Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies

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)

December 2025
Drug Safety

Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies

Guidance for Industry

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/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
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

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)

December 2025
Drug Safety

TABLE OF CONTENTS

Contains Nonbinding Recommendations

Sponsor Responsibilities — Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies
Guidance for Industry[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 provides recommendations to help sponsors comply with the expedited safety reporting requirements for human drug and biological products[2] that are being investigated (1) under an investigational new drug application (IND) (21 CFR 312.32); or (2) as part of a bioavailability (BA) or bioequivalence (BE) study that is exempt from the IND requirements (21 CFR 320.31(d)(3)).

This guidance provides interpretations of terms used for safety reporting, makes recommendations on when and how to submit a safety report, and provides information on other safety reporting issues raised by sponsors.

To facilitate appropriate IND safety reporting practices, this guidance also provides recommendations related to the two IND safety reporting provisions (§ 312.32(c)(1)(i)(C) and (c)(1)(iv)) that require assessment of aggregate data.

This guidance finalizes the draft guidance of the same title issued in June 2021 (the June 2021 draft guidance), which incorporated content from the final guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (December 2012) (the 2012 final guidance) and from the draft guidance for industry *Safety Assessment for IND Safety*

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

[2] This guidance applies to drugs, including biological products. 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.

Reporting (December 2015) (the 2015 draft guidance).[3] This guidance includes revised recommendations initially described in the 2015 draft guidance and June 2021 draft guidance on the following topics: (1) planned unblinding of safety data and implications for trial integrity (see section VI); (2) increased flexibility regarding the party reviewing aggregate safety information for IND safety reporting purposes (see section VI.B); (3) clarification regarding the scope and methodology of aggregate analyses (see section VI.C); and (4) clarification regarding the plan for safety surveillance, including what elements should be included in the plan (see section V.A).

With respect to the content from the 2012 final guidance that was incorporated into this guidance, a considerable amount remains unchanged. However, this guidance includes updated recommendations on submissions of IND safety reports and replaces the 2012 final guidance in terms of sponsors' responsibilities for safety reporting requirements for INDs and BA/BE studies. This guidance does not incorporate content on investigator reporting (§ 312.64(b)) from the 2012 final guidance. Concurrent with the publication of this guidance, FDA issued the guidance for investigators, industry, and institutional review boards *Investigator Responsibilities — Safety Reporting for Investigational Drugs and Devices* (December 2025) on investigator responsibilities for adverse event reporting that replaces the corresponding recommendations for investigators in the 2012 final guidance. Accordingly, the 2012 final guidance was withdrawn upon the publication of these two guidances.

This guidance addresses reporting of serious adverse events (SAEs) in the setting of a clinical investigation conducted under an IND. Drugs used in such clinical investigations may be unapproved drugs or those that are already marketed or approved in the United States. For drugs already marketed or approved, additional reporting requirements for safety information from clinical studies are specified by the relevant postmarketing safety reporting requirements (e.g., under 21 CFR 314.80, 329.100, 600.80, or 606.170; see also § 312.32(c)(4)). This guidance does not address those obligations.

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

On September 29, 2010, FDA published a final rule (75 FR 59935) amending the IND safety reporting requirements under 21 CFR 312.32 and adding safety reporting requirements for persons conducting IND-exempt BA and BE studies under § 320.31. The IND safety reporting regulations distinguish between circumstances in which it is appropriate to submit IND safety

[3] 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. The 2015 draft guidance was withdrawn upon the publication of the June 2021 draft guidance.

reports based on individual cases (§ 312.32(c)(1)(i)(A) and (B)) and circumstances in which an IND safety report would need to be based on an aggregate analysis of SAEs to determine whether the events occur more frequently in the drug treatment group (§ 312.32(c)(1)(i)(C)). Compliance with these requirements increases the likelihood that submitted information will be interpretable and will meaningfully contribute to the developing safety profile of the investigational drug and improve the overall quality of safety reporting.

Timely reporting of the required safety information allows FDA to consider whether any changes in study conduct should be made beyond those initiated by the sponsor and allows investigators to make any changes that are needed to protect participants.[4] An effective systematic approach by sponsors to safety surveillance, coupled with limiting the scope of IND safety reports to FDA and participating investigators (and subsequent reporting to involved institutional review boards) to **suspected adverse reactions that are both serious and unexpected**, allows all parties to focus on important safety issues and take actions needed to minimize the risks of participation in a clinical trial.[5]

The 2010 final rule also requires sponsors to report findings from other studies (§ 312.32(c)(1)(ii)) and findings from animal[6] or in vitro testing (§ 312.32(c)(1)(iii)) that suggest a significant risk to humans exposed to the drug and to report an increased occurrence of serious suspected adverse reactions over those listed in the protocol or investigator brochure (§ 312.32(c)(1)(iv)).

III. DEFINITIONS

A. Adverse Event (§ 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, an active control, or a 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 the FDA-approved indication or in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

---

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

[5] In most cases, such events will lead to an update to the investigator brochure and/or informed consent.

[6] We support the principles of the *3Rs*, to *reduce, refine, and replace* animal use in testing when feasible. We encourage sponsors to consult with us if they wish to use a non-animal testing method they believe is suitable, adequate, validated, and feasible. We will consider if such an alternative method could be assessed for equivalency to an animal test method.

B. Adverse Reaction[7] and Suspected Adverse Reaction (§ 312.32(a))

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

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. Therefore, if no drug has been administered, an adverse event is not reportable under IND safety reporting regulations.[8]

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.

---

[7] 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 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)).

[8] However, for clinical investigations 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 drug is not administered.

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 make a judgment about the likelihood that the drug caused the adverse event. For an adverse event to be considered a suspected adverse reaction, the sponsor should conclude that there is a reasonable possibility that the drug caused the adverse event. FDA considers the application of the *reasonable possibility* causality standard to be consistent with the discussion about causality in the International Council for Harmonisation (ICH) guidance for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1995) (the ICH E2A guidance). However, FDA notes there is a difference between the IND safety reporting regulation under § 312.32 and the ICH E2A guidance with respect to who is responsible for making a judgment about whether there is evidence to suggest a causal relationship between the drug and the adverse event for reporting purposes. Although the ICH E2A guidance[9] recommends reporting the adverse event as a suspected adverse reaction if either the investigator or the sponsor makes a judgment that there is a reasonable suspected causal relationship, under § 312.32, the sponsor is responsible for making this judgment.

C. Unexpected (§ 312.32(a))

An adverse event or suspected adverse reaction is considered *unexpected* if (1) it is not listed in the investigator brochure[10] or it is not listed at the specificity or severity that has been observed in the study population; or (2) if the investigator brochure is not required or available, it is not consistent with the risk information described in the general investigational plan. For example, if the listed term in the investigator brochure is erythema, a reported event of Stevens-Johnson Syndrome is both more specific and more severe than the term in the investigator brochure and would therefore be considered unexpected. In addition, if the event occurs at a rate that is meaningfully higher than listed in the investigator brochure,[11] that rate would be considered to make the event more specific or severe than that listed in the investigator brochure, and it would also be considered unexpected. Events must be listed in the investigator brochure, when one is required, if they have been observed with the particular drug under investigation and a causal relationship with the drug is suspected or confirmed (see §§ 312.23(a)(5) and 312.55).[12]

---

[9] See the ICH E2A guidance, pages 6–7.

[10] For an FDA-approved drug, an unexpected adverse event would include adverse events not listed in the FDA-approved labeling.

[11] Not all adverse events listed in an investigator brochure will have incidence estimates. To the extent that incidence estimates of adverse events are provided early in a development program, they may be an overestimation based on small numbers.

[12] The investigator brochure should not list adverse events that are unlikely to have been caused by the drug because such lists could dilute clinically meaningful risk information.

When new adverse event information is received, it is the sponsor's responsibility to determine whether the event is *unexpected* for IND safety reporting purposes.

For example, under this definition of *unexpected*, if the investigator brochure referred only to elevated hepatic enzymes or hepatitis, an event of hepatic necrosis would be unexpected (by virtue of greater severity). Similarly, intracerebral hemorrhage and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. *Unexpected* also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as predicted to occur from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation. For example, although angioedema is known to occur in some individuals exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and therefore would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes until angioedema is included in the investigator brochure as occurring with the drug under investigation. Likewise, safety-related findings from animal studies that have not been observed with the drug under investigation in humans would also be considered *unexpected* until such an event occurs in humans and is listed in the investigator brochure as an adverse or suspected adverse reaction.

There has been some confusion about the terms *expected* and *anticipated* as used for the purposes of IND safety reporting. The terms have distinct meanings:

- *Expected* refers to adverse or suspected adverse reactions to the drug that are listed in the investigator brochure or, if an investigator brochure is not required or available, that are consistent with the risk information described in the general investigational plan. Events that are listed in the investigator brochure are considered *expected* because they have been observed with the particular drug under investigation and a causal relationship with the drug is suspected or confirmed.

- *Anticipated* refers to adverse events that are likely to occur in the study population because the adverse events (1) reflect consequences of participants' underlying disease or factors such as age and (2) are events that may occur in the study population unrelated to an effect of a drug (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population).

The term *expected* has been incorrectly used to describe adverse events that are *anticipated* in individuals with the disease being treated or population being studied but are not listed in the investigator brochure as adverse or suspected adverse reactions. For reporting purposes, events that are *anticipated* for the disease being treated or the population being studied would be considered *unexpected* if the events are not listed in the investigator brochure (i.e., the investigational drug is not suspected or known to cause the events).

To summarize, an adverse event that is *anticipated* in the population being studied refers to an event that would be seen in this population *independent of investigational drug exposure.* An *expected* adverse or suspected adverse reaction refers to an adverse event that is known or

suspected to be *caused by the investigational drug* and is listed in the description of the adverse or suspected adverse drug reactions in the investigator brochure or, if an investigator brochure is not required or available, as consistent with the risk information described in the general investigational plan.

D. Serious (§ 312.32(a))

An adverse event, adverse reaction, or suspected adverse reaction 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. 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)).

E. Life-Threatening (§ 312.32(a))

An adverse event or suspected adverse reaction is considered *life-threatening* —

> if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death. (§ 312.32(a))

For example, not all seizures are considered life-threatening, although the most severe form, status epilepticus, is a life-threatening medical emergency.

As with the definition of *serious*, the determination of whether an adverse event is life-threatening can be based on the opinion of either the investigator or sponsor. Thus, if *either* believes that the adverse event meets the definition of life-threatening, it must be considered life-threatening for reporting purposes (§ 312.32(a)).

IV. OVERVIEW OF IND SAFETY REPORTING REQUIREMENTS

Under § 312.32(c), the sponsor is required to notify FDA and all participating investigators through an IND safety report of potential serious risks from clinical trials or any other source as soon as possible but no later than 15 calendar days after the sponsor determines that the information qualifies for reporting in an IND safety report. Participating investigators include all investigators, at U.S. and non-U.S. sites, to whom the sponsor is providing the drug under any of its INDs or under any investigator's IND (§ 312.32(c)(1)).[13] For unexpected fatal or life-threatening suspected adverse reaction reports, the sponsor must notify FDA as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information (§ 312.32(c)(2)). (See the Appendix for a flowchart to help determine whether an adverse event meets the criteria for IND safety reporting to FDA. See section VIII.E of this guidance for a discussion of IND safety reporting time frames.)

In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information known to the sponsor (i.e., conduct an analysis of similar events including, for example, similar IND safety reports from all INDs for the same drug held by the sponsor and related reports or adverse events available from pre- and postmarketing studies) (see § 312.32(c)(1)). For example, if the sponsor plans to submit an IND safety report for pulmonary embolus, the sponsor should look to see if IND safety reports were previously submitted for other thrombotic events (e.g., deep vein thrombosis) to analyze the occurrence of medically related adverse events. Similarly, for an IND safety report for fracture, the sponsor should consider whether IND safety reports previously submitted for falls are relevant to the analysis of the significance of the event.

Sponsor-investigators, as defined in § 312.3(b), are required to comply with both the sponsor and the investigator responsibilities under 21 CFR part 312. FDA recognizes that a sponsor-investigator may need to rely on the investigational drug supplier for updated safety information in order to meet their obligations under the IND safety reporting regulations (see § 312.32(b)). To protect participants, FDA recommends that entities that provide a drug to or receive a drug from other entities share safety information with each other.

[13] Although not required by regulations, FDA recommends that sponsors notify investigators at non-IND sites of information meeting IND safety reporting criteria in a similar time frame as required for IND safety reports to protect participant safety.

A. Serious and Unexpected Suspected Adverse Reaction (§ 312.32(c)(1)(i) and (c)(1)(iv)[14])

The sponsor must report in an IND safety report any suspected adverse reaction to the study treatment that is both serious and unexpected (§ 312.32(c)(1)(i)).[15] Before submitting an IND safety report, the sponsor needs to ensure that the event meets three criteria: (1) it is serious; (2) it is unexpected (i.e., is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed) or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan; and (3) there is evidence to suggest a causal relationship between the drug and the adverse event (i.e., it is a suspected adverse reaction). **If the adverse event does not meet all three criteria, it should not be submitted as an IND safety report**.[16]

Deciding whether the SAE meets the definition of a *suspected adverse reaction* is usually the most difficult determination, but this decision is critical to avoiding the submission of uninformative IND safety reports. Once the adverse event is determined to be serious and unexpected, the *sponsor* must evaluate the available information and decide whether there is a reasonable possibility that the drug caused the adverse event and, therefore, that the event also meets the definition of a *suspected adverse reaction* (§ 312.32(c)(1)(i)). Serious and unexpected suspected adverse reactions must be reported in an IND safety report (§ 312.32(c)(1)(i)).

Under § 312.64(b), investigators are required to provide a causality assessment for each SAE reported to the sponsor. The sponsor should consider the investigator's assessment but must submit an IND safety report *only* for those events for which the *sponsor* determines there is a reasonable possibility that the drug caused the event (§ 312.32(c)(1)(i)). Thus:

- The sponsor *should not* report events for which the investigator's assessment is positive for causality but the sponsor's evaluation did not find evidence to suggest a causal relationship between the drug and the event.

[14] FDA considers a clinically important increase in the rate of occurrence of expected serious suspected adverse reactions over that listed in the protocol or investigator brochure to be unexpected. In this guidance, "expected serious suspected adverse reactions" refer to serious suspected adverse reactions listed in the investigator brochure or, if an investigator brochure is not required or available, that are consistent with the risk information described in the general investigational plan.

[15] For study treatments that are marketed or approved in the United States, postmarketing safety reporting requirements (§§ 314.80 and 600.80) apply to the application holder. As a result, unless the IND sponsor and application holder are the same, or the application holder becomes aware of the suspected adverse reaction, these reactions would not be submitted as a postmarketing 15-day Alert report. Requiring sponsors to report all suspected adverse reactions that meet the standard for reporting, even those that occur with the control drug, in IND safety reports will minimize the risk that suspected adverse reactions will not be reported to FDA. Such reporting is essential for participant safety. FDA also recommends that if the sponsor is not the application holder, the sponsor should also forward the report to the application holder of the marketed drug.

[16] Adverse events that do not meet the criteria for reporting in an IND safety report must still be reported in accordance with the periodic reporting regulations, when applicable (e.g., § 312.33 IND annual report).

- The sponsor *must* report events for which the investigator's assessment is negative for causality but the sponsor's evaluation found evidence to suggest a causal relationship between the drug and the event (§ 312.32(c)(1)(i)).

The investigator's assessment of causality must be included in the report submitted to the sponsor (see § 312.64(b)). If the investigator fails to provide a causality assessment or assesses the causality as unknown, the sponsor will need to evaluate the event without the investigator's assessment (see § 312.32(b) and (c)).

Serious and unexpected suspected adverse reactions reported in an IND safety report can be divided into four categories depending on the type of event. As discussed below in sections IV.A.1.a and b, the first two categories (§ 312.32(c)(1)(i)(A) and (B)) can generally be assessed on the basis of an individual or a small number of events. Aggregate analyses are needed for (1) anticipated SAEs for which it is difficult or impossible to make a causal determination based on a single case or a small number of cases (see § 312.32(c)(1)(i)(C)); or (2) expected serious suspected adverse reactions that must be reported if there is a clinically important increase in the rate over that described in the protocol or investigator brochure (§ 312.32(c)(1)(iv)). For the first of the two situations, an aggregate analysis comparing the rate of such SAEs in the intervention arm compared to a control is needed. For the second of the two situations, an aggregate analysis is needed to determine the rate in the investigational arm compared to the known rate from the investigator brochure or labeling.

If the study under an IND uses a control drug that is approved or marketed in the United States, serious and unexpected adverse events in the control group that can be assessed as *suspected adverse reactions* based on an individual or small number of events must be reported by the IND sponsor in a safety report as individual events as described in § 312.32(c)(1)(i)(A) and (B). If the sponsor is not the application holder[17] of the control drug, the sponsor should also forward the report to the application holder. If the sponsor is also the application holder for the control drug, the serious and unexpected suspected adverse reaction must also be submitted as required under postmarketing regulations. See § 312.32(c)(4); see also §§ 310.305, 314.80, and 600.80.

An aggregate analysis to determine whether there is an increase in anticipated SAEs in the group receiving the investigational drug (that would need to be reported under § 312.32(c)(1)(i)(C)) may demonstrate that the rate of the anticipated adverse event is higher in the control arm than in the investigational drug arm. This is not likely to be a frequent occurrence, and FDA recognizes that additional context may be needed to interpret such aggregate analysis results if the sponsor is not the application holder for the control drug (e.g., if the aggregate event rate is higher in the active control group than in the investigational drug group, it could be that the investigational drug is protective rather than that the control drug is causing an increased rate of the adverse event). For an imbalance suggesting a substantially higher rate of an anticipated SAE in the control group not explained by a protective effect of the investigational drug, FDA recommends

[17] We note that the postmarketing reporting requirements concerning the submission of postmarketing 15-day Alert reports (§ 314.80(c)(1)(i) and (ii)) apply not only to the application holder but also to any other person whose name appears on the label of an approved drug product as the manufacturer, packer, or distributor of the marketed drug. See § 314.80(c)(1)(iii).

that the sponsor report such an imbalance to the application holder, who is in a better position to assess the event and determine if reporting is necessary. If the sponsor does not share it with the application holder, then it should be reported to FDA. FDA acknowledges that a small number of events in a single trial may not inform the known safety profile of a well-characterized approved control drug; thus the reporting threshold (i.e., the threshold at which the sponsor determines that there is a reasonable possibility that the drug caused the anticipated SAE) for a well-characterized approved control drug could be higher than for the investigational drug. The sponsor should also consider sharing with the application holder the events that suggest a higher rate in the active control group even if the events do not rise to the level of IND safety reporting.

1. Events That Do Not Require Aggregate Analyses

a. Individual occurrences (§ 312.32(c)(1)(i)(A))

Certain SAEs are informative as single cases because they are "uncommon and known to be strongly associated with drug exposure" (§ 312.32(c)(1)(i)(A)). Some examples include angioedema, certain blood dyscrasias (e.g., agranulocytosis), rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome. The occurrence of even one case of such an SAE, where another cause has not been established, would meet the definition of *suspected adverse reaction* (i.e., there is a reasonable possibility that the drug caused the event) and therefore must be reported in an IND safety report (§ 312.32(c)(1)(i)(A)).

The blind should ordinarily be broken for these types of IND safety reports that are submitted to FDA and all participating investigators. Knowledge of the treatment received is necessary to interpret the event and determine whether it is a suspected adverse reaction. Further, such knowledge may be essential for the medical management of the participant and may provide critical safety information about a drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). Because these cases are expected to occur infrequently, FDA does not anticipate that unblinding single or small numbers of serious and unexpected adverse event cases will compromise trial integrity. For example, a single case of liver injury would be unblinded but would have no effect on overall study integrity. Moreover, when a study participant experiences this type of SAE that is individually reportable, it is unlikely that the participant will continue receiving the drug treatment. The challenges arising from unblinding safety data for aggregate data analyses are discussed in sections VI.B through D of this guidance.

If the blind is broken and a participant with an adverse event that would meet the criteria for reporting as a single event was receiving a placebo, the event should not be reported in an IND safety report. If the blind is broken and the participant was receiving drug treatment (investigational drug or active comparator), it must be reported in an IND safety report (§ 312.32(c)(1)(i)(A)).

b. One or more occurrences (§ 312.32(c)(1)(i)(B))

One or more occurrences of an SAE "that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug" meets the definition of a suspected

adverse reaction and therefore must be reported in an IND safety report (§ 312.32(c)(1)(i)(B)). If the event occurs in association with other factors strongly suggesting causation (e.g., strong temporal association, event recurs on rechallenge), a single case may be sufficiently persuasive to report in an IND safety report. Often, more than one occurrence from one or multiple studies would be needed before the sponsor could determine that there is a *reasonable possibility* that the drug caused the event. Examples include tendon rupture or heart valve lesions in young adults or intussusception in healthy infants. For reasons similar to those given above in section IV.A.1.a regarding individual occurrences, such events should be unblinded.

2. Events That Require Aggregate Analyses

a. Events anticipated to occur in the study population, independent of drug exposure (§ 312.32(c)(1)(i)(C))

Certain SAEs can be anticipated to occur in the study population independent of investigational drug exposure. Such events include:

- Events common in the study population, such as:
  - Events related to the underlying disease or condition under investigation (e.g., death due to progressive disease in an oncology trial, pneumonia in participants with chronic obstructive lung disease, diabetic ketoacidosis in a trial of type 1 diabetes management, hospitalization for gait disturbance reported in a multiple sclerosis trial)
  - Events that are common in a population regardless of the underlying condition being studied (e.g., cardiovascular events or hip fracture in an older adult population)
- Events known to occur with drugs administered as part of a background regimen (e.g., neutropenia with a myelosuppressive chemotherapeutic agent, intracerebral hemorrhage with an anticoagulant, cytomegalovirus colitis with an immunosuppressive regimen)

Although these anticipated SAEs would meet the definition of unexpected in § 312.32(a) if they are not listed in the investigator brochure (see section III.C of this guidance), they do not warrant expedited IND safety reporting as individual cases or even when there are a number of such events where the incidence is consistent with background rates in the study population. Such anticipated SAEs will occur even if the investigational drug does not cause them, and their occurrence alone will generally not support a conclusion that there is a reasonable possibility that the drug caused the events. To assess whether the drug could have caused or contributed to the SAE that is anticipated in the population, the sponsor should perform an aggregate analysis that will enable an assessment of whether there is a greater occurrence of the anticipated adverse event in a population exposed to the drug as compared to the rate of the same SAE in a similar population not exposed. (See section VI of this guidance for details on conducting an aggregate analysis.)

An anticipated SAE must be reported to FDA in an IND safety report if an aggregate analysis reveals there is an imbalance between study arms that is sufficient to conclude that there is a

reasonable possibility that the drug caused the increased incidence of the SAE (§ 312.32(c)(1)(i)(C)). The sponsor should consider all relevant drug development data (in addition to the clinical trial data) when determining whether there is a reasonable possibility that the drug caused the SAE. (See section IV.B.1 of this guidance for factors to consider when interpreting imbalances in aggregate data and section V of this guidance for a list of sources of safety information that must be evaluated.)

b. Increased occurrence of an expected serious suspected adverse reaction (§ 312.32(c)(1)(iv))

The sponsor must report any clinically important increase in the rate of an expected serious suspected adverse reaction over that listed in the protocol or investigator brochure or that is otherwise evident from the risk information described in the general investigational plan (§ 312.32(c)(1)(iv)). The sponsor should perform an aggregate analysis to compare the rate of a serious suspected adverse reaction seen in the study to the rate listed in the protocol or investigator brochure or otherwise estimated.

The sponsor's determination of whether the increase in the rate of an expected serious suspected adverse reaction is clinically important and is thus required to be reported under § 312.32(c)(1)(iv) is a matter of judgment based on a variety of factors, including the study population, the nature and seriousness of the reaction, and the magnitude of the observed increase in the incidence rate. Monitoring the rate of these events in a blinded trial requires a systematic safety surveillance process that will protect the integrity of the trial; this is discussed in section VI of this guidance.

B. IND Safety Reporting Criteria for Aggregate Data

Determining when the aggregate safety data provide evidence suggesting (1) a causal relationship between the drug and an SAE (e.g., myocardial ischemia) or (2) that there has been a clinically important increase in the rate of an expected serious suspected adverse reaction (i.e., determining whether the reporting threshold has been met) is a complex judgment. It is almost never a simple application of a planned statistical analysis, and the determination may change as data accumulate. FDA recognizes that these determinations can be difficult and require judgment. It may be helpful for sponsors to document in internal records all aggregate analyses of SAEs, including those that are determined not to meet the reporting threshold. In the event of a disagreement regarding a causality assessment between the sponsor and an entity designated to evaluate aggregate safety data, detailed documentation of the justification for submitting or not submitting an IND safety report is recommended. Documentation of such justification and of the aggregate analysis is important because FDA will focus primarily on the robustness of the sponsor's process and the reasoning underlying the sponsor's decision if, during FDA's review of trial safety data, FDA reaches a different conclusion about whether an IND safety report was warranted. The sponsor may also prespecify reporting thresholds in its safety surveillance plan that, if exceeded, would lead to submission of an IND safety report.

1. Serious and Unexpected Suspected Adverse Reactions (§ 312.32(c)(1)(i)(C))

As noted previously, for the purposes of IND safety reporting, a suspected adverse reaction means there is a *reasonable possibility* that the drug caused the event (i.e., evidence to suggest a causal relationship between the drug and the adverse event) (§ 312.32(a)). When interpreting imbalances in aggregate data between study arms, both clinical and statistical (if applicable) expertise will usually be needed to determine whether that reasonable possibility exists, based on the totality of available information.

Factors to consider when determining whether the reasonable possibility threshold has been met:

- Extent of the increase in incidence seen in the test group compared to the control group(s) and the uncertainty around that difference
- Evidence of a dose response
- Temporal relationship (for example, early increase post-drug initiation, such as drug-induced liver injury occurring in the usual 1- to 6-month window, or malignancy events occurring after a lag period between the dates of exposure and date of event onset)
- Consistency of the increase in multiple trials
- Presence of a plausible mechanism of action
- Nonclinical evidence (from toxicology or pharmacology animal studies, genetic studies such as knock-out or knock-in mouse models, or human genetic data) to support the finding
- Pharmacology of the drug (including results from receptor, transporter, or enzyme binding or activation studies, and animal models) and known class effects
- Pattern across the study population (for example, the event is observed more frequently in individuals likely to be susceptible to it (e.g., acute kidney injury in individuals with prior chronic kidney disease, myocardial infarctions in older individuals or those with existing coronary heart disease, hyperkalemia in individuals on ACE inhibitors))
- Occurrence of other potentially related adverse events (for example, occurrence of both strokes and transient ischemic attacks, unexpectedly large increase in creatine kinase and events of rhabdomyolysis)

2. Increased Rate of Occurrence of Expected Serious Suspected Adverse Reactions (§ 312.32(c)(1)(iv))

For previously recognized serious suspected adverse reactions, clinical judgment is needed to determine whether a suspected adverse reaction to the investigational drug is occurring at a clinically important increased rate relative to the rate provided in the investigator brochure or

otherwise estimated based on data or analysis in the investigator brochure. Factors to consider when making the judgment may include (1) the magnitude of the increase in rate of occurrence for the investigational drug treatment group over the rate listed in the investigator brochure or elsewhere in the current IND application, or otherwise estimated, and (2) the consistency of the increase over time and across multiple trials, if applicable.

C. Other Reporting Requirements

1. Findings From Other Sources (§ 312.32(c)(1)(ii) and (iii))

The sponsor must also report any findings from clinical, epidemiological, or pooled analyses of multiple studies and any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug, regardless of whether they are conducted under the IND or by the sponsor (§ 312.32(c)(1)(ii) and (iii)). A finding that suggests a *significant risk* would "ordinarily . . . result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation" (§ 312.32(c)(1)(ii) and (iii)). For example, actions often taken in response to a significant risk finding include (1) an immediate revision of the informed consent, (2) an intensification of participant monitoring, (3) a revision to the eligibility criteria or screening procedures, (4) an enrollment hold, or (5) a consideration of discontinuation of the trial. The sponsor is also required to submit protocol amendments that describe certain changes to the protocol (§ 312.30(b)) in addition to the IND safety report.

a. Findings from other studies (§ 312.32(c)(1)(ii))

Findings that suggest a significant risk generally arise from ongoing or completed clinical studies, pooled data from multiple studies, and epidemiological studies. Findings from clinical studies that are subject to this requirement are those that have not already been reported under § 312.32(c)(1)(i). For example, any significant risk finding from a drug interaction study, a study evaluating changes in the QT interval on an electrocardiogram, or a study of a marketed drug would be reported under this provision. An example of such a finding would be a significant prolongation of the QT interval in participants receiving the investigational drug.

b. Findings from animal or in vitro testing (§ 312.32(c)(1)(iii))

Before reporting a finding from animal or in vitro testing to FDA, the sponsor should use judgment to decide whether the finding suggests a significant risk in humans or is too preliminary to interpret without replication or further investigation. Findings from animal studies, such as carcinogenicity, mutagenicity, teratogenicity, or reports of significant organ toxicity, are examples of the types of findings that suggest a significant risk, especially when the exposure to the investigational drug is at or near human exposures. Even if the findings from animal studies arise from exposures at a margin above clinical exposure, they may raise important risks to human use of the drug and should be reported. For example, if the no observed adverse effect level (NOAEL) is determined to be marginally above clinical exposure, findings from animal studies involving exposures at such NOAEL should be reported. Also,

certain findings, for example, carcinogenicity, even if seen at levels markedly above clinical exposures, may suggest an important risk that warrants reporting.[18]

2. IND Safety Reports for Study Endpoints (§ 312.32(c)(5))

Generally, study endpoints refer to outcomes that sponsors are measuring to evaluate efficacy. For trials designed to evaluate the effect of a drug on disease-related mortality or major morbidity, endpoint information should be collected, tracked, and monitored, usually by a data monitoring committee (DMC), during the course of the trial.[19] The study endpoints must be reported according to the protocol and are not ordinarily reported in IND safety reports, except when there is evidence of a causal relationship between the drug and the event (§ 312.32(c)(5)). For example, a death ordinarily would not be reported as an individual case in an expedited report from a trial designed to compare all-cause mortality in participants receiving either an investigational drug or a placebo. If, however, the death occurred as a result of an anaphylactic reaction that coincided with initial exposure to the drug or was the result of fatal hepatic necrosis, the death must be reported as an individual case in an IND safety report because of the evidence suggesting a causal relationship between the drug and the event (§ 312.32(c)(5)). This is analogous to a single uncommon event required to be reported under § 312.32(c)(1)(i)(A).

In addition to the study endpoints described above, some trials also evaluate the effect of the drug on several other pre-identified specific adverse events, often called *safety endpoints* or *adverse events of special interest*. These safety endpoints should be identified in the protocol and monitored and reported by the sponsor as specified in the protocol.

V. SYSTEMATIC APPROACH FOR REVIEW OF SAFETY INFORMATION (§ 312.32(b))

Sponsors should have a systematic approach to safety surveillance[20] to comply with the IND safety reporting requirements and to improve the overall quality of safety reporting. Such an approach should include a process for promptly reviewing, evaluating, and managing both individually reported SAEs and accumulating data on all SAEs from the entire drug development program that are obtained or otherwise received from domestic or foreign sources.

---

[18] See the guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005).

[19] See the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006) and the draft guidance for industry *Use of Data Monitoring Committees in Clinical Trials* (February 2024) (when final, this guidance will represent FDA's current thinking on this topic).

[20] For more discussion of this subject, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*, the draft guidance for industry *Use of Data Monitoring Committees in Clinical Trials* (when final, this guidance will represent FDA's current thinking on this topic), and the guidance for industry *Premarketing Risk Assessment* (March 2005).

During the course of drug development, investigators who conduct clinical trials generally report adverse event information to the sponsor; however, a sponsor may become aware of new safety information from a variety of sources, both domestic and foreign.

The sponsor must review and evaluate safety information from any source, regardless of whether the data came from studies conducted under the IND (§ 312.32(c)(1)(ii) and (iii)), to determine if there is a newly identified significant risk to trial participants.[21] Sources include but are not limited to:

- Animal or in vitro studies
- Clinical or epidemiological investigations
- Reports in the scientific literature, including unpublished reports of which the sponsor becomes aware
- Information presented at professional or scientific meetings (e.g., abstracts)
- Reports from foreign regulatory authorities
- Reports from commercial marketing experience, including outside the United States

The sponsor's review should include examining data from all sources and deciding whether the information meets the criteria for expedited reporting (see section IV of this guidance), as well as evaluating all accumulating data at regular intervals to update safety information and to identify new safety signals. Monitoring the progress of investigations is necessary to identify previously undetected potential serious risks (§ 312.56(a)); to update investigator brochures, protocols, and consent forms with new information on adverse events; and, when necessary, to take steps to protect participants (e.g., modifying dosing, participant selection, or monitoring) that will allow an investigational drug to be safely developed despite potential risks or to discontinue investigations for drugs with unreasonable and significant risks (§ 312.56(d)).

A. Prospective Development of a Plan for Safety Surveillance

The prospective development of a plan for assessing all SAEs — particularly those SAEs that are only interpretable in the aggregate — and other important safety information is an important component of IND safety reporting. The plan should describe processes and procedures for assessing SAEs and other important safety information in a drug development program.

A plan for safety surveillance should include descriptions of the following elements:

[21] Although sponsors must examine all information relevant to the safety of the drug obtained or otherwise received by the sponsor (§ 312.32(b)), not all safety information from available sources will need to be reported in an IND safety report. For example, sponsors do not have to submit to the IND spontaneous reports of adverse events for a drug marketed or approved in the United States resulting from commercial marketing experience for the same drug (see section VII.C of this guidance).

- Clearly defined roles and responsibilities of the entities and participating individuals that have responsibility for any or all of following: reviewing, analyzing, and making decisions regarding IND safety reporting. The positions and names of individuals and/or entities who have access to unblinded individual safety data and/or unblinded aggregate data should be specified in the safety plan.

- A plan for regular review of all SAEs and other important safety information, including related AEs and relevant safety information from the sources listed above, with unblinding if necessary for interpretation.

- A process for aggregate safety reviews (see section VI of this guidance for considerations for aggregate data analysis), including:

  - A list of anticipated SAEs for the study population (see section IV.A.2.a of this guidance for more information about identifying anticipated SAEs) that the sponsor does not plan to report individually, regardless of the investigator's assessment of causality. The preferred terms (PTs) for such events should be specified in a standardized coding convention or dictionary such as MedDRA (Medical Dictionary for Regulatory Activities). The events should each reflect a cohesive medical concept and not necessarily a single PT: the medical concept associated with an SAE may be reflected by a number of different PTs. For example, the medical concept of myocardial infarction may be reflected by the PTs of myocardial infarction or acute myocardial infarction (see section VII.B of this guidance). Sponsors may communicate with the applicable FDA review division during protocol development and prior to trial initiation, as appropriate, about how anticipated SAEs will be handled. It is not expected that the prespecified list of anticipated SAEs will cover all clinical events that may be considered to be anticipated for the population. For complex programs that include multiple indications, the anticipated SAEs may differ by the population(s) in the trial(s) under the same development program. The failure to identify an anticipated SAE up front does not mean that it necessarily requires IND safety reporting as a single event. Rather, such non-prespecified but anticipated SAEs should be carefully reviewed to determine if they meet the criteria for IND safety reporting when such a determination cannot be made based on a single case. (See section VI of this guidance.)

  - A plan to monitor the incidences of SAEs that require aggregate reporting. These include anticipated SAEs (both prespecified and those not on the anticipated SAE list but reviewed and assessed as consistent with an anticipated SAE and hence not immediately reported) and expected serious suspected adverse reactions (those listed in the package insert or investigator brochure).

  - For studies that use a trigger approach (see section VI.C.1.b of this guidance) to decide when such SAEs should be unblinded, the predicted rates of anticipated SAEs and the basis for the predicted rates should be specified.

- The frequency and approach with which aggregate reviews of safety data will be performed (see section VI.C.1 of this guidance).

- Pre-planned assessments of the trial and program safety database when trials within the program are completed and unblinded, when safety information from trials of other drugs in the same class are reported, or when any information relevant to safety is presented (e.g., pharmacology, toxicology, genetic).

- Methods that may be used to evaluate events, including graphical, tabular, or statistical approaches.

- Unblinding practices and controls and processes for maintaining trial integrity (see section VI.D of this guidance).

The sponsor should evaluate the safety surveillance plan as the development program progresses and the safety profile of the product evolves to determine whether the plan should be updated. The plan should be maintained by the sponsor and must be available for FDA inspection as required for all sponsor records and reports of an investigation under § 312.58(a).

VI. CONSIDERATIONS FOR AGGREGATE DATA ANALYSES FOR IND SAFETY REPORTING

Analyses of aggregate data to identify imbalances in the types of SAEs discussed in §§ 312.32(c)(1)(i)(C) or 312.32(c)(1)(iv) generally will become more informative as drug development progresses and data accumulate. Unless differences are large, detection of a clinically meaningful imbalance often requires a database of significant size. Clinical judgment is important because imbalances of events between arms may result from chance, even with larger databases. Interpreting imbalances may be particularly challenging for smaller programs where the number of events is small (for additional considerations regarding aggregate analyses for small programs, see section VI.C.3 of this guidance). Reporting should not rely solely on a statistical assessment because even imbalances that have marginally small p-values or confidence intervals (CI) that do not or that minimally exclude the null (for between-group difference) may be relevant, and interpretation requires a broader evaluation including detailed assessment of trial data such as time to event, detailed case assessments, and reliance on information outside of the trial, such as the pharmacology of the drug, class effects, and nonclinical findings. Waiting for a smaller p-value (i.e., $p < 0.05$) or a CI that has a greater separation from a null difference when other evidence points to a potential causal association may unduly delay reporting SAEs of concern. It is particularly difficult to detect differences in rates of SAEs that may be anticipated in the population being studied but that are not expected to be common during the trial (e.g., prostate cancer in middle-aged men). Recognizing the complexity of the judgments, FDA will focus primarily on the sponsor's process and the reasoning underlying the sponsor's decision in the event FDA and the sponsor reach different conclusions regarding whether SAEs evaluated by analyses of aggregate data meet IND safety reporting criteria.

A. Identify Serious Adverse Events Anticipated to Occur in the Study Population

As discussed in section V of this guidance, regarding the safety surveillance plan, the first step in preparing for an aggregate analysis of anticipated SAEs is developing a list of these events in the plan for safety surveillance and documenting a plan for monitoring these events. This will enable the safety assessment team to identify SAEs that should not be assessed for IND safety reporting on the basis of an individual or a small number of events, even if they are assessed by the investigator as drug-related. As discussed in section V.A above, an SAE that occurs during a trial can be classified and managed as an anticipated SAE if the SAE is determined to be an event that could occur in the population in the absence of exposure to the drug. While prespecifying such events is the goal, an SAE that was not included in the prespecified list of anticipated SAEs can be treated as such for the purposes of IND safety reporting if it meets the criteria of an anticipated event. Clinical judgment should be used to determine whether the event could occur in the population even in the absence of exposure to the drug.

Reported SAEs should be based on prospectively grouped adverse event terms that represent closely related medical concepts (see section VII.B of this guidance for information about the importance of standardized coding).

B. Entities That Review Aggregate Data for IND Safety Reporting

Under § 312.32, sponsors are responsible for promptly reviewing all information relevant to the safety of the drug, determining whether safety information meets the IND safety reporting criteria, notifying FDA and all participating investigators in an IND safety report of potential serious risks, and promptly investigating all follow-up safety information they receive. Sponsors may choose to designate an entity (an individual or group of individuals) to review the unblinded accumulating safety information in a drug development program (e.g., over time in a late-stage clinical trial, across trials, across INDs for the same drug) and to make a recommendation to the sponsor regarding whether the safety information must be reported under § 312.32. Sponsors have flexibility in determining which entity, entities, and/or sponsor personnel should perform this function. There does not need to be a single entity to evaluate all SAEs; for example, there could be one entity used to assess individual occurrences or a small number of adverse events that are not anticipated in the population (reported under § 312.32(c)(1)(i)(A) and (B)), and there may be a different entity assessing aggregate adverse events reported under § 312.32(c)(1)(i)(C), or there could be some combination thereof. It is essential that roles are clearly defined in study plans and that firewall procedures are in place to ensure that individuals whose roles do not include access to unblinded aggregate data are insulated from knowledge of any unblinded aggregate data (see section VI.D of this guidance).

1. Features and Composition of the Entity

The entity or entities reviewing aggregate safety information should include an individual or individuals with knowledge about the investigational drug; the disease being treated, including the epidemiology of the disease; and the characteristics of the study population (e.g., natural history of the disease being treated, background rates of anticipated adverse events). Such

individual(s) should be qualified by training and experience to make clinical judgments about the safety of the drug. Identification of a new type of clinical safety concern (e.g., ocular toxicity, renal toxicity) may warrant adding additional expertise to the entity reviewing safety data.

The positions, roles, and responsibilities of each individual or group of individuals in the entity should be clearly defined in the plan for safety surveillance (see section V.A of this guidance).

2. Identifying the Entities That Review Safety Information

If a DMC is in place, the DMC may be used to conduct aggregate analyses of safety information to help the sponsor assess whether the reporting criteria in § 312.32(c)(1)(i)(C) and (c)(1)(iv) have been met. An advantage of having a DMC conduct this review is that the DMC could access unblinded data and can utilize existing controls for maintaining trial integrity. FDA recognizes that analyzing these data for the purpose of providing a recommendation to the sponsor regarding whether the IND safety reporting criteria have been met would be a new role for most DMCs, distinct from their role in monitoring risks and benefits to make recommendations for trial continuation or modification. If this role is allocated to the DMC, the DMC charter should reflect this new role.

If the sponsor does not use a DMC for the purpose of reviewing safety analyses to detect events meeting the criteria for IND safety reporting, the sponsor should identify an entity within or outside the sponsor's organization for this purpose. If the entity consists of more than one individual, it may have sponsor representation and/or external representation. It is important that no unblinded data, including references to masked treatment group assignments (e.g., treatment groups A, B, or C), be revealed to internal or external personnel participating in the conduct or analysis of an ongoing clinical trial program. Only DMC members and any firewalled personnel designated to conduct unblinded analyses of safety data should have access to such data. (See section VI.D of this guidance for information regarding maintaining trial integrity when reviewing aggregate data.)

C. Aggregate Analyses of Safety Data

1. Approach to Aggregate Analyses

For anticipated SAEs and expected serious suspected adverse reactions, an aggregate analysis of the data is necessary to determine whether these events meet the criteria for reporting under § 312.32(c)(1)(i)(C) and (c)(1)(iv), respectively. The unblinding of participant treatment for anticipated SAEs or expected serious suspected adverse reactions that may be necessary for aggregate analyses requires scrupulous, thoroughly planned, and well-documented efforts to protect trial integrity, ensuring that the entity or persons carrying out the review are completely firewalled from the staff conducting the trial and assessing blinded data (see section VI.D of this guidance).

a. Aggregate analyses by a DMC

If a DMC (or other firewalled external entity)[22] is responsible for assessing accumulating unblinded safety data for the purpose of IND safety reporting, the DMC should review unblinded safety data on a periodic basis to assess the incidence of anticipated SAEs and expected serious suspected adverse reactions by treatment arm. The DMC should be given access to accumulating information from the drug development program, not just the specific trial, and should be aware of preclinical and early clinical data that bears on safety issues.

If the DMC identifies either an imbalance between study arms of an anticipated SAE suggesting a causal relationship between the investigational drug and the SAE or an increased rate of an expected serious suspected adverse reaction in the treatment arm above what is expected according to the available safety information for the investigational drug, the DMC would be expected to make a recommendation[23] to the sponsor regarding whether the safety information should be reported under § 312.32. Such recommendations should be made to the sponsor personnel who are specifically assigned the responsibility to review unblinded data (and who are not involved in the conduct or analysis of the study) to determine if an IND safety report is appropriate (see section VI.C.2 of this guidance).

The cadence for review of unblinded data by the DMC for purposes for expedited IND safety reporting should be specified in the charter. If the DMC is reviewing safety information for the purposes of IND safety reporting as well as their usual role of assessing the ongoing benefit-risk ratio of the trial, in the absence of a specific concern, an aggregate analysis by the DMC should occur at regular intervals (e.g., every 6 months, or more or less frequently as appropriate). However, it is also reasonable for the DMC to conduct the aggregate analyses at intervals based on volume of safety data collected or based on participant accrual into the trial (e.g., as each 25 percent of the recruitment target is reached) or on event rates (e.g., that might be higher in a study population with more severe illness and/or greater comorbidities). The frequency may be modified, as needed, if safety concerns arise that require follow-up (e.g., an imbalance might be determined not to require an IND safety report but could lead to more frequent monitoring). In addition, in determining the appropriate frequency of aggregate reviews, the sponsor should consider factors such as experience with the drug, the condition being treated, the study population, and enrollment rates. The frequency of review and the rationale behind it should be described in the plan for safety surveillance (see section V.A of this guidance).

b. Unblinding trigger approach

In this approach, a predicted rate of an anticipated SAE or expected serious suspected adverse reaction across the study population is determined such that if the rate is exceeded to a potentially meaningful extent, an unblinded analysis by treatment group is then performed to

[22] While a sponsor could establish an external entity that is appropriately firewalled like a DMC to periodically review all unblinded safety data, likely in the absence of a DMC, the unblinding trigger approach as discussed in this guidance would be the preferred approach.

[23] Though the DMC may make a recommendation regarding whether the safety information should be reported under § 312.32, this determination is ultimately the sponsor's responsibility under § 312.32.

evaluate whether the anticipated SAE or expected serious suspected adverse reaction meets the criteria for IND safety reporting. In the case where there is no external entity responsible for conducting periodic unblinded reviews of safety data, FDA recommends the use of this approach for aggregate analysis.

- *Anticipated SAEs*

For anticipated SAEs, the predicted rate for the SAE across the population should be specified based on information that is applicable to the specific study population (e.g., based on age, comorbidities, concomitant treatments). Sponsors should use all available data, including placebo databases, historical data, literature, external epidemiological databases, electronic health records, and disease-specific registries, to determine predicted rates of SAEs anticipated to occur in the study population. When data are available such that accurate population-based rates can be calculated for the study population, a precise trigger for unblinding can be used.

Utilizing the predicted SAE rates, sponsors should specify unblinding criteria based on a comparison of the predicted rate of the SAE with the observed blinded SAE rate.[24] If the results of the overall blinded analyses demonstrate that the rate of events in the pooled treatment groups is notably higher (i.e., exceeding the predicted rate by more than a minor difference and meeting the unblinding criteria), the next step would be to examine the rates by treatment group using an unblinded analysis and compare the numbers of events for the specific SAE in each arm to determine whether the IND safety reporting criteria in § 312.32(c)(1)(i)(C) have been met. Note that clinical judgment should be incorporated into any assessment because there may be circumstances that mitigate the need for unblinding even if a trigger rate is exceeded. For example, in the setting of a known seasonally higher rate of pneumonia in a community, such information should be taken into account before unblinding based on a trigger rate for pneumonia that was established before the seasonal information was known.

FDA recognizes that in some cases, the data necessary to establish a predicted rate of some anticipated SAEs in the specific study population may be limited or unavailable, for example:

- When the rate of the anticipated SAE is low in the study population and it is difficult to determine an accurate rate
- In drug development programs for rare diseases or other small programs
- For the specific study population
  - For example, although it may be possible to find data on the rates of cardiovascular events in the general population aged 40 to 70 years, data specific to a similarly aged population with a specific condition may not be available.

[24] Generally, the comparison of the predicted SAE rate to the observed blinded SAE rate should account for uncertainty in the comparison rather than relying on a simple comparison of one value to another. Methods for comparisons should be provided in the plan for safety surveillance.

For anticipated SAEs with limited or no available data regarding rates for the study population, the trigger for unblinding may be based on factors including statistical probability and clinical judgment. For example, unblinding should be done if there are more than a few SAEs of a certain type such that if the majority occurred in the investigational arm, it would lead one to suspect that the investigational drug may have a causal role. Such a trigger should be set based on review of blinded data for anticipated events that do not occur frequently in the population and have not been prespecified.

For anticipated SAEs that are prespecified in the plan for safety surveillance, the predicted rates also should be included in the plan (see section V.A of this guidance). It is not expected that all anticipated SAEs, particularly for less common anticipated SAEs, would be prespecified in the safety surveillance plan. For SAEs that are classified as anticipated during the trial (i.e., not prespecified as anticipated in the safety surveillance plan), the unblinding trigger should be set as described in this section during the trial, with appropriate documentation.

- *Expected Serious Suspected Adverse Reactions*

For expected serious suspected adverse reactions, the trigger to unblind is based on rates listed in the protocol or investigator brochure and takes into account whether the events being monitored could occur in the control group. Sponsors should have processes for comparing the rates of expected serious suspected adverse reactions to the rates listed in the protocol or investigator brochure in order to determine whether there is a clinically important increased rate of occurrence that must be reported under § 312.32(c)(1)(iv).

2. Considerations for Small Programs/Rare Diseases

In drug development programs for rare diseases or other small programs that are not using an external entity such as a DMC for aggregate analyses, external data sources used to predict anticipated SAE rates are often limited, and thus the trigger for unblinding would likely be based on clinical judgment and probability (see section VI.C.1.b of this guidance). Additionally, for small programs where the number of SAEs is expected to be small, the trigger for unblinding may be lower given the size of the population.

When unblinding of treatment is necessary for the evaluation of an anticipated SAE or expected serious suspected adverse reaction, interpreting imbalances between treatment arms may be particularly challenging for smaller programs because the number of events is small. Furthermore, the clinical trial to support effectiveness in these programs may be an open-label, single-arm trial (i.e., a trial with no concurrent comparator group). These settings are especially challenging, and sponsors should use judgment in determining whether there is a reasonable possibility that the drug caused the event.

3. Considerations When Evaluating Aggregate Data Across a Development Program

Aggregate analyses should generally be performed across multiple studies under the IND and, as appropriate, across all INDs for the drug held by the sponsor, including both completed and

ongoing trials. Clinical and statistical judgment is needed to evaluate the totality of the information related to a specific anticipated SAE or expected serious suspected adverse reaction, including information from trials in different populations, particularly when the trials have different study designs (e.g., different dosing schedules, varying durations of follow-up, different indications). FDA recognizes that these differences between studies may make it difficult to compare event rates across trials; therefore, documentation of this clinical assessment is recommended. The draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018)[25] provides recommendations regarding combining data and comparative analyses of data from multiple trials.

4. Updating Safety Information

For aggregate analysis, after an anticipated SAE is reported under § 312.32(c)(1)(i)(C) or the increased rate of occurrence of an expected serious suspected adverse reaction is reported under § 312.32(c)(1)(iv), the investigator brochure, the protocol, informed consent, and other safety-related information should be updated as appropriate and as soon as possible during the conduct of the ongoing clinical trial. After the anticipated event is listed in the investigator brochure, the event should no longer be reported in IND safety reports because it would then be considered expected, unless there is a clinically important increase in the event rate (§ 312.32(c)(1)(iv)). Similarly, the increased rate of occurrence of an expected serious suspected adverse reaction reported under § 312.32(c)(1)(iv) should no longer be reported in IND safety reports after the investigator brochure, the protocol, and other safety-related information have been updated to reflect the updated rate of occurrence, unless a further increase in occurrence is observed and meets the reporting criteria.

The IND sponsor should in some circumstances develop, in consultation with the FDA review division and other safety oversight bodies (e.g., a DMC), an approach for reporting, in an IND safety report, subsequent occurrences of certain events that the sponsor has added, as expected events, to the investigator brochure, the protocol, and other safety-related information. Although IND safety reporting of a particular SAE is no longer required after that SAE is listed in the investigator brochure, ongoing reporting of subsequent events may still be appropriate. For example, for certain events that are infrequent with immediate health implications or an event that is uncommon in a specific study population (e.g., stroke in young adults), prompt notification of subsequent events after the first IND safety report may be warranted to ensure that the benefit-risk ratio remains acceptable to continue the trial (see § 312.56(d)). A plan for reporting should be developed in consultation with the FDA review division and other safety oversight bodies (e.g., a DMC). For an event that is known to occur independent of drug exposure in the study population, the sponsor may specifically describe an approach for reporting to FDA and all participating investigators (e.g., an updated aggregate narrative summary report once a certain number of additional cases are identified or after a specified period of time, as appropriate). Additionally, the sponsor must submit to FDA any additional data or information that FDA deems necessary as soon as possible but in no case later than 15 calendar days after receiving the request (§ 312.32(c)(1)(v)).

[25] When final, this guidance will represent FDA's current thinking on this topic.

D. Maintaining Trial Integrity When Reviewing Aggregate Data

Recommended steps to protect trial integrity include ensuring that:

- Internal personnel conducting unblinded safety reviews do not participate in the conduct or analysis of the trial or trials.

- Appropriate procedural controls and processes are prospectively specified in the safety surveillance plan to prevent sponsor personnel involved with the conduct or analysis of the trial(s) from being unblinded to participants' treatment. If a firewalled external entity other than the DMC is set up to look at aggregate data, it should have access only to the unblinded analyses necessary to conduct the safety review. For example, it may be necessary to unblind the treatment of participants who experienced an SAE, or it may be necessary to unblind additional data that is relevant to interpreting the observed imbalance (e.g., related adverse events). Study endpoints, efficacy data, and other data collected for the trial that do not pertain to the adverse event should not be unblinded.

FDA acknowledges that serious suspected adverse reactions may be unblinded at the site level if knowledge of the treatment received is assessed as necessary for the medical management of the participant.

To address sponsor concerns about unblinding large numbers of participants' treatment to investigators when submitting aggregate reports, FDA recommends sending only the narrative summary portion of the IND safety report to all participating investigators, without the individual unblinded case safety reports that are summarized in the narrative summary report, to meet the requirement of § 312.32(c)(1) for a sponsor to notify all participating investigators in an IND safety report of potential serious risks (see section VIII.D of this guidance for information about narrative summary reports for IND safety reports of aggregate analyses).

VII. OTHER SAFETY REPORTING ISSUES

A. Alternative Reporting Arrangements (§ 312.32(c)(3))

The requirement in § 312.32(c)(1) specifies the format and time frame for reporting potential serious risks in an IND safety report (see section VIII of this guidance). Sponsors may request and adopt different reporting formats or frequencies if agreed to in advance by the director of the FDA review division responsible for reviewing the IND (§ 312.32(c)(3)). In addition, FDA may require a sponsor to submit IND safety reports in a different format or at a different frequency than required under § 312.32(c)(1) (see § 312.32(c)(3)). FDA may require a sponsor to continue to report expeditiously a medically significant suspected adverse reaction that is listed in the investigator brochure as observed with the drug (i.e., expected) so that its rate can be carefully monitored (§ 312.32(c)(1)(v)). For example, if a single occurrence of Stevens-Johnson Syndrome was observed in a participant receiving the investigational drug (and hence listed in the investigator brochure), FDA may nonetheless require expedited reporting of additional cases

of rash of a lesser severity. FDA may also require an alternative format or frequency for reporting suspected adverse reactions. For example, once a drug has been identified as posing a potential or previously unforeseen risk to participants in a clinical trial, FDA may require expedited reporting of specific suspected adverse reactions for monitoring purposes.

B. Importance of Standardized Coding

As part of the sponsor's responsibility to promptly review all SAEs under § 312.32(b), sponsors should review the verbatim (reported) term and how it was coded to a MedDRA PT to ensure that coding was appropriate. To define these medical concepts, sponsors should plan to prospectively group adverse event terms that represent closely related medical concepts (e.g., for the medical concept of renal failure, appropriate PTs might include PTs of renal failure, renal failure acute, renal failure chronic, renal impairment, acute prerenal failure, azotemia, urine output decreased, postoperative renal failure, and other relevant terms). Varying approaches are available, such as Standardized MedDRA Queries (SMQs) or Higher Level Terms (HLTs) that sponsors should consider as appropriate. See the guidance for industry *Premarketing Risk Assessment* (March 2005) for additional discussion of coding.

C. Investigations of Marketed Drugs (§ 312.32(c)(4))

According to § 312.32(c)(4), a sponsor of a clinical study of a drug marketed or approved in the United States that is conducted under an IND must submit IND safety reports for suspected adverse reactions that meet reporting criteria under § 312.32 and are observed in the study at domestic or foreign sites. If the sponsor is not the application holder,[26] the sponsor should also forward the report to the application holder of the marketed drug. If the sponsor is also the application holder, the sponsor must also submit safety information from the clinical study as prescribed by the relevant postmarketing safety reporting requirements (e.g., under §§ 314.80 or 600.80).

In addition, under § 312.32(c)(1)(ii), a sponsor must report findings from other studies, including clinical studies that are not conducted under an IND or by the sponsor, that suggest a significant risk in humans exposed to the drug. Generally, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure, or other aspect of study conduct. Therefore, as long as the sponsor maintains an open IND for a marketed or approved drug, safety information from foreign and domestic studies, including non-IND studies, must be reported to the IND. If the sponsor is also the application holder, such safety information must be reported in accordance with the postmarketing requirements if it also meets the criteria for reporting, regardless of whether there is an ongoing clinical study under the IND.

If the IND sponsor (who may also be the application holder) for a drug approved in the United States becomes aware of a spontaneous report of an adverse event from U.S. or foreign commercial marketing experience for the drug that is under investigation (i.e., an experience occurring outside of a clinical trial), the report would be submitted based on required

[26] See footnote 17.

postmarketing reporting and does not also need to be submitted as an IND safety report, even if it meets the criteria for being a serious and unexpected suspected adverse reaction.

If a drug is **not approved and not marketed in the United States** but is approved outside the United States, a sponsor conducting a study under an IND must submit an IND safety report for serious adverse reactions received through foreign commercial marketing experience if the event meets reporting criteria for IND safety reports (§ 312.32(c)(1)). If there is no approved drug product in the United States that has the same active moiety, such reports would not come to FDA as a postmarketing report. Therefore, the only way for FDA to receive such safety information is through the IND for the investigational drug.

D. Duration of Safety Reporting

The purpose of sending IND safety reports to investigators is to provide investigators with the information they need to protect clinical trial participants. Once investigators are no longer enrolling or monitoring participants and the site is officially closed, this information is no longer necessary. Cutoff dates for sending IND safety reports to investigators may be described in the protocol. If no cutoff dates are specified, once a site has been officially closed out, the sponsor usually does not need to continue sending IND safety reports to that site, and an investigator does not need to receive or review them (see generally § 312.32(c)(1)).

In unusual cases, safety information related to delayed toxicity may be reported after a site is officially closed out. For example, if a late toxicity is discovered that would affect participants who received the investigational drug, the investigator should be notified so participants can be followed up with if necessary (e.g., serious unexpected suspected adverse reactions that are detected and reported during the long-term follow-up for gene therapy products).

VIII. SUBMITTING AN IND SAFETY REPORT (§ 312.32(c)(1)(v))[27]

The guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (April 2024) 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 § 312.32(c)(1)(i) for serious and unexpected suspected adverse reactions.[28] As discussed in the guidance, IND safety report types required under § 312.32(c)(1)(i)(A), (B), and (C) contain individual data from one or more participants and should be submitted as individual case safety reports (ICSRs) to the FDA Adverse Event Reporting System (FAERS). Other types of required IND safety reports under § 312.32(c)(1)(ii), (iii), and (iv) are reports of overall

[27] Under section 745A(a) of the FD&C Act (21 U.S.C. 379k-1(a)), at least 24 months after issuance of the final guidance document in which FDA has specified the electronic format for submitting submission types to the Agency, such content must be submitted electronically and in the format specified by FDA. See the guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*.

[28] See the guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*, which describes the format required for the electronic submission of IND safety reports for serious and unexpected suspected adverse reactions that are required under § 312.32(c)(1)(i).

findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies and reports of increased rates of occurrences of expected serious suspected adverse reactions. The sponsor should submit these other types of reports in a narrative format in electronic common technical document (eCTD) format and should not submit these reports to FAERS.

Submission of safety information to FAERS as structured data elements will improve FDA's ability to review and track potential safety signals that occur during the conduct of clinical trials and will provide sponsors with a reporting format that is consistent with the ICH guidance for industry *E2B(R3) Electronic Transmission of Individual Case Safety Reports Implementation Guide — Data Elements and Message Specification; and Appendix to the Implementation Guide — Backwards and Forwards Compatibility* guidelines and reporting requirements to other regulatory agencies.

Until the electronic submission requirements specified in the guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* become effective on April 1, 2026, the most recent effective version of the eCTD guidance[29] will continue to apply to sponsors electronically submitting IND safety reports for serious and unexpected suspected adverse reactions. FDA will also accept IND safety reports to FAERS as part of an implementation period of the electronic submission program. During the implementation period of electronic submission, if sponsors choose to submit IND safety reports to FAERS using the ICH E2B(R3) data standards, they should no longer submit those IND safety reports in eCTD format. Sponsors must use either the Electronic Submission Gateway Next Generation (ESG NextGen) or the Safety Reporting Portal (SRP) when submitting IND safety reports to FAERS. See the FAERS Electronic Submissions web page[30] for more information on the electronic submission process during the implementation period.

IND safety reports must be submitted to all of the sponsor's INDs under which the drug is being administered (§ 312.32(c)(1)). When submitting IND safety reports to the FAERS database, sponsors should refer to the *Electronic Submission of IND Safety Reports — Technical Conformance Guide* (Technical Conformance Guide)[31] for information on appropriate IND number data fields, including cross-reporting.

A. Method of Submission for IND Safety Reports to FAERS

The Technical Conformance Guide discusses general information and the format for the submission of IND safety reports required under § 312.32(c)(1)(i) to FAERS and provides

[29] See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (September 2024).

[30] The FAERS Electronic Submissions web page is available at https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

[31] The *Electronic Submission of IND Safety Reports — Technical Conformance Guide* is available at https://www.fda.gov/media/132078/download. Technical conformance guides are also available on the FDA guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

recommendations to sponsors who elect to submit such reports to FAERS before the requirement for submission to FAERS is in effect for applicable INDs.[32]

B. Method of Submission for IND Safety Reports in eCTD Format[33]

IND safety reports are required to be submitted electronically in eCTD format for findings from other studies (§ 312.32(c)(1)(ii)), findings from animal or in vitro testing (§ 312.32(c)(1)(iii)), and findings of an increased rate of occurrence of expected serious suspected adverse reactions (§ 312.32(c)(1)(iv)).[34] If the findings are published, in full or in abstract form, the sponsor should include a copy of the publication. The sponsor should submit these other types of reports in a narrative report in eCTD format and should *not* submit the reports to FAERS.[35] Complete information on eCTD specifications and guidance can be found on the FDA eCTD website,[36] and sponsors may contact ESUB@fda.hhs.gov for assistance.

C. INDs That Are Exempted From Electronic Submission Requirements

FDA has exempted all submissions regarding noncommercial INDs from the electronic submission requirements under section 745A(a) of the FD&C Act.[37] For the 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).[38] Although noncommercial INDs (and their associated IND safety reports) are exempt from the requirements of section 745A(a) of the FD&C Act, FDA encourages the electronic submission of IND safety reports from sponsors of noncommercial INDs as per sections VIII.A and VIII.B of this guidance.[39]

Sponsors with INDs that are exempted from the electronic submission requirement under section 745A(a) and who are not submitting IND safety reports required under § 312.32(c)(1)(i)(A), (B),

---

[32] See the *Electronic Submission of IND Safety Reports — Technical Conformance Guide.*

[33] See the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*.

[34] Ibid.

[35] See the *Electronic Submission of IND Safety Reports — Technical Conformance Guide*.

[36] See the Electronic Common Technical Document (eCTD) web page, available at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/electronic-common-technical-document-ectd.

[37] 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).

[38] Ibid.

[39] See the guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports*.

and (C) to FAERS or IND safety reports required under § 312.32(c)(1)(ii), (iii), and (iv) in eCTD format should submit IND safety reports according to the following options:

1. Alternate Electronic Format

FDA has provided guidance to sponsors of INDs exempted from the 745A(a) electronic reporting requirements describing an alternate electronic format sponsors should use for submissions covered under such exemption.[40] An IND safety report containing individual data from one or more participants required under § 312.32(c)(1)(i) should be submitted to FDA using Form FDA 3500A and should be submitted electronically as a portable document format (PDF) submission in the alternate electronic format according to the guidance for industry *Providing Regulatory Submissions in Alternate Electronic Format* (June 2022).

Other types of IND safety reports required under § 312.32(c)(1)(ii), (iii), and (iv), which do not contain individual data from one or more participants, are reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies and reports of increased rates of occurrences of serious suspected adverse reactions. The sponsor should submit these other types of reports to FDA using a narrative format and should submit these other types of reports electronically as a PDF submission in the alternate electronic format.[41]

This recommendation is consistent with the efforts of Federal Agencies to transition their business processes and recordkeeping to a fully electronic environment.[42]

2. Other Means of Rapid Communication

If the IND safety report is not submitted to FAERS, in eCTD format, or in an alternate electronic format, a safety report may be submitted on a Form FDA 3500A via other means of rapid communication (e.g., telephone, fax, email). The sponsor should complete all sections of Form FDA 3500A that apply to IND safety report submissions.[43] If the sponsor intends to submit IND safety reports by fax or email, the sponsor should address the submissions to the Regulatory Project Manager and the Chief, Project Management Staff in the FDA review division that has responsibility for review of the IND. In addition, if the sponsor intends to submit IND safety reports by email, FDA recommends that the sponsor obtain a secure email account with FDA.[44]

---

[40] See the guidance for industry *Providing Regulatory Submissions in Alternate Electronic Format*.

[41] Ibid.

[42] Ibid.

[43] For instructions for completing Form FDA 3500A, see https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting.

[44] For details on obtaining a secure email account with FDA, visit https://www.fda.gov/drugs/forms-submission-requirements/electronic-regulatory-submission-and-review.

D. Submitting IND Safety Reports Based on Aggregate Analyses

IND safety reports required for submission based on aggregate analyses should include a narrative summary report that provides a summary of the cases and the analysis the sponsor conducted and should identify all individual cases that contributed to the analysis. The narrative summary report should include a summary of the analysis of the individual cases that are reportable because of aggregate analysis findings. Sponsors should use judgment in deciding what to include in the summary of the analysis. Generally, this summary should include:

1. A description of the suspected adverse reaction, along with a brief overall summary of the cases. This summary could include demographic factors, symptoms, comorbid conditions, medical history, pertinent test results, concomitant medications, and timing of events relative to drug exposure.

2. A description of the characteristics and results of the analysis, including a description of the safety data sources, how the conclusion was reached, who reviewed the analysis, any planned changes in monitoring or to study documents (e.g., informed consent, investigator brochure), and any additional analyses planned.

Additionally, the narrative summary report must identify any previously submitted IND safety reports concerning a similar suspected adverse reaction, and the sponsor must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information, as required for all IND safety reports (§ 312.32(c)(1)).

Before submission to FDA, each individual case that comprises an IND safety report of an aggregate analysis should be unblinded to include data that is necessary for FDA to evaluate the event. (See section VI.D of this guidance for reporting aggregate analyses to participating investigators.)

When submitting IND safety reports that are a result of aggregate analysis of anticipated SAEs under § 312.32(c)(1)(i)(C), the sponsor should submit each ICSR that contributed to the aggregate analysis to FAERS. For such reports that occurred under multiple INDs, sponsors should reference the 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 the appropriate data elements to include in IND safety reports from aggregate analyses as per § 312.32(c)(1)(i)(C); on how to link all supporting IND safety reports to the narrative summary report; and on where to include the narrative summary report. This information may also be applicable for IND safety reports submitted as per § 312.32(c)(1)(i)(B) that include more than one case and where a narrative summary report is provided.[45]

[45] See the technical specifications document *FDA Regional Implementation Guide for E2B(R3) Electronic Transmission of Individual Case Safety Reports for Drug and Biological Products*, available on the FAERS Electronic Submissions website at https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions, and the *Electronic Submission of IND Safety Reports — Technical Conformance Guide*, available at https://www.fda.gov/media/132078/download.

IND safety reports required under § 312.32(c)(1)(iv) should be submitted in eCTD format. (See section VIII.B of this guidance.)

E. Reporting Time Frame

The time frame for submitting an IND safety report to FDA and all participating investigators is as soon as possible but no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting (§ 312.32(c)(1)). The IND safety reporting regulations were modified describing the reporting time frame applicable to IND safety reports of more than one event (e.g., reports of events qualifying for reporting under § 312.32(c)(1)(i)(B) and (C) and increases in rates of occurrence of serious suspected adverse reactions (§ 312.32(c)(1)(iv)), because these events generally require more than one occurrence to make the determination that the event meets the criteria for reporting. Thus, the date of initial receipt of the first event would likely be well before it was determined that the information must be reported.

FDA expects that events that are interpretable as single cases (i.e., uncommon and known to be strongly associated with drug exposure (§ 312.32(c)(1)(i)(A)) will be reported to FDA within 15 calendar days from sponsor's initial receipt of the information because it will be immediately apparent that such events meet the reporting criteria (§ 312.32(c)(1)). For events that require more than one occurrence to assess causality and events evaluated in the aggregate, the time clock starts from whatever date the sponsor determines that the events qualify for expedited reporting. This means that, for example, incomplete cases must be promptly followed up for additional information so that a determination can be made about whether the event is reportable as an IND safety report (§ 312.32(d)).

Under § 312.32(d)(3) —

> If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable under paragraph (c) of this section is . . . [determined to be] reportable, the sponsor must report such [a] suspected adverse reaction in an IND safety report as soon as possible but in no case later than 15 calendar days after the determination is made.

This applies to reporting of single and aggregate events and to events that would individually or in the aggregate qualify for either 7- or 15-day reporting. FDA expects that any entity responsible for making recommendations to the sponsor regarding submitting an IND safety report based on aggregate data will promptly provide the recommendation to the sponsor so that the sponsor can meet its obligations under § 312.32. The sponsor must promptly review the information to determine whether the IND safety reporting criteria have been met (§ 312.32(b)).

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and must be reported more rapidly to FDA (§ 312.32(c)(2)). The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is as soon as possible but no later than 7 calendar days after the sponsor's initial receipt of the information (§ 312.32(c)(2)).

Day zero for 7- and 15-day reports is considered as (1) the day the sponsor initially receives information for a case that is interpretable as a single case or (2) the day the sponsor determines that multiple cases qualify for expedited reporting.

If FDA requests any additional data or information, the sponsor must submit it to FDA as soon as possible but no later than 15 calendar days after receiving the request (§ 312.32(c)(1)(v)). Additionally, the sponsor must submit relevant follow-up information to a 7- or 15-day IND safety report as soon as the information is available (§ 312.32(d)(2)). (See section IX of this guidance.)

Day zero for the 7- and 15-day reporting time frames and the date of the adverse event may not be the same. FDA considers the date of an adverse event to be the actual or best estimate of the date of first onset of the adverse event.[46] FDA interprets the date of first onset of the adverse event to be the date that the participant first experienced the symptoms that were related to the adverse event. FDA recognizes that this determination is not always straightforward and requires clinical judgment to relate the prodromal symptoms to the adverse event.

IX. FOLLOW-UP INFORMATION (§ 312.32(d))

Most IND safety reports are derived from observations from clinical trials. In the setting of a clinical trial, information is usually collected in a controlled environment so that the information needed to evaluate the suspected adverse reaction (e.g., as an IND safety report submitted to the FAERS database[47]) is generally readily available. If any information necessary to evaluate the suspected adverse reaction is missing or unknown, the sponsor should actively seek such information from the source of the report. In the event that the participant withdraws consent from participating in a clinical trial, FDA recognizes that the sponsor cannot continue to provide SAE reports related to that participant once the consent is withdrawn unless those reports are associated with publicly available records.

Any relevant additional information obtained by the sponsor that pertains to a previously submitted IND safety report must be submitted as a Follow-up IND Safety Report to the FAERS database using the same unique case identification number/manufacturer control number as the initial IND safety report without delay, as soon as the information is available (§ 312.32(d)(2)), but should be submitted no later than 15 calendar days after the sponsor receives the information. The sponsor should maintain records of its efforts to obtain additional information.

For example, if information on concomitant medications is obtained after the initial IND safety report is submitted and such information is relevant to evaluating the suspected adverse reaction, a sponsor must submit a Follow-up IND Safety Report as soon as the information is available (§ 312.32(d)(2)). However, if the sponsor obtains other information that is not relevant to

[46] See Form FDA 3500A Supplement (4/16) — Form Instructions, available at https://www.fda.gov/media/82655/download.

[47] See the guidance for industry *Electronic Submission of IND Safety Reports Technical Conformance Guide* (April 2022).

evaluating the suspected adverse reaction, records of such information should be maintained by the sponsor and, if applicable, submitted in an information amendment (§ 312.31) or in an IND annual report (§ 312.33).

To help sponsors determine whether follow-up information is relevant to an IND safety report, FDA provides in this section additional guidance on the types of information that generally would require a follow-up IND safety report.

For an individual case that was submitted as an IND safety report under § 312.32(c)(1)(i)(A) and (B), examples of the types of information that trigger the follow-up IND safety reporting requirements include (1) a change in diagnosis of the adverse event, (2) an important change in outcome of the adverse event (e.g., death), (3) autopsy findings, and (4) other new information that significantly impacts the assessment of causality.

For aggregate data that were submitted as an IND safety report under § 312.32(c)(1)(i)(C) and (c)(1)(iv), examples of the type of information that would trigger follow-up IND safety reporting requirements include (1) additional occurrences of the adverse event that, in the aggregate, suggest a significant change in the rate of occurrence from the initial aggregate report and (2) information about individual events that comprise the aggregate report that significantly impacts the assessment of causality such that there is no longer a reasonable possibility that the drug caused the event or strengthens the causal relationship between the adverse event and the drug. The sponsor should evaluate whether additional occurrences of the adverse event represent a clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure, which must be reported under § 312.32(c)(1)(iv).

X. SAFETY REPORTING REQUIREMENTS FOR BA AND BE STUDIES

The IND safety reporting requirements under § 312.32 apply to BA and BE studies that are conducted under an IND. BA and BE studies that meet the conditions for IND exemption under § 320.31(d) are not conducted under an IND and are not subject to the IND safety reporting requirements. Earlier iterations of § 320.31(d) that also exempted certain in vivo BA and BE studies in humans from the requirements of part 312, including the IND safety reporting requirements under § 312.32, did not establish separate safety reporting requirements for these studies. As FDA stated in its preamble to the final rule updating § 320.31(d) in 2010, the Agency determined that "the occurrence of a serious adverse event is very unusual in a [BA or BE] study because the number of participants enrolled in the study is small, the participants are usually healthy volunteers, and drug exposure is typically brief."[48] However, for these same reasons, "the occurrence of any serious adverse event [in a BA or BE study] is of interest." Therefore, FDA revised § 320.31(d) to require reporting of SAEs as one of the conditions under which certain BA and BE studies are exempt from the requirements of part 312, including from the IND safety reporting requirements in § 312.32 (see § 320.31(d)(3)).

[48] 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" (75 FR 59953), published September 29, 2010.

Timely review of this safety information is critical to ensuring the safety of BA/BE study participants, whether they are healthy volunteers or individuals with the specified medical condition and whether the trial has a single-dose or steady-state design.

A. BA/BE Study Safety Reporting Requirements (§ 320.31(d)(3))

The person conducting an IND-exempt BA or BE study, including any contract research organization, must notify FDA and all participating investigators of any SAE observed for the test or reference drug during conduct of the study, regardless of whether the event is considered drug-related, as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence (§ 320.31(d)(3)). This includes, for example, SAEs listed in the reference listed product's approved labeling, the investigator brochure, and the protocol.

If any information necessary to evaluate the SAE is missing or unknown, the company conducting the study should actively seek such information and maintain records of efforts to obtain additional information. Any relevant additional information obtained that pertains to a previously submitted safety report must be submitted as a Follow-up Bioavailability/Bioequivalence Safety Report as soon as the information is available (§ 320.31(d)(3)) but should be submitted no later than 15 calendar days after the company receives the information. In addition, upon request from FDA, the company conducting the study must submit to FDA any additional data or information that FDA deems necessary as soon as possible but in no case later than 15 calendar days after receiving the request (e.g., hospital record, autopsy report) (§ 320.31(d)(3)). Study drug exposure for the participant who experienced the SAE should be unblinded.

If the adverse event is fatal or life-threatening, the company conducting the study must also notify the Director in CDER's Office of Generic Drugs as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence (§ 320.31(d)(3)). In doing so, the company should also notify the appropriate review division in CDER's Office of New Drugs or the Division of Clinical Safety and Surveillance in CDER's Office of Generic Drugs.

The requirements under § 320.31(d)(3) do not apply to human BA and BE studies that are exempt from IND requirements and conducted outside the United States. However, 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 drug, adverse event information from foreign clinical studies must be included in the NDA submission or the abbreviated new drug application (ANDA) submission as appropriate, based on the purpose of the BA/BE study.[49]

[49] See § 314.50(d)(5)(iv) and 75 FR 59935 at 59954 (interpreting § 314.97(a)(7) to require adverse event reports that occurred in foreign clinical studies to be included in the ANDA submission).

B. How and Where to Submit a Report (§ 320.31(d)(3))

For an IND-exempt BA/BE study conducted to support changes to an already approved NDA or ANDA, SAE reports must be submitted to FDA and should be submitted to FAERS.

For a BA/BE study conducted to support a new ANDA for a generic drug product, the entity conducting or sponsoring the study should request a pre-assigned application number at https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number. FDA recommends requesting this application number prior to starting the BA/BE study to avoid delays in expedited reporting. As stated on the website, it can take up to 3 business days following the online request to receive the pre-assigned application number.

The entity should use this application number for the following:

1. Submission of all adverse event reports from BA/BE studies

2. Submission of the ANDA for the test drug, when complete

FDA encourages electronic submission of IND-exempt BA/BE safety reports to FAERS.[50] FDA provides two methods for electronically submitting safety reports from BA/BE studies conducted to support the approval of generic drugs:

1. Database-to-Database (E2B) Transmission via the ESG NextGen

    - For more information about adverse event reporting via E2B submission, visit https://www.fda.gov/drugs/fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-electronic-submissions.

2. SRP submission, available at https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=9c063e08-5d1f-4c6d-aedd-03b018c54cc0.

    - The portal requires entering the six-digit pre-application ANDA number for submission of an adverse event report.

For fatal or life-threatening adverse events that require 7-day expedited reporting, FAERS will automatically route submissions to the appropriate group in the Office of Generic Drugs for review for notifications generally submitted through the ESG NextGen or SRP.

In situations when the ESG NextGen and SRP routes of submission are unavailable, sponsors should submit expedited reports of SAEs from IND-exempt BA/BE studies via email to OGD-PremarketSafetyReports@fda.hhs.gov. Such reports should be submitted to FDA via email

[50] See the guidance for industry *Electronic Submission of Expedited Safety Reports from IND-Exempt BA/BE Studies* (April 2024).

using Form FDA 3500A and completed with all the available information, including a brief narrative describing the SAE, an assessment of causality, and any other relevant information (§ 320.31(d)(3)). If applicable, the narrative should also include identification of other similar reports and an analysis of the significance of the SAE. A summary of the study protocol should be submitted with the report.

Each report must prominently identify its contents (§ 320.31(d)(3)). Reports should be labeled as follows:

- "Bioavailability/Bioequivalence Safety Report" for 15-day reports
- "Follow-up Bioavailability/Bioequivalence Safety Report" for follow-up information
- "7-day Bioavailability/Bioequivalence Safety Report" for unexpected fatal or life-threatening adverse reaction reports

Box G4 of Form FDA 3500A should include the pre-application ANDA number, and the "Pre-ANDA" box should be checked.[51] The type of report should be checked in box G6 on Form FDA 3500A. The report can also be identified in box B5 or in a cover letter, or both, submitted with Form FDA 3500A.

Each field in the "C" subsection of Form FDA 3500A should be completed appropriately. For example, in box C1, the study drug or drugs to which the participant was exposed prior to onset of the SAE should be listed (this may include active drug, placebo, and/or vehicle depending on the study). In box C2, the participant's concomitant medications should be listed. If the SAE began prior to administration of a study drug but after study enrollment, this event should not be submitted, because it is unassociated with study drug exposure. In box B5, the timeline of drug exposures as they relate to the SAE or SAEs should be clearly described.

[51] See Form FDA 3500A Supplement (4/16) – Form Instructions, available at https://www.fda.gov/media/82655/download.

APPENDIX: FLOWCHART FOR DETERMINING WHETHER AN ADVERSE EVENT MEETS THE CRITERIA FOR IND SAFETY REPORTING TO FDA AND INVESTIGATORS