Reporting Procedure [7-11]

In FDA two type reporting procedure

- Paper Submission
- Electronic Submission

2.4.1 Safety Report in Paper Format

In FDA safety report submitted in FDA form 3500A for adverse event occurred in country. For foreign report FDA accepts report in form CIOMS I form (Council for international organization of medical science) and vaccines adverse event report use FDA vaccines adverse event reporting form.

2.4.2 Electronic Reporting of Expedited Safety Report

FDA accepts electronic submission of individual case safety report since 2000. In FDA two type of electronically safety report mandatory safety report and voluntary safety report electronically.

2.4.2.1 For mandatory safety report

FDA provides a two option for electronic transmission of individual case safety report to FDA Adverse event reporting system.

- Database to database transmission (E2B)
- Safety reporting portal

2.4.2.1.1 Database to database transmission (E2B) or Submission through ESG

This method provides a direct transmission of the information from firm to FDA database through ESG (Electronic Submission Gateway).

ESG is central transmission point in FDA database. In this method

- ICSR must be in xml format
- Attachment must be in pdf format

2.4.2.1.2 Submission through Safety Report portal

On May 24, 2010, the Food and Drug Administration and the National Institutes of Health launched a new website. This provides submission of safety report for premarket and postmarked. Applicant or non-applicant who has not capability submits safety reports by database to database system are submitting a safety report by a safety reporting portal.

2.4.2.2 Voluntary Reporting

Voluntary reporting form includes a form 3500 and form 3500 B for health care professional and consumer respectively.

Voluntary Reports Submitted By

- Health Professional
- Consumer/Patients

2.5 Aggregated Safety Update Report[7-8,12-13]

FDA requires two type aggregated safety report Development Safety Update Report for Drug (DSUR) for Clinical Trial and Periodic Benefit and Risk Evaluation Report (PBRER) for marketing approval drug.

2.5.1 Clinical Trial Aggregated Safety Update Report

FDA requires IND annual Safety Update report under 21 CFR 312.33. IND application sponsor required to submit report within 60 days of anniversary date of application went in effect.

IND annual Safety report is submitted FDA includes information on All Serious Adverse Event occurred in clinical Trial.

Periodicity and Data Lock Point

The Development International Birth Date (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.

Data lock point is last date of one year reporting period. The report submitted within 60 days of data lock points.

Reference Safety Information

Investigational brochure is used as reference safety information. If there is investigational brochure is not required by law or regulation applicable regional and national product label is used.

FDA adopts Guidance for Industry: E2F Development Safety Update Report (DSUR) which describes common standard for reporting.

Format of Clinical Trial Aggregated Safety Report

FDA requires Clinical trial aggregated safety report in ICH E2F Development safety updater report format.

2.5.2 Post Marketing Aggregated Safety Report

FDA requires Post marketing aggregated safety report under 21 CFR 314.80 (C) (2) and 21 CFR 600.80 (C) (2) for human marketed and biological products respectively.

Periodicity and Data Lock Point

Periodicity of submission depends on data lock point and International birth date. IBD is first date of marketing approval and DLP is date designed s cutoff date of report. Applicant can submit report every 6 months for 2 years after approval, annually for next 3 years and then every 5 years thereafter.

Time interval between data locks point and submission

- PBRERs covering intervals of 6 or 12 months: within 70 calendar days
- PBRERs covering intervals in excess of 12 months: within 90 calendar days
- PBRER requested by regulatory authority: 90 calendar days, unless otherwise specified in the ad hoc request.

Post Marketing Safety Update Report format

FDA requires Post Marketing Aggregated safety report in ICH E2C(R2) format.

Submitting PBRER

Submission of Safety report to CDER and CBER.

3. EMA Safety Report Regulation

EMA's Committee of Medical Products for Human Use (CHMP) and Pharmacovigilance Risk Assessment Committee (PRAC) regulate safety reports submission process and assessment.

3.1 Provision for Safety Report in EMA[14-19]

Table No. 3: Provision for Safety Report in EMA.

Code	Article	Provision
Directive 2001/20/EC	18	Presentation of Adverse event report in Clinical Trial
EC regulation 536/2014	40-42	Reporting Responsibility and electronic reporting for clinical trial safety report
	43	Clinical Trial Annual Safety Report by Sponsor to Agency
Regulation EC No 726/2004	28a	Reporting adverse event in Eudravigilance database
Directive 2001/83/EC	107	Record and Reporting of Suspected Adverse Drug Experience for Marketed Drug.
	107b	Periodic Safety Report for Marketed Products

3.2 Type of Safety Report in EMA In EMA, there are two type safety reports Expedited Safety Reports

- Clinical Trial Expedited Safety Report.
- Post Marketing Expedited Safety Report Aggregated Safety Reports.
- Clinical Trial Annual safety report.
- Post marketing Aggregated Safety Report.

3.3 Time Periods for Expedited Safety Reports[18-19]

Clinical Trial and Post Marketing

Investigator should report all serious adverse events to sponsor which are not listed in investigational brochure or study protocol and post marketing according to Article 107(3) and 107a (4) of Directive 2001/83/EC.

Table No. 4: Time period for clinical trial safety report.

Type of Safety Report	Report to	Time Period
suspected serious unexpected adverse reactions that are fatal or life threatening	competent authorities in all the Member States Ethics Committee	7 Days
Suspected serious unexpected adverse reactions	competent authorities in all the Member States Ethics Committee	15 Days

3.4 Reporting Procedures[17-18]

EMA adopt ICH E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting for safety report in June 1995 and ICH E2D Post Approval Safety Data Management which provide harmonized format for expedited safety report. EMA requires safety report in two formats as paper format and electronic format.

3.4.1 Paper Format

EMA accepts CIOMS-I form for safety reporting for Clinical trial and Post marketing safety reports.

3.4.2 Electronic Format

Eudravigilance is a data processing network and management system for reporting and evaluating suspected adverse reactions during the development and following the marketing authorization of medicinal products in the EEA. The first operating version was launched in December 2001.

3.5 Aggregated Safety Update Report[19-20]

EMA requires two type of periodic safety report Clinical trial periodic safety report and Post marketing periodic safety update report Clinical Trial Aggregated Safety Report.

As per article 43 of EU Regulation 536/2014, EU Directive 2011/C 172/01 and Article 17(2) of Directive 2001/20/EC Sponsor of clinical trial report annual safety report to agency.

Reporting Format

FDA adopts Guidance for Industry: E2F Development Safety Update Report (DSUR) which describes common standard for reporting.

Periodicity and Data Lock Point

The Development International Birth Date (DIBD) is used to determine the start of the annual period for the DSUR. This date is the sponsor's first authorization to conduct a clinical trial in any country worldwide. The start of the annual period for the DSUR is the month and date of the DIBD.

Data lock point is last date of one year reporting period. The report submitted within 60 days of data lock points. If the trial is short term (i.e. less than 6months), the Annual Safety Report is due within 90 days of the end of the trial, together with the notification of end of trial.

Reference Safety Information

Investigational brochure is used as reference safety information. If the IMP has a marketing authorization in several Member States concerned with different Summary of product characteristics (SmPC), the sponsor should select the most appropriate SmPC, with reference to subject safety.

3.5.1 Post Marketing Periodic Safety Update Report

EMA requires periodic safety update report as per European Commission Directive regulation EC No 726/2004 article 25 and Article 107b of Directive 2001/83/EC marketing authorizer holder of drug product submit periodic safety update report to agency.

Periodicity and Data Lock Point

Date of submission of safety report depend upon the date of marketing authorization date.

- If a medicinal product has been placed on the market, at least every 6 months during the first 2 years following the initial placing on the market, once a year for the following 2

years and at three-yearly intervals thereafter.

- As per the GVP module VII marketing authorization holder summit report within 70 days from data lock point for report interval up to 12 months. Within 90 days submit safety report if intervals exceed 12 months.

Format of Post Marketing Aggregated Safety Update Report

EMA requires a post marketing aggregated safety report as per ICH E2C (R2) Periodic benefits and risk evaluation report format.

4. Japan Safety Report Regulation

In Japan safety report for pharmaceutical are regulated by Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA).

4.1 Provision of Safety Report Regulation for Pharmaceuticals in Japan[21-23]

Table No 5: Describe Regulatory Codes for safety reports.

Provision	Code
Clinical trial safety report for drug	Article 273 (1) Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices
Clinical trial safety report for device used	Article 273 (3) Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices
Post marketing safety report for marketed drug	Article 68-10 (1) The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices
Post marketing safety report for marketed device	Article 68-24 (1) The Law on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical devices.
Post marketing Safety report for marketed pharmaceutical drug.	Article 228- 20 Paragraph 1, item 1 Enforcement Regulations of the Law on Securing Quality, Efficacy and
	Safety of Products including Pharmaceuticals and Medical Devices
Post marketing Safety report for marketed pharmaceutical device.	article 228-20, Paragraph 2, item 1 Enforcement Regulations of the Law on Securing Quality, Efficacy and Safety of Products including Pharmaceuticals and Medical Devices

4.2 Types of Safety Report in Japan[21]

There are two type safety reports

- Expedited Safety Report: Expedited safety reports are also called as so alert report.
  - ➢ Clinical trial expedited safety reports
  - ➢ Post marketing expedited safety reports
- Aggregated Safety Reports: Submitted periodically.
  - ➢ Clinical trial aggregated safety report
  - ➢ Post marketing aggregated safety report

4.3 Time Period for Expedited Safety Report Submission[21]

Clinical Trial and Post marketing

Table No.6: Time Period for Expedited Safety Report Submission

Type of Safety Report	Time
Death or Cause that result in death`	7 Days for Clinical Trial Product 15 Days for Post marketing Product
Serious Adverse Event	15 Days
Research reports about the drug concerned, which demonstrate that it does not have an approved indication in Japan and overseas.	30 Days

4.4 Reporting Procedure (24-25)

Japan accept safety report in

- ➢ Paper Report
- ➢ FD Report
- ➢ Electronic Submission

4.4.1 Paper format

- ICH E2B (R3) format is used for making paper safety report.
- Mandatory items are marked with “ɵ”.
- Seriousness criteria set in Paper report as

a. Results in Death
b. life-threatening
c. inpatient hospitalization
d. Results in persistent or significant disability/incapacity congenital anomaly/birth defect medically important event or reaction.

4.4.2 Electronic Format

Adverse drug reaction submitted within 15 days by FAX and other electronic safety database. At the end of 1999 establishment of "Drug Information System" which used for transmission of information on safety related aspect of pharmaceutical products.

Electronic safety reports submitted by Health care professionals, Marketing authorization holders and Patients, Facility provides by agency for electronic transmission includes FAX and Data base transmission.

Sender of safety report send XML file format.

4.5 Aggregated Safety Update Report[22-24]

Japan requires two type aggregated safety report Development Safety Update Report for Drug (DSUR) for Clinical Trial and Periodic Benefit and Risk Evaluation Report (PBRER) for marketing approval drug.

4.5.1 Clinical Trial Aggregated Safety Update Report

As per Notification No. 1228-(1) of the Evaluation and Licensing Division, PFSB Marketing authorization holder are requiring to submit periodically a Clinical trial aggregated safety report to agency.

Submission format

Marketing authorization holder is submitting a report in Development Safety Update Report ICH E2F format.

Reference Safety Information: Investigational brochure is used as reference safety information.

4.5.2 Post marketing Aggregated Safety Update Report

Agency requires a Periodic safety update report as per Pharmaceutical affairs law in April 1997.

Periodicity and Data Lock Point

As per Article 228-20, paragraph 1, item 3 of the Enforcement Ordinance initial date of reporting is fist approval date of drug in Japan or foreign countries which is refers as International birth date.

As per Article 63, paragraph 1 of the Enforcement Ordinance report is made within a 70 days from the expiration date of data lock point.

A periodic report should submit every six months for two years after date of approval and after two year of approval submit every year.

Format of Post Marketing Aggregated Safety Report

Japan requires post marketing aggregated safety report in ICH E2C (R2) Periodic benefit and risk evaluation report Format.

Submission of Report

Safety Information Division, the Office of Safety I, PMDA for Drug Product and for medicinal device Office of Safety II, Pharmaceuticals and Medical Devices Agency(PMDA).

5 India Safety Report Regulation Introduction

Central Drug Standard Control Organization (CDSCO) is the national regulatory body for Indian Pharmaceutical and medical devices. CDSCO is controlled and governed by Director General of health Service which comes under ministry of health and family welfare, Government of India. The central authority responsible for approval of new drugs, clinical trial in the country, laying down the standards for drug, control over the quality of imported drugs, coordination of the activities of state Drug Control Organization and providing expert advice with a view of bringing about the uniformity in the enforcement of the drugs and Cosmetics Act.

5.1 Provision of Safety Report Regulation in India[26]

Table No.7: Provision of Safety Report Regulation in India.

Code	Regulation
Schedule Y (2) (iii) of Drug and cosmetic act and rules	Report of Clinical trial adverse event report
Schedule Y (2) (9) of Drug and Cosmetic act and rule	Report of post marketing averse event
Schedule Y (4) of Drug and Cosmetic act and rule	Report of Post marketing Periodic adverse event report

5.2 Types of Safety Report in India[26]

- Expedited Safety Report: Expedited safety reports are also called as so alert report.
  - Clinical trial expedited safety reports
  - Post marketing expedited safety reports

- Aggregated Safety Reports: Submitted periodically.

➢ Post marketing aggregated safety report.

5.3 Time Period for Expedited Safety Report Submission[26-30]

Table No.8; Time Period for Expedited Safety Report Submission.

Type of Adverse event	Time
Serious adverse event occurred in clinical trial by Sponsor to licensing authority	Within 14 days of incident
Serious adverse event occurred by marketing authorization drug	Within 14 days of incident
Non serious adverse event by marketing authorized drug	Within 30 days of incident

5.4 Procedure[27-29]

5.4.1 Two type adverse event reporting system in India

- Paper format
- Electronic format

5.4.2 Clinical Trial safety reporting procedure

As per regulation all unexpected adverse drug reaction is reported to CDSCO within 14 days.

- Subject Detail
- Suspected Drug(s)
- Other Treatment(s)
- Details of Serious Adverse Event
- Outcome
- Details about the Investigator

Clinical trial adverse event report submits to The Drugs Controller General (India) Directorate General of Health Services Central Drugs Standard Control Organization FDA Bhawan, Kotla Road, New Delhi –110 002.

Processing of ICSR

As per office order of Indian Pharmacopoeia Commission adverse event of their pharmaceutical products to near ADRs monitoring Centres (AMC) under pharmacovigilance programme of India (PVPI) in E2B XML format.

Date of receipt

Marketing authorization holder should record date of receipt which used in Follow-up communication for adverse event report.

5.4.3 Post Marketing Safety Report

Marketing authorization holder can collect information about adverse drug reaction by solicited and unsolicited study.

Consumer and Health Care Adverse Drug Reaction Report

Healthcare professionals can fill the "Suspected Adverse Drug Reaction Reporting Form" and consumers reporting form is available for consumers and send it to nearest the Adverse Drug Reaction Monitoring Centre (AMC) or directly to the National Coordinating Centre (NCC). You can directly mail the form to pvpi@ipcindia.net or ipclab@vsnl.net.

Toll free helpline (1800-180-3024) number can also be used to directly report an ADR.

5.5 Post Marketing Aggregated Safety Update Report[26]

As per schedule Y of Drug and Cosmetic act 1940 and Rules 1945, Section (4) Post marketing surveillance (PMS) and ICH E2C (R2) required Periodic Safety Update report.

Periodicity

PSUR report submitted every six months for first 2 year of marketing authorization. After 2-year safety report is submitted annually to licensing authority.

Format of post marketing aggregated safety report submission

CDSCO requires post marketing periodic safety report in ICH E2C (R2) Periodic benefit and risk evaluation report format.

CONCLUSION

From study it concluded that US, Europe and Japan have strict regulation for submission of safety report. They make easy and decrease bias in submission of safety report from marketing authorization holder and health care professional by adopting harmonized safety report format presented by ICH and providing electronic safety reporting system. India required a harmonized format for post marketing aggregated safety report.

ACKNOWLEDGEMENT

The authors are thankful to Dr. K. Pundarikakshudu, Director of L. J. Institute of Pharmacy; Ahmedabad, India for providing all the facilities and encouragement to carry out the work and also thankful to Dr. Jignesh S. Shah for providing support and knowledge.

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