Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies

Guidance for Industry

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2022
Generic Drugs

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Electronic Submission of Expedited Safety Reports From IND-Exempt BA/BE Studies Guidance for Industry[1]

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I. INTRODUCTION

This guidance provides instructions for the electronic submission of expedited individual case safety reports (ICSRs) from investigational new drug (IND)-exempt bioavailability (BA)/bioequivalence (BE) studies[2] through the FDA Adverse Event Reporting System (FAERS) database. An ICSR captures information necessary to support the reporting of an adverse event related to an individual subject that is associated with the use of an FDA-regulated product.[3] The electronic submission of the ICSRs from IND-exempt BA/BE studies is a voluntary option for submission.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in FDA guidance means that something is suggested or recommended, but not required.

II. BACKGROUND

[1] This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research at the Food and Drug Administration.

[2] 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. The safety reporting requirements under § 320.31(d)(3) apply to persons conducting BA or BE studies that are exempt from the IND requirements.

[3] See additional information on the *Individual Case Safety Reports* web page, available at https://www.fda.gov/industry/fda-resources-data-standards/individual-case-safety-reports.

In the *Federal Register* of September 29, 2010,[4] FDA published a final rule that revised the IND (including Bio-IND)[5] safety reporting requirements for human drug and biological products under 21 CFR part 312.[6] It added safety reporting requirements for persons conducting IND-exempt BA/BE studies under 21 CFR 320.31.[7] This regulation outlines when BA and BE studies are exempt from the IND requirements.[8] The exemption from IND requirements may apply to studies conducted to support abbreviated new drug applications (ANDAs) and other drug applications.

A safety report documenting a serious adverse event (SAE)[9] experienced by a study subject during conduct of an IND-exempt BA/BE study must be submitted on Form FDA 3500A or in an electronic format that FDA can process, review, and archive.[10] As required by regulation, a safety report documenting a fatal or life-threatening adverse event from the study must be submitted to FDA as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence (7-day report).[11] Safety reports documenting other SAEs observed during the conduct of the study must be submitted to FDA as soon as possible but no later than

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[4] "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans" (75 FR 59935, September 29, 2010).

[5] See § 320.31(a) through (b) that describes when any person conducting an in vivo BA or BE study must submit an IND. The term Bio-IND refers to such an IND. MAPP 5210.5 Rev. 3 *Review of Investigational New Drug Applications (Bio-INDs) by the Office of Generic Drugs* (April 14, 2022).

[6] For Bio-INDs, the IND safety reporting requirements under 21 CFR 312.32(c)(1)(i) apply.

[7] For additional information on meeting safety reporting requirements for Bio-IND or IND-exempt BA/BE studies, see the following documents: the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012), (see also the draft guidance for industry *Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021), which when final, will represent the FDA's current thinking on this topic and includes recommendations to help the companies conducting IND-exempt BA/BA studies comply with reporting requirements); the draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (October 2019) ,which when final, will represent the FDA's current thinking on this topic; and the guidance for industry*, Electronic Submission of IND Safety Reports Technical Conformance Guide* (April 2022). 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. FDA's Study Data Standards Resources are available at https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

[8] § 320.31(d).

[9] Serious adverse event (SAE) is defined at § 312.32(a). An adverse event is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

[10] § 320.31(d)(3).

[11] Id.

15 calendar days after becoming aware of the SAE occurrence (15-day report).[12] The expedited reporting requirements for IND-exempt BA/BE studies apply only to BA/BE studies conducted in the United States.

In addition to the requirements for expedited safety reporting described in § 320.31(d), as part of the information required to establish that the drug product can be expected to have the same therapeutic effect as the listed product, adverse events information from IND-exempt BA/BE studies, regardless of whether the study is conducted inside or outside of the United States, must be included in an ANDA or NDA submission, as appropriate based on the purpose of the BA/BE study.[13]

In the past, expedited safety reports from IND-exempt BA/BE studies have been submitted to the Office of Generic Drugs (OGD) by email, telephone, or facsimile using the Form FDA 3500A. However, enhancements to FAERS will allow electronic submission of ICSRs from IND-exempt BA/BE studies. This guidance provides recommendations on how to electronically submit ICSRs[14] to the FAERS database as an alternate avenue for submitting reports to OGD once these enhancements are activated.[15]

III. ELECTRONIC SUBMISSION OF EXPEDITED SERIOUS ADVERSE EVENT REPORTS FROM IND-EXEMPT BA/BE STUDIES

ICSRs are used by investigators, pharmaceutical companies, institutional review boards, ethics committees, contract research organizations, etc., to perform pharmacovigilance monitoring activities and to communicate information about these adverse events to FDA and other regulatory bodies. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E2B data standards working group developed common

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[12] Id.

[13] See 21 CFR 314.94(a)(7) and 21 CFR 314.50(d)(5)(iv). As FDA explained in the 2010 final rule on "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans" (see 75 FR at 59954) in response to comments about submitting SAEs that occurred during conduct of studies outside of the United States, "as part of the information required to establish that the proposed drug product can be expected to have the same therapeutic effect as the reference listed product, adverse event reports that occurred in foreign clinical studies must be included in the ANDA submission . . ." See guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012), (see also draft guidance for industry *Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021)).

[14] § 320.31(d)(3).

[15] See the website *FDA Adverse Event Reporting System (FAERS) Electronic Submissions*, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions, for updates on the FAERS enhancements.

data elements for the electronic transmission of ICSRs globally among relevant stakeholders.[16] FDA also developed regional data elements for reporting on drug-device combination products and premarket (IND and BA/BE study) safety reports for drug products and some biological products.[17]

A. Methods for Electronic ICSR Submission

FDA provides two options for electronic submission of ICSRs and ICSR attachments to the FAERS database:

(1) ICSR Option A: Database-to-Database Transmission ("E2B")

- Submitters who have database-to-database transmission capability may directly submit ICSRs in the XML format[18] via the Electronic Submissions Gateway (ESG). The ESG is a central transmission point for sending information electronically to FDA.[19] Once received through the ESG, the submitted ICSRs are processed into the FAERS database.
- The direct electronic submission of ICSRs and ICSR attachments through the ESG is described on the FDA FAERS Electronic Submissions web page.[20] Submitters should reference FDA's technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products* for instructions on organizing, preparing, and submitting ICSR and ICSR attachments using the direct submission method through the ESG.

(2) ICSR Option B: Safety Reporting Portal (SRP)

- Submitters who do not have database-to-database transmission capability may submit electronic ICSRs using the SRP. Submitters can enter the ICSR information manually

[16] See *E2B(R3) Individual Case Safety Report (ICSR) Specification and Related Files,* available at https://www.ich.org/page/e2br3-individual-case-safety-report-icsr-specification-and-related-files.

[17] See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products* (April 2022). For the most recent version **of** the technical specifications document, check the FAERS Electronic Submissions web page at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

[18] For additional instruction on how to begin submitting ICSRs in the XML format, check the *Steps to Submitting ICSRs Electronically in the XML Format* link, available at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

[19] See FDA's *Electronic Submissions Gateway* web page, available at https://www.fda.gov/industry/electronic-submissions-gateway.

[20] See the *Questions and Answers on FDA's Adverse Event Reporting System (FAERS)* web page at https://www.fda.gov/drugs/surveillance/questions-and-answers-fdas-adverse-event-reporting-system-faers.

into a web-based form in the SRP, and this information is then submitted to FDA to be uploaded into the FAERS database.

- Submitters who are Gateway partners cannot use the SRP. Gateway partners are those that submit ICSRs electronically via the ESG. For information on how to submit ICSRs and ICSR attachments through the SRP, refer to the FDA's SRP web page.[21]

Both routes of submission are available 24 hours a day, 7 days a week. To submit ICSRs electronically, either through the E2B or SRP, each submitter needs to have an account with FDA. A separate account is needed for each option. To create an account, submitters should notify the FAERS electronic submissions coordinator at faersesub@fda.hhs.gov. The FAERS electronic submissions coordinator will assist submitters to help ensure that all steps are completed for successful submission of ICSRs and ICSR attachments.

B. Identification of the ICSRs

FDA has established business rules to distinguish premarket ICSRs from postmarket ICSRs.[22] These rules enable identification and rejection of premarket ICSRs that are incorrectly submitted to the postmarket pathway in FAERS. See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products* for additional details on these business rules.

To voluntarily submit a premarket IND-exempt BA/BE ICSR in E2B data standard, submitters should use the E2B data element FDA.C.5.5b titled "Pre-ANDA Number where serious AE Occurred" to provide a valid pre-assigned ANDA (referred to as a *Pre-ANDA*) number in an appropriate format ("123456").[23, 24, 25, 26]

C. ICSR Attachments

[21] Available at https://www.safetyreporting.hhs.gov/SRP2.

[22] See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products*.

[23] For information on requesting a pre-assigned ANDA number, see https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number.

[24] Although these are pre-assigned ANDA numbers and the term *Pre-ANDA* is used with these numbers, these submissions may or may not be associated with OGD's Pre-ANDA program for complex drug products. See https://www.fda.gov/drugs/generic-drugs/pre-anda-program.

[25] See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products*.

[26] See FDA E2B(R3) Core and Regional Data Elements and Business Rules. For the most recent version of this document, check the FAERS Electronic Submissions web page at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

Attachments to ICSRs provide important supporting information and may include (but are not limited to): study protocols, case report forms (including assessments and test results), relevant medical records, and/or autopsy reports. Attachments can also be used for narrative portions of the ICSR that exceed character limitation for that E2B data field; however, FDA encourages providing informative narratives that fit within the character limitations. The ICSR attachment can be sent at the same time as the ICSR submission either through the ESG[27] or SRP[28] route.

D. Initial and Follow-Up ICSRs

Each ICSR should have a unique case identification number created by the submitter of the report that is the same for the initial report and all subsequent follow-up reports. Follow-up ICSRs should include new information in the E2B data fields along with information previously reported in prior ICSR submissions for the SAE. To avoid duplication, ICSR attachments submitted with an initial ICSR should not be resubmitted with a follow-up ICSR. Follow-up ICSRs should be submitted electronically only if the initial ICSR for the SAE was submitted electronically.

E. Product Names for Study Drugs

Submitters should use the drug substance name or nonproprietary name of the drug in the appropriate E2B data fields for study drugs (see section F). The name should fit within the established E2B character lengths.

Submitters should report all drugs to which the subject was exposed using the appropriate E2B data fields referenced in FDA's technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products*. Exposures to study drugs should be unblinded for the subject who experienced the SAE before submission. Knowledge of the treatments and interventions received is necessary for interpreting the event, may be essential for the medical management of the subject, and may provide critical safety information about the study drug, which could have implications for the ongoing conduct of the study (e.g., monitoring, informed consent, other protocol modifications).[29] FDA does not believe that unblinding single or small numbers of SAE cases will compromise the integrity of the study, in part because such "unblinding" should be infrequent.[30]

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[27] See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products*.

[28] Safety Reporting Portal: Frequently Asked Questions "What types of files may be attached to a report?," available at https://www.staging2.safetyreporting.hhs.gov/SRP2/en/FAQ.aspx.

[29] See the guidance for industry *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012), (see also the draft guidance for industry *Sponsor Responsibilities - Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (June 2021)).

[30] Id.

F. Description of Drug Exposure

Each of the subject's drug exposures should fit into one of the following classifications and E2B data fields:

(1) Past Drug Therapy
Past drug therapy includes any drug the subject was taking before study enrollment that was discontinued before study initiation. These drugs should be reported using section D.8.r titled "Relevant Past Drug History." The narrative should describe the indication, treatment regimen, duration of treatment, and the date of the last dose.

(2) Drug Exposure or Treatment During Study Enrollment and Follow-up Period
Drug exposure or treatment during study enrollment may include test, reference, placebo, vehicle, and/or other drugs taken by or administered to the subject during the study or protocol-defined follow-up period. These drugs should be reported using the recommendations below.

Table 1 displays the descriptions of the ICH E2B data elements (G.k.1, FDA.G.k.10a.r and G.k.2) used for reporting subject's drug exposures that occur after enrollment in the IND-exempt BA/BE study. Submitters should use data element G.k.1 to characterize the drug's potential role in the SAE and data element FDA.G.k.10a.r to provide additional information on the drug exposure. Submitters should use data elements G.k.2.2 and/or G.k.2.3.r.1 under G.k.2 to identify the drug by name.

Table 1. Descriptions of E2B Data Elements for Reporting Drug Exposure

Data Element	Title	Element Values
G.k.1	Characterization of Drug Role	1 = Suspect 2 = Concomitant 3 = Interacting 4 = Drug not administered
FDA.G.k.10a.r	FDA Additional Information on Drug (coded)	1 = Test 2 = Reference nullFlavor=NA
G.k.2	Drug identification	(Header – no element value)
G.k.2.2	Medicinal Product Name as Reported by the Primary Source	Medicinal product name (free text)
G.k.2.3.r.1	Substance/Specified Substance Name	Drug substance name (free text)

Submitters should provide the drug substance name using the data element G.k.2.3.r.1 and the medicinal product name (or proprietary name), if available, using the data element G.k.2.2. If a drug has no proprietary name, submitters should only provide the drug substance name using the data element G.k.2.3.r.1 and leave the data element G.k.2.2 empty. The submitters should use one of the following element values for the data element FDA.G.k.10a.r: '1' for Test, '2' for Reference or 'NA' (nullFlavor) for all other drugs or if the information is not available. An ICSR should include completed data elements that describe the drug(s) to which the subject was

exposed.

G. Notification of Receipt of Electronic ICSR Submission by the FDA

See FDA's ESG website for further information about receipt of submissions through the ESG.[31] Acknowledgements and notifications indicating the status of each ICSR or ICSR attachment submission, successful acceptance or rejection with reason for rejection, are sent to the submitter. If the acknowledgements or notifications are not received, the submitter should contact the FAERS electronic submission coordinator at faersesub@fda.hhs.gov for assistance. For information on the official FDA receipt date of the submission, refer to *guidance for Industry Providing Regulatory Submissions in Electronic Format — Receipt Dates* (February 2014).

For the SRP, upon completion and submission of the ICSR, the SRP will present a confirmation page that indicates the ICSR was successfully submitted. This confirmation page is your official acknowledgement that FDA has received your completed report.

H. Other Considerations

For submitting IND-exempt BA/BE safety reports as ICSRs, refer to the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products* and the FAERS Electronic Submissions web page[32] for the following information:

- ICH E2B data elements
- Regional specifications of the ICH E2B data elements
- FDA ICSR XML instances with Read Me descriptions

I. Additional Supportive Resource

- *FDA E2B(R3) Core and Regional Data Elements and Business Rules*, available at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

[31] See FDA's *ESG Submission Process*, available at https://www.fda.gov/industry/about-esg/esg-submission-process.

[32] See *FDA Adverse Event Reporting System (FAERS) Electronic Submissions* available at https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.