
Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry

**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)**

**April 2024
Electronic Submissions**

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RELATED DOCUMENTS

Technical specifications associated with this guidance are provided as separate documents and are updated periodically.

For a complete listing of all documents and supportive files needed to submit investigational new drug application safety reports to FDA's Adverse Event Reporting System (FAERS), refer to 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>.

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Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry¹

I. INTRODUCTION

This guidance describes the electronic format sponsors will be required to use when they electronically submit to the Food and Drug Administration (FDA or Agency) investigational new drug application (IND) safety reports for serious and unexpected suspected adverse reactions that are required under 21 CFR 312.32(c)(1)(i). FDA is establishing the electronic format requirements described in this guidance under section 745A(a) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).² When the requirements of this guidance are in effect, this guidance will supersede the effective version of the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (eCTD guidance) as applicable to the electronic submission of IND safety reports required under 21 CFR 312.32(c)(1)(i) that are within the scope of this guidance (see section III., Scope of This Guidance). This guidance will not replace any requirements in the eCTD guidance other than those relating to the electronic submission of IND safety reports required under 21 CFR 312.32(c)(1)(i) that are within the scope of this guidance. This guidance also references several technical specification documents that provide additional details about the format for electronic submission of IND safety reports to the FDA Adverse Event Reporting System (FAERS).³

This guidance implements the electronic submission requirements of section 745A(a) of the FD&C Act for the electronic format of the content submitted for IND safety reports that are required under 21 CFR 312.32(c)(1)(i) for serious and unexpected suspected adverse reactions. This guidance applies to IND safety reports that are submitted to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). This guidance changes the electronic submission requirements for this category of IND safety reports by requiring sponsors to submit the IND safety reports to FAERS in accordance with this guidance. This requirement will be effective 24 months after the publication of the notice of

¹ This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

² For additional information on how FDA interprets and intends to implement the electronic submission requirements of section 745A(a) of the FD&C Act, please see the guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (December 2014) (745A(a) Implementation guidance). We update guidances periodically. 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>.

³ See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products* (August 2022) and the *Electronic Submission of IND Safety Reports: Technical Conformance Guide* (April 2022), 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>.

availability of this guidance in the *Federal Register* (April 1, 2026). Until the requirements in this guidance become effective, the most recent effective version of the eCTD guidance will continue to apply to sponsors electronically submitting IND safety reports for serious and unexpected suspected adverse reactions.⁴ Before the effective date of the requirements outlined in this guidance, FDA will accept IND safety reports to FAERS as part of a voluntary submission program. During the voluntary submission program, if sponsors choose to submit IND safety reports to FAERS, they should no longer submit those IND safety reports in eCTD format. Please see the FAERS Electronic Submissions web page⁵ for more information on the voluntary submission process.

Once the requirement is effective, sponsors of INDs subject to this guidance are required to submit IND safety reports electronically in the format specified in this guidance unless the sponsor is exempted from the electronic submission requirements (see section III. C., Types of Submissions That Are Exempted From the Electronic Submission Requirement Described in This Guidance) or a waiver is obtained (see section IV. D., Waiver Requests).

In section 745A(a) of the FD&C Act, Congress granted explicit statutory authorization to FDA to specify in guidance the format for the electronic submissions required under that section. Accordingly, to the extent that this document provides such requirements under section 745A, as indicated by the use of the words *must* or *required*, this document is not subject to the usual restrictions in section 701(h) of the FD&C Act, FDA’s good guidance practice regulations that guidances not establish legally enforceable responsibilities (see 21 CFR 10.115(d); see also the 745A(a) Implementation guidance).

To comply with the good guidance practice regulations and make sure that regulated entities and the public understand that guidances are nonbinding, FDA guidances ordinarily contain standard language explaining that guidances should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance because it is not an accurate description of all of the effects of this guidance. Insofar as this document specifies the format for electronic submissions or provides “criteria for waivers of and exemptions from” the requirements of section 745A(a) of the FD&C Act, it will have binding effect 24 months after the publication of this guidance in the *Federal Register*.

⁴ For further information about IND safety reports, see 21 CFR 312.32, the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012), and the draft guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021). When final, this guidance will represent the FDA’s current thinking on this topic. These guidances do not cover electronic submissions requirements. 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>.

⁵ The FAERS Electronic Submissions web page is found at <https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions>.

II. BACKGROUND

Section 745A(a) of the FD&C Act applies to submissions under section 505(b), (i), or (j) of the FD&C Act and under section 351(a) or (k) of the Public Health Service Act, including certain INDs. Section 745A(a) of the FD&C Act also applies to all subsequent submissions, including amendments, supplements, and reports to the submission types identified. FDA considers IND safety reports to fall within the scope of requirements set forth in section 745A(a) of the FD&C Act.

A sponsor of a clinical trial conducted under an IND must report serious and unexpected suspected adverse reactions to FDA in an IND safety report within 7 or 15 days depending on the severity of the event (21 CFR 312.32).⁴ These reports have traditionally been submitted to FDA on MedWatch Form FDA 3500A or on a Council for International Organizations of Medical Sciences I Form or other narrative forms. Submission of this important safety information to FAERS as structured data elements will improve FDA's ability to review and track these potential safety signals that occur during the conduct of clinical trials and will provide sponsors with a reporting format that is consistent with International Council for Harmonisation (ICH) guidelines and reporting requirements to other regulatory agencies.

The IND safety reporting requirements under 21 CFR 312.32 apply to bioavailability (BA) and bioequivalence (BE) studies that are conducted under an IND. However, BA and BE studies that meet the conditions for exemption under 21 CFR 320.31 are not conducted under an IND and are not subject to the IND safety reporting requirements. Safety reporting requirements under 21 CFR 320.31(d)(3) apply to persons conducting BA or BE studies that are exempt from the IND requirements.

III. SCOPE OF THIS GUIDANCE

A. Types of Submissions That Will Be Required to Comply With the Electronic Submission Requirement Described in This Guidance

This guidance applies only to IND safety reports for serious and unexpected suspected adverse reactions required under 21 CFR 312.32(c), which includes both 7- and 15-day reporting requirements depending on the severity of the event (see 21 CFR 312.32(c)(1)(i), (c)(2)). Under 21 CFR 312.32(c)(1)(i), sponsors must report any suspected adverse reaction that is both serious and unexpected if there is evidence to suggest a causal relationship between the drug and the adverse event, such as in the following circumstances:

- A single occurrence of an adverse event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson syndrome) (21 CFR 312.32(c)(1)(i)(A))
- 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 (e.g., tendon rupture) (21 CFR 312.32(c)(1)(i)(B))

- 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 adverse 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))

B. Types of Submissions for Which the Electronic Submission Requirement Described in This Guidance Does Not Apply

This guidance does not apply to IND safety reports for anything other than serious and unexpected suspected adverse reactions covered by 21 CFR 312.32(c)(1)(i) and 21 CFR 312.32(c)(2).

Below are examples of IND safety reports for which the requirements of this guidance do *not* apply:⁶

- Findings from other studies, as required under 21 CFR 312.32(c)(1)(ii)
- Findings from animal or in vitro testing, as required under 21 CFR 312.32(c)(1)(iii)
- Increased rate of occurrence of serious suspected adverse reactions, as required under 21 CFR 312.32(c)(1)(iv)

This guidance also does not apply to IND safety reports for devices that are regulated by CBER as biological products under section 351 of the Public Health Service Act and that require the submission of an IND before the submission of a biologics license application.⁷

C. Types of Submissions That Are Exempted From the Electronic Submission Requirement Described in This Guidance

Section 745A(a) of the FD&C Act allows FDA to establish exemptions from the electronic submission requirements. Accordingly, FDA has exempted all submissions regarding noncommercial INDs from the requirements under section 745A(a) of the FD&C Act.⁸ For

⁶ For information on the electronic format requirements for the types of IND safety reporting required under 21 CFR 312.32(c)(1)(ii)-(iv), sponsors should consult the eCTD guidance and the *Electronic Submission of IND Safety Reports: Technical Conformance Guide*.

⁷ Although a discussion of which devices CBER regulates as biological products is outside the scope of this guidance, in general, this category of INDs would include investigational devices that are used to screen blood donors for certain transfusion-transmissible diseases and to test human cells, tissues, or cellular- or tissue-based products to make a donor-eligibility determination. These submissions are subject to the requirements under section 745A(b) of the FD&C Act. See the guidance for industry and FDA staff *eCopy Program for Medical Device Submissions* (April 2020), which implements the electronic copy provisions of section 745A(b) of the FD&C Act for medical device submissions to FDA.

⁸ See the 745A(a) Implementation guidance, section III. B.

purposes of the section 745A(a) exemption, the term *noncommercial IND* refers to an IND for a product that is not intended for commercial distribution and includes investigator-sponsored INDs and expanded access INDs (e.g., emergency use INDs and treatment INDs).⁹ Although noncommercial INDs (and IND safety reports associated with them) are exempt from the requirements of section 745A(a) of the FD&C Act, FDA encourages the submission of IND safety reports from sponsors of noncommercial INDs using the format described in this guidance.

IV. REQUIREMENT TO SUBMIT ELECTRONICALLY UNDER THIS GUIDANCE

The following section sets forth the requirements for electronic submission of IND safety reports that are within the scope of this guidance.

A. Timetable for Implementation of Electronic Submission Requirements

The requirement to submit IND safety reports as described in this guidance will become effective 24 months after the publication of this guidance in the *Federal Register* (April 1, 2026). FDA will accept IND safety report submissions as described in this guidance before the date that the requirement is in effect as noted in section I., Introduction.

B. Specifications for Submission of IND Safety Reports to FAERS

Sponsors must submit IND safety reports to FAERS using either the Electronic Submission Gateway (ESG) or the Safety Reporting Portal (SRP). For sponsors using the ESG, consult the FDA Data Standards Catalog¹⁰ for information about the ICH E2B data standard currently supported by FDA.

For additional information about submitting IND safety reports to FAERS, please consult the following technical specification documents:¹¹

- *Electronic Submission of IND Safety Reports: Technical Conformance Guide*
- *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products*

Instructions for submitting IND safety reports to FAERS as individual case safety reports can be found on the FAERS Electronic Submissions web page.¹²

⁹ See the 745A(a) Implementation guidance, section III. B.

¹⁰ The FDA Data Standards Catalog is available on the Study Data Resources web page at <https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources>.

¹¹ 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>.

¹² 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>.

C. Presubmission Considerations

Before submitting an IND safety report to FAERS for the first time, whether through the ESG or SRP, the sponsor should create an account with FDA if one has not been previously established. To create an account, the sponsor should notify the FAERS electronic submission coordinator at faersesub@fda.hhs.gov of the intent to submit. The FAERS coordinator will help the sponsor create an account, ensure that all steps have been completed for successful submission, and provide instructions for optional test submissions. It is not necessary to contact the FAERS coordinator before submitting subsequent IND safety reports in electronic format.

D. Waiver Requests

Section 745A(a)(2) of the FD&C Act allows FDA to establish criteria for waivers from the electronic submission requirements. The Agency anticipates that temporary waivers will be needed only in rare circumstances. FDA may grant temporary waivers of the requirement for submission of certain IND safety reports in FAERS, as described in this guidance, if one or more of the following events or circumstances exist:¹³

- Extraordinary events or circumstances occur that are beyond the control of the submitter that justify a waiver, including but not limited to natural disasters that impact computer operations
- An unplanned, long-term internet disruption or other unplanned event occurs that would preclude the sponsor from submitting in FAERS (e.g., malware attacks)

1. Content of Waiver Requests

The sponsor should make a request in writing to waive the requirement to submit IND safety reports to FAERS. Include the IND number for which the request is being made, the reason for the request, and information justifying the waiver.¹⁴ The waiver request also should include a proposed end date for the waiver and the proposed alternative reporting method, such as submission on physical media.

2. Where to Submit Waiver Requests

Waiver requests for drug and biological products conducted under an IND may be sent through the following means:

- CDER: By email to ESUB@fda.hhs.gov
- CBER: By email to ESUBPREP@fda.hhs.gov

¹³ See 21 CFR 312.10.

¹⁴ See 21 CFR 312.10.

3. *FDA Response to Waiver Requests*

FDA reviews waiver requests on a case-by-case basis. FDA will generally respond to the requestor¹⁵ in writing, stating whether the waiver is granted or denied. If the waiver is granted, FDA will also generally include in the response letter a description of the alternate submission method(s) the Agency intends to accept and the time frame for the waiver. Waivers of the requirements to submit to FAERS, if granted, will be temporary, will apply only to the requestor, and will not be transferrable to another sponsor.

¹⁵ To follow up with the company, FDA will generally contact the individual who submitted the waiver request unless an alternate contact person is provided.