Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices

Guidance for Investigators, Industry, and Institutional Review Boards

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)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

December 2025
Drug Safety

51798224fnl

Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices

Guidance for Investigators, Industry, and Institutional Review Boards

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
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
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
Phone: 800-835-4709 or 240-402-8010
Email: industry.biologics@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances
and/or
Office of Policy
Center for Devices and Radiological Health
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 66, Room 5441
Silver Spring, MD 20993-0002
Email: CDRHClinicalEvidence@fda.hhs.gov
https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/guidance-documents-medical-devices-and-radiation-emitting-products

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)
Center for Devices and Radiological Health (CDRH)
Oncology Center of Excellence (OCE)

December 2025
Drug Safety

Contains Nonbinding Recommendations

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices Guidance for Investigators, Industry, and Institutional Review Boards[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 clinical investigators (investigators) comply with the following safety reporting requirements:

- Investigational new drug application (IND) studies[2] under § 312.64(b) (21 CFR 312.64(b)) and § 312.66 (21 CFR 312.66)
- Investigational device exemption (IDE) studies under § 812.150 (21 CFR 812.150)

Recommendations are provided to help investigators identify the following:

1. For drugs[3]
    - Serious adverse events (SAEs) that must be immediately reported to the sponsor under § 312.64(b)
    - Safety information that is considered an unanticipated problem involving risk to human participants[4] or others and, therefore, requires prompt reporting to institutional review boards (IRBs) under § 312.66

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research, the Center for Devices and Radiological Health, and the Oncology Center of Excellence at the Food and Drug Administration.

[2] This guidance also provides relevant information for persons reporting serious adverse events (SAEs) for bioavailability/bioequivalence (BA/BE) studies that meet conditions for IND exemption under 21 CFR 320.31(d)(3) (IND-exempt BA/BE studies).

[3] In this guidance, *drug* or *drug product* is used to refer to human drugs and to human biological products that are regulated under section 351 of the Public Health Service Act.

[4] FDA's regulations under 21 CFR parts 312, 320, and 812 use the terms *subject* or *human subject*; however, in this guidance, we use the term *participant* instead except when directly quoting the regulations.

2. For devices

    - Safety information that meets the requirements for reporting unanticipated adverse device effects (UADEs) to sponsors and IRBs under § 812.150(a)(1)

This guidance also provides information on investigator review of IND safety reports received from sponsors, reports of safety information from IND-exempt BA/BE studies received from persons conducting the studies, and UADE reports received from sponsors.

This guidance, in conjunction with the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (issued concurrently with this guidance), replaces corresponding recommendations previously provided in the final guidance documents *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012) (the 2012 final guidance) and *Adverse Event Reporting to IRBs—Improving Human Subject Protection* (January 2009) (the 2009 procedural final guidance), which focus on sponsor and investigator responsibilities for safety reporting for investigational medical products. These final guidance documents were withdrawn concurrently with the issuance of this guidance and the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (December 2025).

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

FDA issued the 2009 procedural final guidance in response to concerns raised by the IRB community that increasingly large volumes of individual adverse event reports were inhibiting, rather than enhancing, the ability of IRBs to adequately protect human participants. The following year, FDA published a final rule (2010 IND Safety Reporting Rule)[5] amending the IND safety reporting requirements under § 312.32 (21 CFR 312.32) and adding safety reporting requirements for persons conducting IND-exempt bioavailability (BA) and bioequivalence (BE) studies under § 320.31(d) (21 CFR 320.31(d)). Subsequently, FDA issued the 2012 final guidance to help sponsors and investigators comply with safety reporting requirements for INDs and for BA/BE studies that meet the conditions for IND exemption under § 320.31(d)(3).

[5] 75 FR 59935, September 29, 2010. The final rule, "Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans," published in the *Federal Register* of September 29, 2010 (21 CFR parts 312 and 320).

To further improve the overall quality of safety reporting, this guidance incorporates and clarifies the concepts in FDA's previously published guidance documents on safety reporting responsibilities for investigators of investigational drugs[6] and investigational devices. This guidance replaces the 2009 procedural final guidance and the 2012 final guidance.

This guidance focuses primarily on safety reporting responsibilities of investigators and thus includes only limited information regarding sponsor responsibilities for safety reporting of investigational drugs, including biological products (see section VIII); that topic is the focus of the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies*.

III. DEFINITIONS

A. Drugs

For ease of reference, the following definitions from the 2010 IND Safety Reporting Rule (§ 312.32(a)) are included in this guidance, along with explanations and examples.[7]

1. Adverse Event (21 CFR 312.32(a))

Adverse event means "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related" (§ 312.32(a)).

FDA considers an *adverse event* (also referred to as an *adverse experience*) to include any unfavorable sign (e.g., an abnormal laboratory finding), symptom, or clinical outcome temporally associated with the use of an investigational drug, active control, or placebo, regardless of whether the event is thought to be related to the drug. An adverse event can arise during any use of a drug (e.g., use for a purpose other than FDA-approved indication or in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

2. Adverse Reaction[8] and Suspected Adverse Reaction (21 CFR 312.32(a))

An *adverse reaction* means any adverse event *caused* by a drug.

---

[6] The IND safety reporting requirements in § 312.32 apply to sponsors and sponsor-investigators, as defined in § 312.3. For more information on sponsor responsibilities for IND safety reporting of investigational drugs, see the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (December 2025).

[7] Although the terms defined in § 312.32 refer to sponsor IND safety reporting responsibilities, FDA is using these terms consistently for the purposes of the investigator reporting requirements for drugs discussed in this guidance.

[8] For the purposes of prescription drug labeling that complies with the content and format requirements of 21 CFR 201.56(d) and 201.57 (established by what is commonly referred to as the Physician Labeling Rule (71 FR 3922, January 24, 2006), the term adverse reaction is defined to mean "an undesirable effect, reasonably associated with

Suspected adverse reaction means —

> any adverse event for which there is a *reasonable possibility* that the drug caused the adverse event. **For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.** Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction[.] (§ 312.32(a)) (emphasis added)

Both an adverse reaction and a suspected adverse reaction require evidence of a causal relationship between the drug and the adverse event (§ 312.32(a)). Therefore, if no drug has been administered, an adverse event is not reportable under IND safety reporting regulations.[9,10]

The following examples are also provided in the IND safety reporting regulation (§ 312.32(c)(1)(i)) and illustrate the meaning of *reasonable possibility* with respect to a determination that there may be a causal relationship between the drug and the adverse event:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).

- One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

- An aggregate analysis of specific events observed in a clinical trial that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group. Examples of such events are known consequences of the underlying disease or condition or events that commonly occur in the study population independent of drug therapy.

For aggregate analysis under § 312.32(c)(1)(i)(C), such events could also be associated with treatment or therapy that is standard of care for the disease or condition.

To determine whether an adverse event should be classified as a suspected adverse reaction, or as an adverse reaction, the sponsor must promptly evaluate the available evidence (§ 312.32(b)) and

---

use of a drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence. This definition does not include all adverse events observed during use of a drug, only those adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence of the adverse event" (see § 201.57(c)(7)). For the purposes of prescription drug labeling that complies with the content and format requirements of §§ 201.56(e) and 201.80, the term adverse reaction is defined to mean "an undesirable effect, reasonably associated with the use of the drug, that may occur as part of the pharmacological action of the drug or may be unpredictable in its occurrence" (see § 201.80(g)).

[9] However, for clinical trials that involve an invasive procedure that would not occur other than due to participation in the trial (e.g., intrahepatic artery administration or a kidney biopsy), FDA may request that sponsors also report SAEs associated with such a procedure, even if the investigational product is not administered.

[10] Investigator reporting requirements under §§ 312.64(b) and 312.66 may still apply even where no drug has been administered.

make a judgment about the likelihood that the drug caused the adverse event. See section VIII below.

3. Serious Adverse Event or Serious Suspected Adverse Reaction (21 CFR 312.32(a))

An adverse event, adverse reaction, or suspected adverse reaction is considered *serious* —

> if, in the view of either the investigator or the 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. (§ 312.32(a))

The sponsor and the investigator must evaluate whether an event meets the definition of *serious* (see §§ 312.32(a), 312.32(c)(1)(i), and 312.64(b)). Because identifying SAEs is critically important for the evaluation of potential significant safety problems, it is important that the sponsor consider the investigator's assessment. Therefore, if the sponsor or investigator believes that the event is serious, the event must be considered serious and must be evaluated by the sponsor for expedited reporting (§ 312.32(a) and (c)(1)).

B. Devices

1. Unanticipated Adverse Device Effect (21 CFR 812.3(s))

An *unanticipated adverse device effect* (UADE) means —

> any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (§ 812.3(s))

2. Serious

What qualifies as a serious adverse effect, as that term is used in the definition of UADE, would be specific to the device and the study in which it is being used or tested. Generally, a serious adverse effect is one that is determined by the investigator or sponsor to be life-threatening, require hospitalization, result in disability or permanent damage, result in a congenital anomaly or birth defect, or require an intervention to prevent permanent impairment or damage.

Examples of adverse effects that could be considered serious include organ perforation and thrombus formation inside an aortic endovascular graft. The investigator should consult the protocol for information on adverse effects to help the investigator determine what would qualify as a serious adverse effect.

IV. INVESTIGATOR RESPONSIBILITY FOR REVIEWING SAFETY REPORTS

The investigator should review all IND safety reports received from sponsors as a part of the investigator's responsibility to protect the rights, safety, and welfare of trial participants (see § 312.60). The investigator should similarly review all reports of safety information from IND-exempt BA/BE studies. IND safety reports and reports of SAEs from IND-exempt BA/BE studies provide participating investigators with important information relevant to the safety of human participants receiving the investigational drug.[11] FDA considers the review of these reports critical to fulfilling the investigator's responsibility under § 312.60 to protect the rights, safety, and welfare of participants under their care.

Similarly, investigators of IDE studies should review UADE reports received from sponsors as part of their responsibility to protect the rights, safety, and welfare of participants according to § 812.100.

V. INVESTIGATOR REPORTING TO SPONSORS FOR IND STUDIES[12,13]

Most of the information about the safety of a drug prior to marketing comes from clinical trials. Adverse event reports from investigators are, therefore, critically important, given that it is the investigator who observes a participant's response to an investigational drug.

A. Serious Adverse Event Reporting

The investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug-related, including those listed in the protocol or investigator brochure, as well as an assessment of whether there is a reasonable possibility that the drug caused the event (§ 312.64(b)).

---

[11] See also the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (December 2025).

[12] Guidance provided in this section may be applicable for persons conducting IND-exempt BA/BE studies to comply with § 320.31(d)(3).

[13] For combination products as defined in 21 CFR 3.2(e), IND or IDE safety reporting by the investigator should include a complete discussion of the event with respect to the combination product as a whole, including each constituent part of the product, as appropriate, based on the available information. For questions related to safety reporting for an investigational product, please contact the sponsor for the IND or IDE. FDA's Office of Combination Products is also available for further assistance at combination@fda.gov.

- The investigator, who monitors the participant's response to the drug, is knowledgeable about the participant's clinical state (e.g., medical history, concomitant medications, symptoms, pertinent test results, timing of events relative to drug exposure). Therefore, the investigator may be sensitive to distinctions between events that may be related to study drug exposure versus those caused by the underlying disease process and/or concomitant therapies.

- The report should generally include information about the trial participant (such as sex, age, other demographic characteristics), a description (as detailed as possible) of the event (including any diagnostic testing results, interventions, outcomes), and the reporting source (if not the investigator).

- Although the sponsor is ultimately responsible for determining whether an SAE should be classified as a serious *suspected adverse reaction* (see section VIII), the investigator's view is important for the sponsor to carefully consider when assessing the safety of the drug, including whether there is a reasonable possibility that the drug caused the event, and determining whether the event is one that is required to be reported to FDA according to § 312.32.

- For the purposes of § 312.64(b), FDA interprets *reasonable possibility* to mean there is evidence to suggest a causal relationship between the drug and the adverse event. This interpretation is consistent with the definition of *suspected adverse reaction* in § 312.32(a).

  – Factors that should be considered when making a causality assessment include, but are not limited to, temporal relationship of the event to drug administration; biologic plausibility; the mechanism of action of the drug or similar drugs in the same class; nonclinical evidence; and dechallenge-rechallenge information.

B. Timing of Serious Adverse Event Reporting

The investigator must immediately report to the sponsor any serious adverse event (§ 312.64(b)), although more data may be collected and submitted after submitting the initial report.

- For the purposes of this guidance, the Agency interprets *immediately* to be as soon as feasible after the investigator recognizes an event is an SAE and obtains relevant information for the sponsor.

- FDA recommends that this time frame for submitting such initial information also be specified in the protocol and anticipates that the time frame for submission of initial information will generally not exceed 1 calendar day.

C. Study Endpoint Reporting

1. The investigator must immediately report to the sponsor all study endpoints that are SAEs (e.g., all-cause mortality) when there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis after exposure) (§ 312.64(b)).

2. When there is ***no*** evidence suggesting a causal relationship between the drug and the event, the investigator must report study endpoints that are SAEs in accordance with the protocol (§ 312.64(b)).

D. Nonserious Adverse Event Reporting

The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol (§ 312.64(b)).

- Often, nonserious events are recorded and submitted to the sponsor and reviewed at regular intervals throughout the course of the investigation.

- The investigator is not required to assess causality of nonserious adverse events under § 312.64(b), although many sponsors may require it in the protocol.

VI. INVESTIGATOR REPORTING TO INSTITUTIONAL REVIEW BOARDS FOR IND STUDIES[14]

The investigator must promptly report to the IRB all unanticipated problems involving risk to human participants or others (§ 312.66),[15,16] and the investigator should be familiar with and adhere to the IRB's written procedures for reporting these unanticipated problems to the IRB (21 CFR 56.108(b)(1)).[17]

- IND safety reports and reports of SAEs from IND-exempt BA/BE studies received from the sponsor describe important safety information representing unanticipated problems involving risk to human participants or others.

[14] Guidance provided in this section may be applicable for persons conducting IND-exempt BA/BE studies to comply with § 320.31(d)(3).

[15] We note that IND-exempt BA/BE studies are not subject to the requirements in § 312.66. However, they must still be conducted in compliance with the requirements for review by IRBs as established in 21 CFR part 56 (see § 320.31(d)(2)). Section 56.108(b)(1) provides that an IRB's written procedures must ensure the prompt reporting to the IRB of "any unanticipated problems involving risks to human subjects or others." FDA interprets this language in a manner consistent with the interpretation of § 312.66 laid out in this guidance.

[16] Sponsors may require investigators to report to them such unanticipated problems as part of the sponsor's clinical trial monitoring responsibility (see, e.g., § 312.50).

[17] A non-U.S. IRB/Ethics Committee in a multinational study may have additional reporting requirements.

  - The investigator must submit IND safety reports[18] to the IRB (§ 312.66) because FDA considers safety information that meets the IND safety reporting criteria under § 312.32(c) to be an unanticipated problem involving risk to human participants or others.

  - FDA considers the occurrence of any SAE in an IND-exempt BA/BE study to be an unanticipated problem involving risk to human participants or others that must be reported to the IRB (§ 56.108(b)(1)). Reporting SAEs in a BA/BE study is important for human participant protection because the occurrence of SAEs in BA/BE studies is unusual: the number of participants enrolled is small, the participants are usually healthy volunteers, and drug exposure is typically brief, although often at the highest available dosage.

- Certain events may not meet the criteria for reporting in an IND safety report or as a BA/BE study premarket SAE, but still must be reported to the IRB because they represent unanticipated problems involving risk to human participants or others.

  - Such events may occur at the participant, site, and/or study level and may include serious and unexpected adverse events that occur prior to test article administration, during a washout period, or that are attributable to a screening procedure.

  - Other examples may include reports of medication errors (such as receipt of wrong dose or contaminated study medication), breach of privacy/confidentiality (such as disclosure of personally identifiable information), untimely destruction of study records, and other scenarios.

- The IRB may have written procedures or institutional policies that require the investigator to submit to them other events, in addition to those that qualify for reporting under § 312.66.

VII. INVESTIGATOR REPORTING TO SPONSORS AND INSTITUTIONAL REVIEW BOARDS FOR IDE STUDIES

The IDE regulations require the investigator to report UADEs to both the sponsor and the IRB (see § 812.150(a)(1)). The investigator is required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (§ 812.150(a)(1)). In addition to reporting UADEs, the

[18] Many study protocols specify that the sponsor will submit IND safety reports to the IRB on the investigator's behalf. In these situations, where the investigator receives confirmation that the sponsor has sent the report to the IRB, FDA would not expect an investigator to provide the IRB with a duplicate copy of the report. Such an agreement should be documented.

investigator is to provide progress reports to the sponsor, the monitor, and the IRB[19] at regular intervals and no less than yearly (§ 812.150(a)(3)). Such reports should provide information about both anticipated and unanticipated adverse device effects.

VIII. SPONSOR RESPONSIBILITIES

While the focus of this guidance is on investigator responsibilities, this guidance discusses some of the sponsor responsibilities[20] given the close relationship between investigators and sponsors in the IND and IDE safety reporting process.

The regulations in § 312.32(c)(1) require the sponsor to notify FDA and all participating investigators (i.e., all investigators to whom the sponsor is providing the drug under the sponsor's INDs or under any sponsor-investigator's IND) in an IND safety report[21] of potential serious risks identified from clinical trials or any other source as soon as possible but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting under § 312.32(c)(1)(i) through (iv), which includes any of the following:

- Serious and unexpected suspected adverse reactions[22]
- Findings from epidemiological studies, pooled analyses of multiple studies, or clinical studies that suggest a significant risk in humans exposed to the drug
- Findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug
- Any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure

For IND-exempt BA/BE studies, § 320.31(d)(3) states that "[t]he person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event [SAE], as defined in § 312.32(a), observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of

[19] The terms *sponsor*, *monitor*, and *IRB* for purposes of the IDE regulations are defined in § 812.3.

[20] For an in-depth discussion of sponsor responsibilities, see the guidance for industry *Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies* (December 2025).

[21] For more information on electronic submission of IND safety reports, see the guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (April 2024) and the guidance for industry *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products* (April 2024).

[22] Note that if the unexpected suspected adverse reaction is fatal or life-threatening, the requirement is to notify FDA as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information (see § 312.32(c)(2)). As with all serious and unexpected suspected adverse reactions, sponsors must report unexpected fatal or life-threatening suspected adverse reactions to all participating investigators (see § 312.32(c)(1)).

its occurrence." Section 320.31(d)(3) also requires the person conducting the study (including any contract research organization) to notify FDA of any "fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence." However, the regulation does not require all investigators to be notified of such events within that time frame.

FDA believes that the sponsor is generally better positioned than the individual investigator to determine whether an SAE should be classified as a serious *suspected adverse reaction*. This is especially true for events that may warrant analysis of more than a single event to determine if any are possibly related to the drug, because the sponsor may have access to SAE reports from multiple study sites and multiple studies and would be able to aggregate and analyze these reports. Moreover, the sponsor is likely to be more familiar with the drug's mechanism of action, class effects, and other information. The sponsor should carefully consider the investigator's assessment of causality; however, it is ultimately the sponsor's responsibility to determine whether an SAE meets the definition of a serious *suspected adverse reaction* (see section III.A.2 and section V.A). It is also the sponsor's responsibility to determine whether an adverse event is *unexpected* (§ 312.32(a) and (c)(1)(i)).

For IDE studies, FDA also believes that the sponsor is generally better positioned than the individual investigator to assess UADEs and their impact on the investigation, given that the sponsor may have access to UADE reports from multiple study sites and multiple studies and is able to aggregate and analyze these reports. Therefore, review of UADE reports by sponsors is critical to the protection of participant safety, and the IDE regulations require not only timely reporting for investigators but also timely evaluation by sponsors. For device studies under an IDE, the regulations in 21 CFR 812.46(b) and 812.150(b)(1) require sponsors to conduct an evaluation of any UADE immediately and to report the results to FDA, all reviewing IRBs, and all participating investigators within 10 working days after the sponsor first receives notice of the effect. What qualifies as a UADE is expected to vary depending on the specific device and the way the device is used within the study. Therefore, sponsors are required to include risk information in the investigational plan, and to provide copies of the investigational plan to all investigators participating in the investigation, which may help investigators identify and assess potential UADEs (§§ 812.25(c) and 812.45).