

ELECTRONIC SUBMISSION OF IND SAFETY REPORTS TECHNICAL CONFORMANCE GUIDE

This Document supplements the following Guidance Document:

Draft Guidance for Industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (October 2019)

For questions regarding this technical specifications document, contact CDER or CBER at faersesub@fda.hhs.gov.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Oncology Center of Excellence (OCE)**

October 2019



**U.S. FOOD & DRUG
ADMINISTRATION**

**ELECTRONIC SUBMISSION OF IND
SAFETY REPORTS
TECHNICAL CONFORMANCE GUIDE**

October 2019

REVISION HISTORY

DATE	VERSION	SUMMARY OF REVISIONS
October 2019	1.0	Initial Version

Table of Contents

- 1. Introduction..... 1
 - 1.1 Background..... 1
 - 1.2 Purpose..... 1
 - 1.3 Document Revision and Control..... 2
 - 1.4 Relationship to Other Documents..... 2
- 2. General Considerations..... 3
 - 2.1 IND Safety Report Submissions 3
 - 2.1.1 ICSR and ICH E2B Data Standards..... 3
 - 2.1.2 IND Safety Reports..... 3
 - 2.1.3 IND Safety Reports That Should NOT Be Submitted to FAERS 4
 - 2.1.4 ICSR Attachments 5
 - 2.1.5 Follow-Up Reports..... 5
 - 2.1.6 Identification of the IND for Submissions of IND Safety Reports..... 5
 - 2.1.6.1 IND Safety Reports From an Aggregate Analysis..... 6
 - 2.1.7 Product Names for Investigational Drugs..... 6
 - 2.1.8 Safety Reports for Marketed Drugs 7
 - 2.1.9 Other Considerations 7
 - 2.1.10 Options For Electronic Submission of ICSRs: Electronic Submissions Gateway or Safety Reporting Portal..... 7
 - 2.1.10.1 Creating an Account Before the First Electronic Submission 8
 - 2.1.10.2 Unique Case Identification Numbers for IND Safety Reports 8
 - 2.1.10.3 Single Submission Versus Batched Submissions of IND Safety Reports 9
 - 2.1.11 Notification of Receipt of Submissions by the FDA 9

Electronic Submission of IND Safety Reports Technical Conformance Guide¹

This document represents the Food and Drug Administration's (FDA's or Agency's) current thinking on this topic. It does not create or confer any rights for or on any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for implementing this guidance or send an email to faersesub@fda.hhs.gov.

1. Introduction

1.1 Background

This Technical Conformance Guide (Guide) provides specifications, recommendations, and general considerations on how to submit electronic investigational new drug application (IND) safety reports to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The Guide supplements the draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (October 2019),² which implements the electronic submission requirements of section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) with respect to electronic submissions for certain IND safety reports submitted to CDER or CBER.

1.2 Purpose

This Guide discusses the format for the submission of IND safety reports as required under 21 CFR 312.32(c)(1)(i) as individual case safety reports (ICSRs) to the FDA Adverse Event Reporting System (FAERS). It provides general information for sponsors of commercial and noncommercial INDs pertaining to electronic submission of IND safety reports and attachments in electronic format to FAERS. It also provides information to sponsors on the format for submission of IND safety reports required under 312.32(c)(1) that should not be submitted to

¹ This technical specifications document has been prepared by the Office of New Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2017-D-6821 (available at <https://www.regulations.gov/docket?D=FDA-2017-D-6821>) (see the instructions for submitting comments in the docket).

² When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

FAERS and should continue to be submitted in electronic common technical document (eCTD) format.³

1.3 Document Revision and Control

Sponsors will be able to access future revisions of this Guide through the FAERS Electronic Submissions web page,⁴ and the revision history page of this Guide will provide information on the changes made to previous versions.

1.4 Relationship to Other Documents

Sponsors should consult the following guidances and web pages for other aspects of electronic IND safety reporting:

- Draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*⁵
- Technical specifications document *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*⁶
- The FAERS Electronic Submissions web page for instructions on submission of ICSRs
- Draft guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports* (June 2014)⁷ for instructions on contingency plans for submission of IND safety reports for notification of receipt of submissions and contingencies when the submissions systems are temporarily unavailable

³ See also the draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*. When final, this guidance will represent the FDA's current thinking on this topic.

⁴ Available at <https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions>.

⁵ When final, this guidance will represent the FDA's current thinking on this topic.

⁶ Available on the FAERS Electronic Submissions web page at <https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions>.

⁷ When final, this guidance will represent the FDA's current thinking on this topic.

2. General Considerations

2.1 IND Safety Report Submissions

2.1.1 ICSR and ICH E2B Data Standards

An ICSR is a description of an adverse drug event experienced by an individual subject. ICSRs are used to communicate information on clinical trial and postmarketing adverse drug events or adverse drug reactions between a variety of entities involved with the review and tracking of safety information (e.g., investigators, regulators, pharmaceutical companies, institutional review boards or ethics committees, reporters).

The International Council for Harmonisation (ICH) E2B data standards working group was created to provide common data elements for the electronic transmission of ICSRs globally between relevant stakeholders. FDA currently requires mandatory postmarketing safety reports to be submitted to FAERS⁸ and Vaccine Adverse Event Reporting System (VAERS) and certain IND safety reports will also be required to be submitted to FAERS when the requirement is in effect.⁹

2.1.2 IND Safety Reports

Certain IND safety report types required under 21 CFR 312.32(c)(1) contain individual data from one or more subjects and should be submitted as ICSRs to FAERS (for these types of reports, hereafter, the terms *IND safety report* and *ICSR* are used interchangeably). Other types of required IND safety reports are reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies. The sponsor should submit these other types of reports in a narrative format in eCTD format and should *not* submit the reports to FAERS. Table 1 describes the types of reports that, in general, fit into each category.

⁸ See the draft guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports*. When final, this guidance will represent the FDA's current thinking on this topic.

⁹ For information on the effective day of the requirement, see the draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*. When final, this guidance will represent the FDA's current thinking on this topic.

Table 1: Types of IND safety reports and location of submission

Type of report	Submit to FAERS*	Submit to eCTD*
A single occurrence of an adverse event that is uncommon and known to be strongly associated with drug exposure (21 CFR 312.32(c)(1)(i)(A))	X	
One or more occurrences of an adverse event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (21 CFR 312.32(c)(1)(i)(B))	X	
An aggregate analysis of specific adverse events observed in a clinical trial (e.g., known consequences of the underlying disease or condition under investigation, other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group (21 CFR 312.32(c)(1)(i)(C))	X	
Findings from other studies (21 CFR 312.32(c)(1)(ii))		X
Findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii))		X
Increased rate of occurrence of serious suspected adverse events (21 CFR 312.32(c)(1)(iv))		X

* FAERS = FDA Adverse Event Reporting System; eCTD = electronic common technical document.

2.1.3 IND Safety Reports That Should NOT Be Submitted to FAERS

IND safety reports that are not submitted to FAERS (see Table 1) are reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies and increased rate of occurrences of serious suspected adverse reactions. Reports of overall findings or pooled analyses as noted above are to be submitted in a narrative format (21 CFR 312.32(c)(1)(v)). These reports should be submitted in the following manner:

- For INDs¹⁰ in eCTD format¹¹ using the following labels:

¹⁰ If a safety report is submitted to a noncommercial IND that is not in eCTD format, then the sponsor can submit the report on physical media in non-eCTD format. The report should be identified in the cover letter as SAFETY REPORT/GENERAL REPORT.

¹¹ See the draft guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using eCTD Specifications* (July 2019). When final, this guidance will represent the FDA’s current thinking on this topic.

Contains Nonbinding Recommendations

- For findings from animal or in vitro testing (21 CFR 312.32(c)(1)(iii)): to appropriate study using the “Safety Report” file-tag in eCTD section 4.2.3, Toxicology
- For findings from other studies (21 CFR 312.32(c)(1)(ii)) and an increased rate of occurrence of serious suspected adverse reactions (21 CFR 312.32(c)(1)(iv)): using the “Safety Report” file-tag in eCTD section 5.3.5.4, Other Safety Reports and Related Information

These IND safety reports in narrative format should not be submitted on MedWatch Form FDA 3500A or Council for International Organizations of Medical Sciences forms.

2.1.4 ICSR Attachments

Attachments to ICSRs include supporting information, such as autopsy reports, or published articles for ICSRs based on scientific literature. Attachments can also be used for narrative portions of the ICSR that exceed character limitation for that ICH E2B data field; however, FDA encourages sponsors to construct informative narratives that fit within the character limitations.

2.1.5 Follow-Up Reports

A follow-up report includes new information about a drug reaction that has been previously reported in an initial ICSR, and all follow-up reports should use the same unique case identification number as the initial ICSR. Follow-up ICSRs should include all information in the structured fields of the ICSR that has been previously reported along with any new information. However, to avoid duplication, ICSR attachments such as scientific literature or autopsy reports submitted with an initial ICSR should not be resubmitted with a follow-up ICSR.

2.1.6 Identification of the IND for Submissions of IND Safety Reports

As discussed in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012), IND safety reports should be submitted to all of the sponsor’s INDs under which the drug is being administered. To submit IND safety reports to all relevant INDs using digital reporting to FAERS, the sponsor should create one IND safety report using the appropriate ICH E2B data elements as described below.

For an IND safety report to be successfully processed in FAERS, it needs to have one valid IND number in the appropriate ICH E2B data field. Sponsors should use the IND number under which the clinical trial where the event occurs is conducted as the *primary IND* number in the indicated ICH E2B data field. Sponsors should also use the indicated repeatable ICH E2B data field to list individually other relevant INDs for which notification is necessary (i.e., *cross-reporting*). The relevant FDA review staff for each IND identified in the FAERS report will be notified that an IND safety report has been submitted for that drug.

Sponsors should see the technical specifications document referenced in this Guide, *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*, for

information on ICH E2B data elements to populate with the appropriate IND numbers as discussed above.

2.1.6.1 IND Safety Reports From an Aggregate Analysis

IND safety reports that are a result of an aggregate analysis (21 CFR 312.32(c)(1)(i)(C)) of clinical trials that are conducted under multiple INDs should be submitted to the *parent IND*. The *parent IND* is the IND under which clinical trials were first initiated in the United States. (If the drug is being evaluated in multiple INDs, the parent IND is generally the IND with the lowest number.)

As discussed in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies*, IND safety reports that are a result of an aggregate analysis should include a narrative report that provides a summary of the cases and the analysis the sponsor conducted and should identify the individual cases that contributed to the analysis (hereafter referred to as a *narrative summary report*). The sponsor should submit one ICSR to FAERS that includes the following:

- Information regarding the drug and the Medical Dictionary for Regulatory Activities term for the event in the appropriate ICH E2B fields
- The term *aggregate* in the ICH E2B field “Patient” to indicate that the report is a report from an aggregate analysis
- The unique case identification number of each ICSR that contributed to the analysis, listed in the appropriate ICH E2B field
- The narrative summary report attached to the ICSR as a PDF and clearly titled “Narrative summary report for an IND safety report from an aggregate analysis.”

Sponsors should reference the technical specifications document *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* for instructions on the appropriate data elements to include in IND safety reports from aggregate analyses as per 21 CFR 312.32(c)(1)(i)(C), on how to link all supportive ICSRs to the report, and on where to include the narrative summary report. This information may also be applicable for IND safety reports submitted as per 21 CFR 312.32(c)(1)(i)(B) that include more than one case and where a narrative summary report is provided.

2.1.7 Product Names for Investigational Drugs

Sponsors should use the established name (international nonproprietary name or United States Adopted Name), if applicable, in the appropriate E2B field for investigational drugs. For investigational drugs without an established name, before submission of IND safety reports to FAERS, the sponsor should submit a clinical information amendment to the IND listing the

names of the active drug substance(s) and medicinal product(s) as they will be reported in E2B submissions to FAERS. The names should fit within the established E2B character lengths.

2.1.8 Safety Reports for Marketed Drugs

For an adverse event associated with a marketed drug evaluated under an IND that meets IND *and* postmarketing safety reporting requirements (21 CFR 312.32(c)(1)(i) *and* 314.80, 600.80, or 310.305), the sponsor should submit two separate ICSRs to FAERS: one ICSR referencing the new drug application or biologics license application (BLA) in the “Authorization/Application Number” field and one ICSR referencing the IND as described under section 2.1.6., Identification of the IND for Submissions of IND Safety Reports.

For adverse events that occur with a marketed vaccine evaluated under an IND that meet IND *and* postmarketing safety reporting requirements as per (21 CFR 312.32(c)(1)(i) and 600.80), the sponsor should submit two separate ICSRs: one to VAERS for the BLA and one to FAERS for the IND.

2.1.9 Other Considerations

Sponsors should reference the technical specifications document *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* and the FAERS Electronic Submissions web page¹² for the following information:

- Required ICH E2B data elements for IND safety reports submitted as ICSRs
- Regional specifications of the ICH E2B data elements
- Use of ICH E2B data elements for a variety of reporting scenarios
- Submission of the narrative summary report and linking to the supporting ICSRs for submission of reports that describe an adverse event that was the result of an aggregate analysis as per 21 CFR 312.32(c)(1)(i)(C) or for several reports submitted as per 21 CFR 312.32(c)(1)(i)(B)) where a narrative summary report is provided.

2.1.10 Options For Electronic Submission of ICSRs: Electronic Submissions Gateway or Safety Reporting Portal

IND safety reports (initial and follow-up reports and all attachments) for drugs addressed by this Guide are submitted as ICSRs to the FAERS database.¹² FDA provides two options for electronic submission of IND safety reports and attachments to FAERS: (1) direct submission through the Electronic Submissions Gateway (ESG) or (2) submission through the Safety Reporting Portal (SRP), both of which are available 24 hours a day, 7 days a week.

¹² See the Questions and Answers on FAERS web page at <https://www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers>.

Contains Nonbinding Recommendations

Direct submission of IND safety reports through the ESG is described on the FAERS Electronic Submissions web page. This option involves direct transmission of IND safety reports from a firm's database to FDA through the ESG. The ESG is a central transmission point for sending information electronically to FDA. Once received through the ESG, the submitted reports are processed into the FAERS database. For instructions on organizing, preparing, and submitting IND safety reports and attachments using the direct submission method through the ESG, see the technical specifications document *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*. The technical specifications document addresses topics such as data elements, electronic transport format, and types of ICSR attachments FDA currently accepts.

The submission of ICSRs and ICSR attachments through the SRP is described on the FDA's SRP web page.¹³ Users enter the ICSR information manually into a web-based form, and this information is then submitted to FDA to be uploaded into the FAERS database.

2.1.10.1 Creating an Account Before the First Electronic Submission

To submit IND safety reports electronically, either through the ESG or SRP, the sponsor needs to have an account with FDA. To create an account, the sponsor should contact the FAERS electronic submissions coordinator at faersesub@fda.hhs.gov. The FAERS electronic submissions coordinator will assist sponsors to ensure that all steps have been completed for successful submission of IND safety reports and attachments.

2.1.10.2 Unique Case Identification Numbers for IND Safety Reports

Each IND safety report should have a unique case identification number. The sponsor should use the same unique case identification number for an initial IND safety report and any of its follow-up reports so that the reports can be associated with an individual case. Case identification numbers are assigned based on one of the three methods of submission described below:

- a. **Via the SRP:** The unique case identification number for an initial report is automatically generated by the SRP once the IND safety report is submitted.
- b. **Via the ESG:** The unique case identification number for an initial report is generated by the sponsor before submitting the report.
- c. **On Paper** (e.g., MedWatch Form FDA 3500A):¹⁴ The unique case identification number is the manufacturer control number that the sponsor assigns for the initial report.

¹³ Available at <https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=0183c2c0-8952-49cb-81f1-0c3d37baa819>.

¹⁴ Sponsors who submit a follow-up report to FAERS for an earlier report that was submitted on paper or in eCTD format should use the same manufacturer control number for the initial and all follow-up reports.

Contains Nonbinding Recommendations

The sponsor should use the same unique case identification number for an initial IND safety report and its follow-up reports even if there is a transfer of ownership of an application. If the current sponsor submits a follow-up IND safety report to an initial report submitted by a previous sponsor, the current sponsor should use the unique case identification number from the initial IND safety report to ensure that the follow-up report can be matched with the initial submission.

Similarly, if the sponsor submits an initial IND safety report through the ESG, the sponsor *cannot* submit the follow-up reports for this case through the SRP because the initial and follow-up reports will have different unique case identification numbers.

2.1.10.3 Single Submission Versus Batched Submissions of IND Safety Reports

When submitting IND safety reports through the ESG, the sponsor can submit the reports either as a single report or as several reports in a batch. See the technical specifications document *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* for information on submitting a single IND safety report versus a batch of IND safety reports through the ESG.

If the sponsor is submitting IND safety reports through the SRP, the sponsor can only submit a single IND safety report at a time because the SRP is not able to process a batched submission.

2.1.11 Notification of Receipt of Submissions by the FDA

For information on the notification of FDA's receipt of a submission, see the draft guidance for industry *Providing Submissions in Electronic Format — Postmarketing Safety Reports*¹⁵ and the FAERS Electronic Submissions web page.

¹⁵ When final, this guidance will represent the FDA's current thinking on this topic.