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REGULATORY REQUIREMENTS FOR ELECTRONIC SUBMISSION OF BA/BE ADVERSE EVENT REPORTS TO FAERS (FDA ADVERSE EVENTS REPORTING SYSTEM)

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ABSTRACT

Safety reports are crucial for various reasons, including death, life-threatening adverse events, inpatient hospitalization, and birth defects. In the US, the FDA regulates safety reports through regulations like 21 CFR 312.32, 21 CFR 314.80, and 21 CFR 803.21 The E2B(R3) standard, which is supported by the International Council for Harmonization (ICH), is currently the accepted format for electronic submission of post-marketing individual case safety reports (ICSRs) to the FDA. These submissions can be either expedited or non-expedited and include biological products regulated by CDER. On June 10, 2014, the FDA published a final regulation mandating that the industry file post-marketing safety reports electronically. There are two types of electronically submitted safety reports: mandatory safety reports and voluntary safety reports. The FDA has launched a new website for submitting safety reports for premarket and postmarked submissions. The FDA requires applicants for human drugs and biological products, as well as accountable personnel at businesses that have reporting duties, to adhere to certain guidelines to submit post-marketing ICSRs and attachments electronically via the Safety Reporting Portal (SRP). PSR submissions include During the reporting period, non-expedited ICSRs as well as a descriptive section were received. To Get in touch with faersesub@fda.hhs.gov to request an SRP account. An email notification of the account's

activation will be sent out within 7 to 10 business days. The FDA requires two types of aggregated safety reports: Development Safety Update Report for Drug (DSUR) for Clinical Trial and Periodic Benefit and Risk Evaluation Report (PBRER) for marketing approval drug.

Keyword: Safety reports, FDA, Electronic submissions, CDER, Safety reporting portal

INTRODUCTION

FDA 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". A safety report is a thorough examination of newly available safety data on pharmaceuticals, including risk assessment, adverse drug reactions, case processing, and data retrieval. Post-marketing safety reports make sure new goods meet stricter safety criteria, whereas clinical trial safety reports identify subject safety information. These papers discuss pre-marketing clinical trial restrictions such limited indications and brief exposure times **[1]**.

Safety report submitted for

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

There are two type safety reports

a) Expedited Safety Report

b) Aggregated Safety Report

Expedited Safety Report: This kind of report, known as an alert report, is filed within 15 days following the incident. Two types of accelerated safety reports exist. Post-marketing expedited safety report and expedited safety report for clinical trials.

Aggregated Safety Report: Periodic safety report is another name for it. This kind of report is sent in on a regular basis. Periodicity is determined by local laws. There are two types of aggregated safety reports: post-marketing and clinical trial aggregated safety reports.

ICH guideline for safety report

- **ICH E2A:** Standards and terminology for expedited reporting in clinical safety data management.
- **ICH E2D**: Standards and definitions for the handling of safety data after approval, allowing for quicker reporting.
- **ICH E2F:** Development safety update report.
- **ICH E2C (R2):** Periodic Benefit and Risk Evaluation Report **[2]**.

Safety Report Regulation in US

In the US, pharmaceutical products are regulated by the USFDA (United States Food and Drug Administration). The FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics

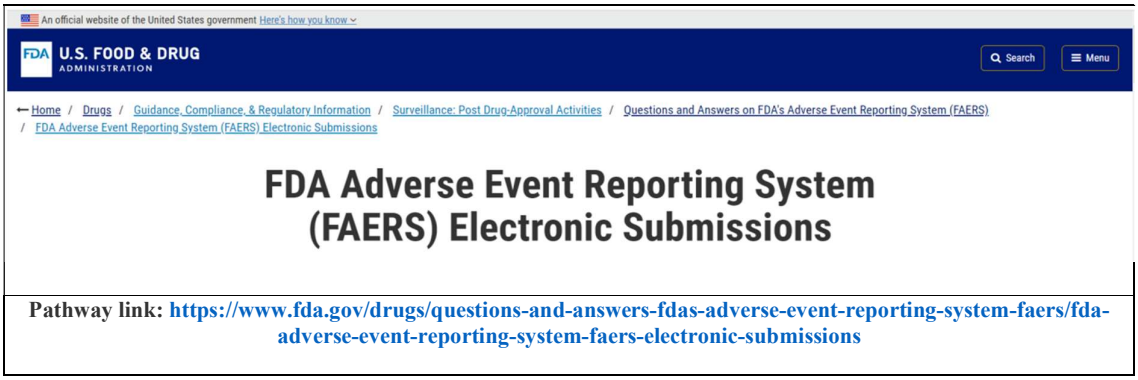
Evaluation and Research (CBER) oversee the regulation of safety reports **[3]**.

Provision of Safety Report Regulation in US [3]

Table 1: FDA Codes for Safety Reports

Code	Regulations
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

Electronic Submissions



Pathway link: https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions

Figure 1: shows the FAERS Pathway

After the International Council for Harmonization (ICH) approved and the FDA accepted the E2B(R3) standard, the FDA started accepting electronic submissions of post-marketing individual case safety reports (ICSRs). These submissions could be either expedited or non-expedited, and they would include biological products regulated by CDER.

The FDA has approved electronic individual case safety reports (ICSRs) in the ICH E2B(R3) standard for premarketing (IND study or IND-exempt BA/BE study). Companies using database-to-database transmission (E2B) to electronically transmit ICSRs must adhere to the following timeframes **[4]**.

Using the E2B standard, post-marketing safety reporting for human pharmaceutical and biological goods:

FDA implemented the E2B(R3) standard for electronic transmission of ICSRs.

In the interim when E2B(R3) is being transitioned to, FAERS submitters may continue to use E2B(R2) data standards. While getting ready to switch to the E2B(R3) standards, keep sending in post-marketing ICSRs in the E2B(R2) format. Once your business starts submitting in E2B(R3), you are unable to go back to earlier procedures or requirements. If you are using the Safety Reporting Portal (SRP) to report ICSRs, there is nothing you need to do. The FDA published a final regulation mandating the electronic reporting of post-marketing safety reports on June 10, 2014 **[4]**.

Objectives:

- To Provide an overview of the regulatory landscape governing the electronic submission of adverse event reports of Bioavailability/Bioequivalence (BA/BE) studies to the FDA's FAERS.
- To describe the specific requirements and guidelines set forth by regulatory bodies for the submission process.
- To Accent any recent updates or changes in regulatory requirements affecting the electronic submission process.

RESULTS & DISCUSSIONS:

Expedited Safety Report

Reporting Procedure

In FDA two type reporting procedure

- **Paper Submission**
- **Electronic Submission**

✓ **Safety Report in Paper Format**

For each adverse event that happened in the nation, an FDA safety report was filed on FDA form 3500A.

Use the FDA's vaccine adverse event reporting form when filing report from outside the country using the CIOMS I form (Council for International Organization of Medical Science).

✓ **Electronic Reporting of Expedited Safety Report**

Individual case safety report submissions in electronic format have been allowed by the FDA since 2000.

In FDA two type of electronically safety report mandatory safety report and voluntary safety report electronically **[4]**.

1. For mandatory safety report

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

1.1 Database to database transmission (E2B)

1.2 Safety reporting portal

1.1.1 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).

ICSRs must be submitted through the Electronic Submission Gateway (ESG) in XML format and in accordance with one of the following standards:

E2B(R3) standard: compliant with both the regional technical specifications of the FDA and the ICH E2B(R3).

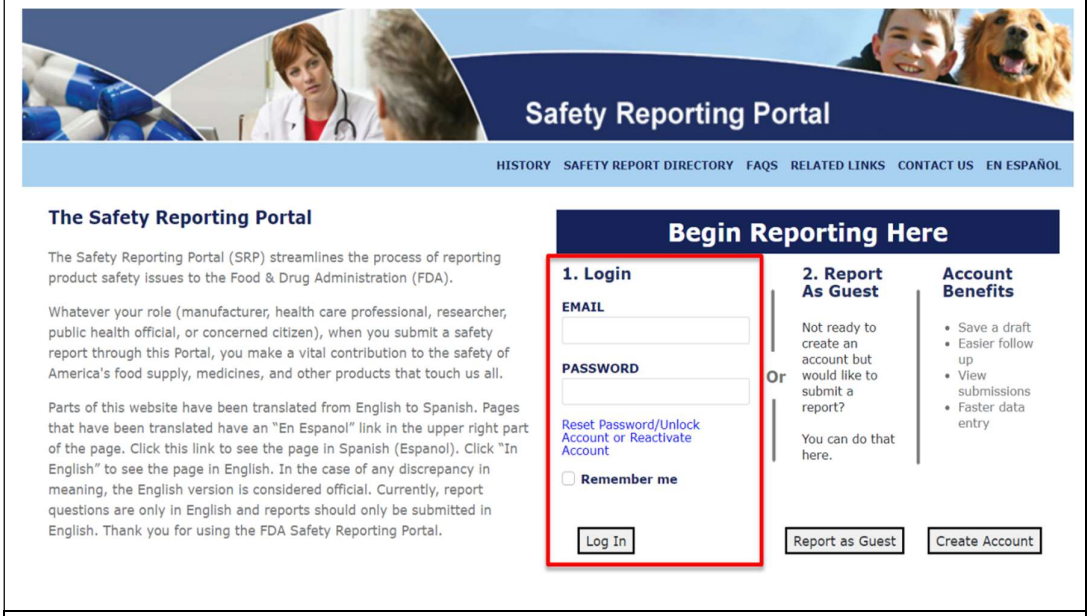
E2B(R2) standard: only applicable to post-marketing ICSRs through April 1, 2026, when E2B(R3) goes into effect.

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

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

1.2.1 Submission through Safety Report portal

Safety Reporting Portal



Pathway link: https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=64545cfe-3a95-4d54-9e7b-18596bae2ab8

Figure 2: shows the Safety Report Portal Pathway

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.

Post-marketing ICSRs and their attachments can be electronically submitted via SRP by manually entering the data into a web form.

This option is available to applicants for human drug and biological products, as well as responsible personnel from organizations with reporting duties who do not have E2B capabilities. You have to register for an SRP account before you may submit through SRP. It is not permitted for gateway partners—that is, businesses that electronically file ICSRs through ESG—to submit ICSRs and their attachments using SRP.

Steps for requesting an SRP account

Make an account and notify FDA of your intention to start submitting through the SRP by contacting faersesub@fda.hhs.gov.

Activation of SRP accounts:

- Following the date of request, your account will be authorized within 7 to 10 business days.
- An email with the subject "SRP Account Activation" will be sent to you, containing your account details and a web connection to the SRP portal.
- Your account will be deemed active upon receipt of this email, at which point you can start submitting your ICSR via SRP.

PSR submission

Please be aware that a PSR submission (21 CFR 314.80(c)(2) and 600.80(c)(2)) consists of both a descriptive section and the non-expedited ICSRs received during the PSR reporting interval.

Characteristic Portion:

To submit electronically, use the Electronic Common Technical Document (eCTD) specifications. Declare in the descriptive section that the ICSRs were electronically sent to the ESG or through the SRP as XML files.

1.2.1 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

Aggregated Safety Update Report

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 **[5]**.

Clinical Trial Aggregated Safety Update Report

Information on all serious adverse events that occurred in clinical trials is included in the IND annual Safety Update report, which is required by FDA under 21 CFR 312.33. The IND application sponsor is required to submit the report within 60 days of the anniversary date of the application going into effect **[6]**.

Time intervals and data locking points

The start of the yearly period for the DSUR is established using the Development International Birth Date (DIBD). The

sponsor has been granted permission to carry out a clinical study in any nation in the entire world as of this date. The month and date of the DIBD mark the beginning of the DSUR's yearly term. The final day of the annual reporting cycle is the data lock point. the report that was turned in 60 days after the data lock points **[7]**.

Reference Safety Information

Reference safety information is included in the investigative brochure. The relevant regional and national product label is used if an investigational brochure is not mandated by law or regulation.

The FDA approves Industry Guidance: E2F Development Safety Update Report (DSUR), which outlines a uniform reporting format **[8]**.

Format of Clinical Trial Aggregated Safety Report

FDA requires Clinical trial aggregated safety report in ICH E2F Development safety updater report format **[9]**.

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

The worldwide birth date and data lock point determine the submission period. The first date of marketing authorization is known as IBD, and the report cutoff date is known as DLP. Once authorized, the applicant may submit a report every six months for the first two years, then once a year for the next three, and finally once every five years.

Time interval between data locks point and submission

• PBRERs covering six- or twelve-month intervals: within seventy calendar days.

• PBRERs for periods longer than a year: within 90 calendar days.

• PBRER sought by regulatory body: 90 calendar days, unless the ad hoc request specifies a different timeframe.

Post Marketing Safety Update Report format

Post Marketing Aggregated Safety Reports in ICH E2C(R2) format are mandated by the FDA **[10]**.

CONCLUSION:

The study claims that strict rules apply to safety report submission in the US. The electronic submission of Bioavailability/Bioequivalence (BA/BE) adverse event reports to the FDA Adverse Events Reporting System (FAERS) is a critical component of post-marketing surveillance and drug safety monitoring. The regulatory requirements for this process ensure that the data is accurate, timely, and consistent, which is essential for maintaining the safety and efficacy of pharmaceutical products. By using the electronic safety reporting system and the

harmonized safety report format offered by the ICH, they make it easier and less discriminatory for medical practitioners and holders of marketing authorizations to submit safety reports. India insisted on a consistent format for post-marketing aggregated safety reports.

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CONFLICT OF INTEREST:

The authors declared that there is no conflict of interest

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