Small Entity Compliance Guide: Safety Reporting Requirements for INDs and BA/BE Studies

Guidance for Industry and Investigators

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)

October 2026
Drug Safety
Revision 1

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Contains Nonbinding Recommendations

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Contains Nonbinding Recommendations

Small Entity Compliance Guide: Safety Reporting Requirements for INDs and BA/BE Studies Guidance for Industry and Investigators[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for 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 office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to help small businesses understand and comply with FDA's expedited safety reporting regulations for human drug and biological products that are being investigated under an investigational new drug application (IND) or as part of a bioavailability (BA) or bioequivalence (BE) study that is exempt from the IND requirements. FDA has prepared this guidance in accordance with section 212 of the Small Business Regulatory Enforcement Fairness Act (Public Law 104-121). This revision updates information about FDA guidance on safety reporting requirements for INDs and IND-exempt BA/BE studies.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

In the *Federal Register* of September 29, 2010,[2] FDA published a final rule that revised the IND safety reporting requirements for human drug and biological products under 21 CFR part 312 and added safety reporting requirements for persons conducting BA/BE studies under 21 CFR part 320. The final rule revised the definitions used for safety reporting and clarified when to submit expedited safety reports. This Small Entity Compliance Guide (SECG) is intended to

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in conjunction with the Center for Biologics 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-2010-D-0482 (available at https://www.regulations.gov/docket/FDA-2010-D-0482).

[2] 75 FR 59935, Sep 29, 2010.

provide further clarification to small businesses by answering several frequently asked questions from investigators and sponsors regarding the amended safety reporting requirements.

FDA first issued this SECG in December 2012[3] concurrently with the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (2012 final guidance). The 2012 final guidance was intended to help sponsors and investigators comply with the revised requirements for IND safety reporting (21 CFR 312.32 and 312.64(b)) and safety reporting for BA/BE studies (21 CFR 320.31(d)).

In December 2025, FDA issued the guidance for industry *Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (2025 sponsor responsibilities guidance),[4] which incorporated content from the 2012 final guidance and replaced the 2012 final guidance in terms of sponsors' responsibilities for safety reporting requirements for INDs and BA/BE studies. Concurrent with the publication of the 2025 sponsor responsibilities guidance, FDA issued the guidance for investigators, industry, and institutional review boards (IRBs) *Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices* (December 2025) (2025 investigator responsibilities guidance) on investigator responsibilities for adverse event reporting to sponsors and IRBs. The 2025 investigator responsibilities guidance replaced the corresponding recommendations for investigators in the 2012 final guidance and in the guidance for clinical investigators, sponsors, and IRBs *Adverse Event Reporting to IRBs — Improving Human Subject Protection* (January 2009) (2009 procedural guidance). Accordingly, FDA withdrew the 2012 final guidance and the 2009 procedural guidance. FDA is revising this SECG to remove references to these withdrawn guidances.

III. QUESTIONS AND ANSWERS

Q1. Do the amended safety reporting requirements for INDs and BA/BE studies apply to small entities?

Yes, small entities are required to follow the safety reporting regulations for INDs under 21 CFR 312.32 and 312.64(b) and for BA/BE studies under 21 CFR 320.31(d)(3).

Q2. What is a sponsor-investigator? Do these safety reporting regulations apply to sponsor-investigators?

A sponsor-investigator, as defined in 21 CFR 312.3, is "an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The requirements applicable to a sponsor-investigator under this part [312] include both those applicable to an investigator and a sponsor." Therefore, the amended IND safety reporting

[3] See 77 FR 75439, Dec 20, 2012.

[4] 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.

requirements under 21 CFR 312.32 and 312.64(b) apply to a study conducted by a sponsor-investigator (often called an investigator-initiated study).

Q3. How do I comply with the safety reporting requirements if I am a sponsor or sponsor-investigator conducting one trial and do not have access to all of the safety data from other entities (e.g., a commercial sponsor)?

For IND safety reporting, the Agency recognizes that a sponsor or sponsor-investigator may not have access to the complete safety data maintained by a commercial sponsor, but sponsors and sponsor-investigators are required to evaluate all safety information that is available to them to determine whether the information qualifies for reporting (21 CFR 312.32). For example, sponsors and sponsor-investigators should examine reports in the scientific literature and perform literature searches to actively seek new safety information about the drug under investigation. To protect human subjects, the Agency recommends that entities that provide a drug to or receive a drug from other entities share safety information with each other.

Q4. The regulations require reporting in an IND safety report when an aggregate analysis of specific events observed in a clinical trial indicates those events occur more frequently in the drug treatment group than in a control group (21 CFR 312.32(c)(1)(i)(C)). How do sponsors comply with this aggregate reporting requirement?

For IND safety reporting in general, sponsors should have a predefined safety monitoring plan that includes processes and procedures for the review, evaluation, and management of safety information. For reporting events in the aggregate, sponsors should perform an aggregate analysis of specific events both for individual studies and across all studies, including across INDs of the drug, to determine whether they meet the criteria for expedited reporting under 21 CFR 312.32(c)(1)(i)(C) or 312.32(c)(1)(iv). As discussed in Q3, the sponsor should perform these analyses on the data available to them.

Q5. Does this final rule change how sponsors report safety information in the IND annual report (21 CFR 312.33)?

No, the revised IND safety reporting requirements did not make any changes to the IND annual report requirements.

Q6. Does this final rule change what investigators report to their IRBs?

No, the final rule did not change the reporting requirements to IRBs.

Q7. Where can I find additional information on the safety reporting requirements for INDs and BA/BE studies?

FDA has issued guidance on the expedited safety reporting requirements for INDs and BA/BE studies. Industry, investigators, and other interested parties should refer to the 2025 sponsor

responsibilities guidance and the 2025 investigator responsibilities guidance for current guidance on this topic.

Q8. If I have questions about how to comply with this final rule, who should I contact at FDA?

For questions on IND safety reporting, contact the review division in the Center for Drug Evaluation and Research or Center for Biologics Evaluation and Research that has responsibility for review of the IND. For questions on BA/BE safety reporting, contact OGD-PremarketSafetyReports@fda.hhs.gov.

Guidance History*	Date	Description
Revisions to Final Guidance	October 2026	Consistent with Level 2 guidance procedures (21 CFR 10.115(g)(4)), a notice of availability was not issued for this guidance. Changes include updating section II to reflect current history of guidance development on this topic, replacing outdated guidance references, and making minor editorial changes.
Level 2 Guidance	December 2012	See notice of availability for more information about this Small Entity Compliance Guide.**

* This table was implemented beginning October 2026, and previous guidance history may not be captured in totality.

** The notice of availability is accessible via the Search for FDA Guidance Documents web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.