Providing Regulatory Submissions in Electronic Format: IND Safety Reports

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Meredith Chuk at 301-796-2340 or (CBER) the Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

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
Electronic Submissions

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Office of Communications, Division of Drug Information
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Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
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Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
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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**.

Revision History

Date	Version	Summary of Revisions
October 2019	1.0	Initial Version

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Providing Regulatory Submissions in Electronic Format: IND Safety Reports Guidance for Industry[1]

I. INTRODUCTION

This draft guidance describes the electronic format sponsors will be required to use when they electronically submit to the Food and Drug Administration (FDA or Agency)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 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 finalized, 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") for the 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 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, which provide additional details regarding the format for electronic submission of IND safety reports to 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 such 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 the FDA Adverse Event Reporting System (FAERS) in accordance with this guidance. This requirement will be effective

[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). We update guidances periodically. To make sure you have 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 *Specifications for Preparing and Submitting Electronic ICSRs [Individual Case Study Reports] and ICSR Attachments* (October 2019) and the *Electronic Submission of IND Safety Reports: Technical Conformance Guide* (October 2019), available on the FDA Adverse Event Reporting System (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.

24 months after the publication of the final guidance on this topic. Before the effective date of this requirement, FDA will accept IND safety reports to FAERS as part of a voluntary submission program. We intend to update the FAERS website with information indicating when we will begin to accept voluntary submissions. Until the requirements in this guidance become effective, the most recent effective version of the eCTD Guidance will continue to apply to sponsors submitting IND safety reports electronically for serious and unexpected suspected adverse reactions.[4]

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, as indicated by the use of the words *must* or *required*, this document is not subject to the usual restrictions in FDA's good guidance practice (GGP) regulations, such as the requirement that guidances not establish legally enforceable responsibilities (see 21 CFR 10.115(d); see also the guidance for industry *Providing Regulatory Submissions in Electronic Format — Submissions Under Section 745A(a) of the Federal Food, Drug, and Cosmetic Act* (745A(a) Implementation guidance)).

To comply with the GGP regulations and make sure that regulated entities and the public understand that guidance documents are nonbinding, FDA guidances ordinarily contain standard language explaining that guidance documents should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. FDA is not including this standard language in this guidance document because it is not an accurate description of all of the effects of this guidance document. 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 the final guidance in the *Federal Register*.

II. BACKGROUND

Section 745A(a) of the FD&C Act applies to certain 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 (PHS) Act, including certain INDs. Section 745A(a) 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).

[4] For further information about IND safety reports, see 21 CFR 312.32 and the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012).

A sponsor of clinical trials 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 type of event (21 CFR 312.32(c)).[5] These reports have traditionally been submitted to FDA on MedWatch Form FDA 3500A or on a Council for International Organizations of Medical Sciences (CIOMS) I Form or other narrative forms. Currently, FDA requires sponsors of commercial INDs that make electronic IND safety report submissions to use eCTD format.[6] Sponsors submit these safety reports within the eCTD structure using PDF files, but review and tracking of these reports in PDF format is inefficient and labor intensive. 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.

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 only applies to IND safety reports for serious and unexpected suspected adverse reactions required under 21 CFR 312.32(c)(1)(i). 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))

[5] Additional information regarding IND safety reporting requirements under 21 CFR 312.32 is addressed in the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* and the draft guidance for industry *Safety Assessment for IND Safety Reporting* (December 2015), which, when final, will represent FDA's current thinking on this topic. Those guidance documents do not cover electronic submissions requirements.

[6] Section 745A(a) of the FD&C Act and eCTD Guidance, section III.A. See also Specifications for File Format Types Using eCTD Specifications available at https://www.fda.gov/media/85816/download.

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).

Below are examples of IND safety reports for which the requirements of this guidance do *not* apply:[7]

- 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 PHS Act and that require the submission of an IND before the submission of a biologics license application.[8]

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

Section 745A(a) 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).[9] For purposes of the section 745A(a) exemption, the term *noncommercial products* refers to products that are not intended to be distributed commercially and includes investigator-sponsored INDs and expanded access INDs (e.g., emergency use INDs).[10] Although noncommercial INDs (and IND safety reports associated with them) are exempt from the requirements of section 745A(a), FDA encourages the submission of IND safety reports from sponsors of noncommercial INDs using the format described in this guidance.

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[7] For information on the electronic format requirements for the types of IND safety reporting required under 21 CFR 312.32(c)(1)(ii)9(iv), sponsors should consult the eCTD Guidance and the *Electronic Submission of IND Safety Reports: Technical Conformance Guide*.

[8] 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* (December 2015), which implements the electronic copy provisions of section 745A(b) for medical device submissions to FDA.

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

[10] See the 745A(a) Implementation guidance, section III.B.

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 the final version of this draft guidance. 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 Catalog[11] 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:[12]

- *Electronic Submission of IND Safety Reports: Technical Conformance Guide*
- *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments*

Instructions for submitting IND safety reports to FAERS as individual case safety reports (ICSRs) can be found on the FAERS Electronic Submissions web page.[13]

C. Presubmission Considerations

Before submitting an IND safety report to FAERS for the first time, whether through the ESG or SRP, the sponsor should notify the FAERS electronic submission coordinator at faersesub@fda.hhs.gov of the intent to submit. The FAERS coordinator will assist the sponsor to 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.

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[11] 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.

[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.

[13] Ibid.

D. Waiver Requests

Section 745A(a) 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:[14]

- 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.[15] 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
  - In eCTD via ESG, if possible

    or

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

[14] See 21 CFR 312.10.

[15] See 21 CFR 312.10.

3. FDA Response to Waiver Requests

FDA reviews waiver requests on a case-by-case basis. FDA plans to respond in writing to the requestor, stating whether the waiver is granted. If the waiver is granted, FDA plans for the response to include the agreed-upon alternative method for submission as well as the timeframe for the waiver. In most circumstances, FDA intends for any waivers from the requirements in this guidance to be temporary.