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

Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Paul Gouge, 301-796-2500, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

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

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Drug Safety

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

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Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 staff 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 312.64(b) and 320.31(d)(3)).

This guidance defines 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 (21 CFR 312.32(c)(1)(i)(C) and 312.32(c)(1)(iv)) that require assessment of aggregate data.

This guidance merges 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 Reporting* (December 2015) (the 2015 draft guidance).[3] This guidance includes revised recommendations initially described in the 2015 draft guidance on the following topics: (1) planned unblinding of

[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. For the purposes of this guidance, *drug* or *drug product* is used to refer to human drugs and human biological products that are regulated as drugs.

[3] We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

safety data and implications for trial integrity; (2) increased flexibility regarding the party reviewing aggregate safety information for IND safety reporting purposes; (3) clarification regarding the scope and methodology of aggregate analyses; and (4) clarification regarding the plan for safety surveillance, including what elements should be included in the plan. The 2015 draft guidance has been withdrawn upon the publication of this guidance.

The content from the 2012 final guidance remains largely unchanged in this draft guidance. When finalized, this guidance will supersede the 2012 final guidance. However, until that time, the 2012 final guidance continues to represent FDA's current thinking about safety reporting requirements for INDs and BA/BE studies. This guidance does not incorporate content on investigator reporting (21 CFR 312.64(b)) from the 2012 final guidance. FDA plans to publish a separate draft guidance for clinical investigators on investigators' responsibilities for safety reporting for human drug and biological products. However, until that draft guidance is finalized, the 2012 final guidance continues to represent FDA's current thinking about investigators' responsibilities for safety reporting for INDs and BA/BE studies.

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, 600.80, or 606.170 or under section 760 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 379aa); see also § 312.32(c)(4)). This guidance does not address those obligations.

The contents of this document do not have the force and effect of law and are not meant to bind the public in any way, unless specifically incorporated into a contract. This document is intended only to provide clarity to the public regarding existing requirements under the law. FDA guidance documents, including this guidance, should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA 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 IND safety reporting requirements under 21 CFR part 312 and adding safety reporting requirements for persons conducting BA and BE studies under 21 CFR part 320. The IND safety reporting regulations distinguish between circumstances in which it is appropriate to submit IND safety 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 subjects. 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.[4]

The 2010 final rule also requires sponsors to report findings from other studies (§ 312.32(c)(1)(ii)) and findings from animal[5] 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 known serious suspected adverse reactions (§ 312.32(c)(1)(iv)).

III. DEFINITIONS (§ 312.32(a))

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 a test drug, active control, or placebo, regardless of whether the event is thought to be related to the drug. An adverse event can arise during any use of a drug or biologic (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.

B. Adverse Reaction[6] and Suspected Adverse Reaction (§ 312.32(a))

An *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**

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

[5] 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.

[6] For the purposes of prescription drug labeling, 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 21 CFR 201.57(c)(7) and 201.80(g)).

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[.]" 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.[7]

The following examples provided in the IND safety reporting regulation (§ 312.32(c)(1)(i)) 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, indicating that they occur more frequently in the drug treatment group than in a concurrent or historical control group. Such events may be known consequences of the underlying disease or condition or events that commonly occur in the study population independent of drug therapy. Such events could also be related to an intervention or therapy that is standard of care for the disease (e.g., background treatment).

To determine whether an adverse event should be classified as a *suspected adverse reaction*, or an adverse reaction, the sponsor must 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) E2A guideline for industry (the ICH E2A guidance).[8] However, FDA notes there is a difference between the IND safety reporting rule and the ICH E2A guidance with respect to who is responsible for making the causality judgment for reporting purposes. The sponsor is responsible for making the causality judgment, according to the IND safety reporting rule; in contrast, the ICH E2A guidance recommends that the judgment for reporting be based on either the investigator's or the sponsor's opinion. This difference is addressed in section IV.A of this guidance.

[7] 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 product is not administered.

[8] ICH guidance for industry *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting* (March 1995), pages 6–7.

C. Unexpected (§ 312.32(a))

An adverse event or suspected adverse reaction is considered *unexpected* if (1) it is not listed in the investigator's brochure[9] or it is not listed at the specificity or severity that has been observed in the study population; or (2) if an investigator brochure is not required or available, it is not consistent with the risk information described in the general investigational plan or elsewhere in the application. For example, if the listed term in the investigator's brochure is erythema, a reported event of Stevens-Johnson Syndrome is both more specific and more severe than the term in the investigator's 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's brochure, that rate would be considered to make the event more specific or severe than that listed in the investigator's brochure, and it would also be considered unexpected. If there is no investigator's brochure, an unexpected adverse reaction is one that is not consistent with the risk information described in the general investigational plan or elsewhere in the current IND, as amended. For reporting purposes, events should be listed in the investigator's brochure if they have been observed with the particular drug under investigation and for which a causal relationship with the drug is suspected or confirmed.[10]

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's 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's brochure only listed cerebral vascular accidents. *Unexpected* also refers to adverse events or suspected adverse reactions that are mentioned in the investigator's 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's 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's 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's brochure as a known 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 known or suspected adverse reactions to the drug, as listed in the investigator's brochure or, if an

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

[10] The investigator's 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.

investigator brochure is not required or available, as consistent with the risk information described in the general investigational plan or elsewhere in the IND. *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 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). Thus, as stated above, events that are listed in the investigator's brochure are considered *expected* adverse reactions for the drug because they are thought to be caused by the drug. However, the term *expected* has also 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's brochure as known or suspected adverse reactions. For reporting purposes, events that are *anticipated* for the disease being treated or the population being studied are considered *unexpected* because the events are not listed in the investigator's brochure (i.e., the test 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 study drug exposure.* An *expected adverse reaction* refers to an adverse event that is known or suspected to be *caused by the study drug* and should be listed in the description of the known or suspected adverse drug reactions in the investigator's brochure or, if an investigator brochure is not required or available, as consistent with the risk information described in the general investigational plan or elsewhere in the IND.

Because anticipated adverse events occur in the study population, the observations of a single event or a small number of such adverse events will generally not meet the criteria for being a suspected adverse reaction. To conclude that the drug may have caused an anticipated adverse event, one would perform an unblinded aggregate analysis to compare the rates in the treatment and comparator groups. The decision as to whether unblinding of an ongoing trial is appropriate to make such an assessment is discussed in section VI of this guidance. Monitoring and reporting anticipated adverse events are further discussed in section IV.

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 the sponsor, it results in any of the following: 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 might not result in death, are not life-threatening, and do not 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, and the development of drug dependency or abuse."

The sponsor and the investigator must evaluate whether an event meets the definition of *serious*. See §§ 312.32(c)(1)(i) and 312.64(b). Because identifying SAEs is critically important for the evaluation of potential significant safety problems, FDA considers it important to take into account both the investigator's and the sponsor's assessments. 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 312.32(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." 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 (i.e., 7- or 15-day expedited report) of potentially serious risks from clinical trials or any other source as soon as possible but no later than 15 calendar days after the sponsor receives the safety information and determines that the information qualifies for reporting in an IND safety report (see section VIII.C of this guidance for a discussion of IND safety reporting time frames). 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)).[11] See Appendix A for a flowchart to help determine whether an adverse event meets the criteria for IND safety reporting to FDA.

The sponsor must identify in each IND safety report 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 (i.e., conduct an analysis of similar events) (§ 312.32(c)(1)). The analysis must include similar IND safety reports from all INDs for the same drug held by the sponsor, any other relevant information known to the sponsor (§ 312.32(c)(1)), and should include related reports or adverse events available from pre- and postmarketing studies.

[11] 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 subject safety.

Sponsor-investigators, as defined in § 312.3(b), are required to comply with both the sponsor and the investigator responsibilities under part 312. FDA recognizes that a sponsor-investigator may not have access to complete safety data maintained by a commercial sponsor or other sponsor-investigators, but sponsor-investigators are responsible for evaluating all safety information available to them, including data from reports in the scientific literature and reports from foreign commercial marketing experience, if known. See § 312.32(b). To protect human subjects, FDA recommends that entities that provide a drug to or receive a drug from other entities share safety information with each other.

A. Serious and Unexpected Suspected Adverse Reaction (§ 312.32(c)(1)(i))

The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (including active comparators) that is both serious and unexpected (§ 312.32(c)(1)(i)).[12] 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., not listed in the investigator's 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 or elsewhere in the IND; 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**.[13]

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* should 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*. 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:

[12] The sponsor must submit an IND safety report for any suspected adverse reaction to study treatment that is both serious and unexpected, including suspected adverse reactions to active comparators that are marketed or approved in the United States. Postmarketing safety reporting requirements (§§ 314.80 and 600.80) apply to the NDA or BLA holder but not to the IND sponsor. As a result, unless the IND sponsor and NDA/BLA holder are the same, or the NDA/BLA 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.

[13] 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 *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.

- 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 section 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 adverse events for which it is difficult or impossible to make a causal determination based on a single case or a small number of cases and where an aggregate analysis comparing the rate of such events in the intervention arm compared to a control is needed (see § 312.32(c)(1)(i)(C)); or (2) adverse or suspected adverse reactions that must be reported if the incidence is higher than described in the protocol or investigator's brochure (§ 312.32(c)(1)(iv)) and therefore for which an aggregate analysis comparing the rate of the adverse or suspected adverse reaction in the study to past rates is needed.

If the study under an IND has an active control group but the sponsor is not the new drug application (NDA) or biologics license application (BLA) holder for the control drug, 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 as individual events as described in § 312.32(c)(1)(i)(A) and (B). If the sponsor is also the NDA or BLA 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 flowcharts in Appendix B.)

During an aggregate analysis to determine whether there is an increase in serious anticipated adverse events in the group receiving the investigational drug that would need to be reported under § 312.32(c)(1)(i)(C), a sponsor who is not the NDA or BLA holder for the control drug may discover that the rate of the anticipated adverse event is higher in the control arm than in the test drug arm. FDA recognizes that additional context may be needed to interpret such aggregate analysis results (e.g., if the aggregate event rate is higher in the active control group than in the test drug group, it could be that the test drug is protective rather than that the control drug is causing an increased rate of the adverse event). For imbalances suggesting a substantially higher rate in the control group (rather than a protective effect of the study drug), the sponsor should report such an imbalance to FDA; FDA acknowledges that the reporting threshold for a well-characterized approved control drug could be higher in light of previous knowledge of the drug. The sponsor should consider sharing with the NDA or BLA 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.

If the sponsor is not the NDA or BLA holder for the control drug, they are not expected to perform aggregate analyses to assess whether there is an increased occurrence of serious **expected** adverse reactions for the control drug (i.e., events reportable under § 312.32(c)(1)(iv)). In general, it should be expected that the control drug is marketed and its safety profile is well established and described in labeling. If, however, it becomes apparent that the expected serious adverse reaction that is listed in the package insert of the control drug occurs at a much higher frequency than is expected, the sponsor should report this finding to FDA in an IND safety report.

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[.]" 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 adverse events 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 for interpreting the event and determining whether it is a suspected adverse reaction. Further, such knowledge may be essential for the medical management of the subject 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). FDA generally does not anticipate that unblinding single or small numbers of serious and unexpected adverse event cases will compromise trial integrity, in part because such unblinding should be infrequent. For example, a single case of liver injury would be unblinded but would have no effect on overall study integrity. The challenges arising from unblinding safety data for aggregate data analyses are discussed in sections VI.B through VI.D of this guidance.

If the blind is broken and a subject with an adverse event that would meet the criteria for reporting as a single event was receiving placebo, the event should not be reported in an IND safety report because it is not possible that the drug caused the adverse event. If the blind is broken and this subject was receiving drug treatment (test 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 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 meet the definition of unexpected in § 312.32(a) because they are not listed in the investigator's brochure (see section III.C of this guidance), they do not warrant expedited reporting as individual cases or even when there are many such events where the incidence is consistent with expected background rates in the study population. Such anticipated SAEs will occur even if the 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 the SAE that is anticipated in the population, the sponsor should perform an aggregate analysis that will enable an assessment of whether the rates of the anticipated adverse event in a population exposed to the drug differ from the rate of the same SAE in a similar population not exposed.

Such anticipated adverse events should be monitored at appropriate intervals, and the numbers of events in treated versus control trial participants should be compared using a safety monitoring process that protects the integrity of blinding (see section VI.D of this guidance). The adverse event must be reported to FDA in an IND safety report if an aggregate analysis reveals there is an imbalance between arms that is sufficient to conclude that there is a reasonable possibility that

the drug caused the adverse event (§ 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 adverse event.

b. Increased occurrence of serious suspected adverse reactions (§ 312.32(c)(1)(iv))

The sponsor must report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator's brochure (§ 312.32(c)(1)(iv)). An incidence rate for such suspected adverse reactions may not always be available, but when one is available or can be estimated from data or analyses in the investigator's brochure (e.g., from a table), a clinically important increase over that rate must be reported (§ 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's brochure. The decision about when to report 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 a serious adverse medical outcome (e.g., myocardial ischemia) or (2) that there has been a clinically important increase in the rate of an expected serious 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. This is 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)). To interpret imbalances in aggregate data, clinical and statistical (if applicable) expertise will 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 groups
- 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 (e.g., occurrence of both strokes and transient ischemic attacks, unexpectedly large increase in creatine kinase and events of rhabdomyolysis)

2. Increased Rate of Occurrence of 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's brochure. Factors to consider when making the judgment may include (1) the size of the increase in rate of occurrence for the test drug treatment group over the rate listed in the investigator's brochure or elsewhere in the current IND application 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 analysis of multiple studies and any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug (§ 312.32(c)(1)(ii) and (iii)). These reports are required for studies from any source, 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." For example, actions often taken in response to a significant risk finding include (1) immediate revision of the informed consent, (2) intensification of subject monitoring, (3) revised eligibility criteria or screening procedures, (4) enrollment hold, or (5) 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, epidemiological studies, and published and unpublished scientific papers. 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 the QT interval, 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 subjects receiving the investigational product.

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

Findings from animal studies, such as "carcinogenicity, mutagenicity, teratogenicity, or reports of significant organ toxicity at or near the expected human exposure" are examples of the types of findings that suggest a significant risk. Before reporting a finding 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.

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 (see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006)). The study endpoints, including unblinded study endpoints, 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 subjects 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*. 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[14] 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 accumulating data on SAEs from the entire drug development program that are sent from domestic or foreign sources.

During the course of drug development, investigators who conduct clinical trials generally report to the sponsor adverse event information; 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.[15] Sources include but are not limited to:

- Animal or in vitro studies
- Clinical or epidemiological investigations

[14] For more discussion of this subject, see the guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006), the guidance for industry *Premarketing Risk Assessment* (March 2005), and additional sources listed in the references section of this guidance.

[15] Although sponsors must examine all information relevant to the safety of the drug obtained (§ 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).

- 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's brochures, protocols, and consent forms with new information on adverse events, and, when necessary, to take steps to protect subjects (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 SAEs—particularly those SAEs that are only interpretable in the aggregate—and other important safety information is usually an important component of IND safety reporting. The plan (also referred to as a safety monitoring 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:

- 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

- A plan for regular review of SAEs and other important safety information, with unblinding as 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 adverse events that are anticipated for the study population 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: an event may be reflected by a number of different PTs. For example, the serious event of myocardial infarction may include a range of

specific PTs. Thus, each anticipated serious event may be reflected by a list of PTs (see section VII. B of this guidance). Sponsors may discuss the anticipated SAEs with the applicable FDA review division during protocol development and prior to trial initiation, as appropriate. It is not expected that the list of anticipated events will cover all clinical events that may be background clinical events in the population; hence, reported SAEs coding to PTs that are not on the anticipated event list (and not on the list of expected events) do not necessarily require IND safety reporting. Rather, such events 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.

- For studies that will use a trigger approach (see section VI.B.1.a 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.

- A plan to monitor the incidences of all events other than those that do not require aggregate reporting (which would be reported without requiring aggregate analysis; see section IV.A.1 above). These include anticipated events (both pre-specified and those not on the anticipated event list but reviewed and assessed as consistent with a background event in the population and hence not immediately reported) and expected events (those listed in the package insert or investigator's brochure).

- The frequency with which aggregate reviews of safety data will be performed.

- 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.

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 ANALYSIS FOR IND SAFETY REPORTING

Analyses of aggregate data to identify imbalances for those events of the types 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, however, detection

of a clinically meaningful imbalance often requires a database of significant size. Regardless of the size of the program, clinical judgment is important because imbalances of events between arms may result from chance. Interpreting imbalances may be particularly challenging for smaller programs where the number of events is small.[16] Even nonstatistically significant imbalances may be relevant, and interpretation may require 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 non-clinical findings. Waiting for a statistically significant difference in event rates, when other evidence points to a potential causal association, may unduly delay reporting serious events of concern. It is particularly difficult to detect differences in rates of adverse events that may be anticipated in the population being studied but are not common (e.g., prostate cancer in middle-aged men). Recognizing the complexity of the judgements, FDA will focus on the sponsor's process and reasoning underlying the sponsor's decision in the event the FDA and 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 events is developing a list of these events in the protocol or in the plan for safety surveillance and documenting a plan for monitoring these events. This will enable the safety assessment team to identify events that should not be individually reported in an IND safety report, even if they are assessed by the investigator as drug-related. As discussed in section V.A above, the fact that the sponsor did not prospectively identify an adverse event as anticipated in its safety surveillance plan does not mean that it needs to be reported as a single event.

For drug development programs in rare diseases, external data sources used to establish anticipated adverse event rates are often limited. Furthermore, the clinical trial to support effectiveness may be an unblinded single-arm trial (i.e., a trial with no concurrent comparator group). These settings are especially challenging, and sponsors should use judgement in determining whether there is a reasonable possibility that the drug caused the event. Sponsors may wish to discuss their plans regarding when an anticipated adverse event should be reported as an IND safety report with the relevant review division.

B. Aggregate Analyses of Safety Data

1. Approach to Aggregate Analyses

For SAEs that are interpretable only based on aggregate data (reportable under §§ 312.32(c)(1)(i)(C) and 312.32(c)(1)(iv)), the entity or entities that conduct the aggregate analyses generally should use one of two possible approaches to identify events that are

[16] For smaller programs, sponsors may need to assess events typically requiring aggregate analysis on an individual case basis and to only report if the event meets the criteria under § 312.32(c)(1)(i)(A) or (B).

reportable. One approach (a) estimates and prespecifies the estimated background rate of the event in the population (e.g., myocardial infarctions in an older adult population) and then utilizes an *unblinding trigger* rate, based on the rate in the blinded data from the study population. If that rate is exceeded, an unblinded analysis by treatment group is conducted. The other approach (b) regularly analyzes unblinded safety data on SAEs by treatment group to assess whether there is a meaningful increase in a particular event in the intervention group compared to the control group. Appendix C illustrates these two approaches to aggregate analyses.

Sponsors should have processes for comparing the rates of expected serious adverse reactions to the rates listed in the protocol or investigator's brochure in order to determine whether they must be reported under § 312.32(c)(1)(iv).

a. Unblinding trigger approach

In the unblinding trigger approach, if the results of the overall blinded analyses demonstrate that the rate of events in the pooled treatment groups substantially exceeds the predicted rate, the next step is to examine the rates by treatment group using an unblinded analysis. The trigger for unblinding by group is that the overall rate for a particular adverse event is substantially higher than the rate that was predicted for the overall study population. To follow this approach, sponsors would prespecify predicted rates for the anticipated SAEs (note that this would involve grouping events reported as preferred terms; see section VII.B of this guidance for information about the importance of standardized coding). Once the unblinding trigger rate is met, the numbers of events for the specific event in each arm would then be compared to determine whether the IND safety reporting criteria in § 312.32(c)(1)(i)(C) have been met. The unblinding trigger rate is set based on information available on anticipated events applicable to the specific study population (based on age, comorbidities, concomitant treatments, etc.). This approach allows for the detection of a possible increase in event rates in the treated population without routine unblinding, and, if the trigger is met, with unblinding only of the event at issue.

Sponsors should use all available data, including placebo databases, historical data, literature, external epidemiological databases, electronic health records, and disease-specific registries, to estimate rates of SAEs anticipated to occur in the study population. The predicted rates should be included in the plan for safety surveillance (see section V of this guidance).

FDA recognizes that it may be challenging to use a trigger approach because data on the rates of some anticipated SAEs in the specific trial population are not always available. For example, although it may be possible to find data on the rates of cardiovascular events in the general population aged 40–70 years, data specific to a similarly aged population with rheumatoid arthritis may not be available. In addition, even when population rates are available from external sources, such as surveys or health care databases, if the population enrolled in a trial is healthier than the general population from which the rate is derived, this could lead to a less sensitive trigger rate (too high) than is appropriate for the trial population.

Therefore, a sponsor may choose to predict rates of certain anticipated SAEs, using a trigger approach, and to not predict rates of others. For example, many SAEs on the anticipated list, as

well as SAEs not placed on the anticipated list but assessed as background events, are not interpretable as single events, but may be expected to occur relatively infrequently (e.g., sepsis or hemorrhagic stroke or hip fracture), especially in a trial of relatively short duration (e.g., 3–6 months). Unblinding to assess incidence by treatment group may be specified for all such less common events when, for example, four or five or more events (depending on the event) are reported. One approach to setting the trigger for such less common background events is to consider what imbalance would suggest a suspected adverse reaction and lead to submitting an IND safety report. Such an assessment may include a detailed review of the individual events, considering all of the factors listed in section IV.B.1 of this guidance. The rationale behind the choice of events for which a prespecified threshold is identified is important, and the sponsor should document how that threshold is determined.

b. Analyses of all events by treatment group

An alternative to the trigger approach is to conduct periodic aggregate analyses of all SAEs, or at least those occurring in more than three or four participants (i.e., a cutpoint where the most extreme unfavorable imbalance would raise concern), comparing numbers of those events across treatment arms, to determine if there is a numerical imbalance that needs further evaluation to determine whether the IND safety reporting criteria in § 312.32(c)(1)(i)(C) have been met. This approach is preferable when it is not possible to accurately predict rates of anticipated SAEs. This approach does not require identifying predicted rates of events and directly assesses rates in treatment and control groups, the issue of primary interest. The routine unblinding of SAEs that occurs with this approach requires scrupulous, thoroughly planned and well-documented efforts to protect data integrity, assuring that the entity carrying out the review is completely firewalled from the staff conducting the trial and assessing efficacy.

2. Frequency of Aggregate Analyses

In the absence of a specific concern, it is reasonable to conduct the aggregate analyses at intervals based on volume of safety data collected or based on subject 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 relatively sick study population). It is likely that the need to conduct aggregate analysis will happen at regular intervals (e.g., 6 months or more frequently as appropriate). 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.B of this guidance).

3. Considerations When Evaluating Aggregate Data

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 adverse event, 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)[17] provides recommendations regarding combining data from multiple trials.

C. 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 it receives. Sponsors may choose to designate an entity (an individual or group of individuals) to review the 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.[18] Sponsors have flexibility in determining which entity or entities should perform this function. The entity used to assess individual occurrences or a small number of adverse events (reported under § 312.32(c)(1)(i)(A) and (B)) may be different from the entity assessing aggregate adverse events reported under § 312.32(c)(1)(i)(C).

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 clinical events) and 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 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 to help the sponsor assess whether the reporting criteria in §§ 312.32(c)(1)(i)(C) and 312.32(c)(1)(iv) have been met. An advantage of having a DMC conduct this review is that the DMC routinely sees unblinded data and can utilize existing controls for maintaining trial integrity. FDA recognizes that

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

[18] See § 312.52 (Transfer of obligations to a contract research organization).

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. While DMCs monitor risks and benefits to make recommendations for trial continuation or modification, entities that review safety information for the purpose of IND safety reporting focus on identifying and characterizing risks of the test drug (i.e., suspected adverse reactions). Although there is certainly overlap in these activities, the assessments may differ in certain circumstances and the DMC could fulfill this new role by (1) reviewing the accumulating safety data collected over time in late-stage drug development and across multiple trials, across INDs for the particular drug, and from other sources, if applicable, and (2) assessing whether the IND safety reporting criteria have been met. 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 both sponsor representation and/or external representation. It is important that no unblinded effectiveness 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 except for DMC members and any personnel designated to conduct unblinded analyses of safety data and who have been appropriately firewalled from those conducting the trial and performing other analyses (See section VI.D of this guidance).

Sponsors may also consider a triage approach in which more than one entity participates in the review. Blinded review by sponsor personnel most familiar with the product and program would be conducted to determine if the number of events being seen in the trial population as a whole meets certain criteria that would trigger an unblinded comparison of event rates in the treatment and control groups. The unblinded analyses would be conducted by a separate firewalled internal or external entity (e.g., a DMC). It is also possible that the initial unblinded analyses by treatment group could be by an individual that is firewalled from the personnel responsible for conducting the trial, and only if there is an imbalance by treatment group[19] would that individual refer the events to an internal or external entity responsible for determining if the threshold for IND reporting is met. Whatever approach a sponsor uses should be documented in the safety surveillance plan.

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

[19] It is possible that the number of events seen in the trial population is above expected but there is no imbalance between treatment groups.

the trial(s) from being unblinded to individual subjects' treatment assignments. If a firewalled entity other than the DMC is set up to look at aggregate data, it should have access only to the unblinded data necessary to evaluate the event. For example, it may be necessary to unblind the treatment assignment of the subjects who experienced an SAE, or it may be necessary to unblind additional data that is relevant to interpreting the observed imbalance (e.g., related clinical 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 subject.

To address sponsor concerns about unblinding large numbers of subjects' treatment assignments to investigators when submitting aggregate reports, FDA considers the sending of the narrative portion of the IND safety report based on data in the aggregate to all participating investigators, instead of sending a completed Form FDA 3500A for each individual event, 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.

If the sponsor proposes and follows a reporting format different from that otherwise required in § 312.32(c), it must be agreed to in advance by the director of the FDA review division responsible for reviewing the IND (§ 312.32(c)(3)).

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 potentially 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's 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 subject receiving the investigational drug (and hence listed in the investigator's 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 preferred term 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 preferred terms 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). Standardized MedDRA queries (SMQs) or Higher Level Terms (HLTs) or sponsor-defined groupings that reflect the anticipated event should be employed. 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 NDA or BLA holder,[20] the sponsor should also forward the report to the NDA or BLA holder, manufacturer, packer, or distributor of the marketed drug. If the sponsor is also the NDA or BLA 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 events 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 its 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 NDA or BLA holder, such safety information must be reported in accordance with the postmarketing requirements if it also meets the criteria for reporting.

If the IND sponsor (who may also be the NDA or BLA 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 postmarketing reporting and does not also need to be submitted to the IND, even if it meets criteria for being a serious and unexpected suspected adverse reaction.

[20] We note that the postmarketing reporting requirements concerning the submission of postmarketing 15-day Alert reports (§ 314.80(c)(1)(i) through (ii)) apply not only to the NDA or BLA 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).

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 adverse reactions received through foreign commercial marketing experience if the event meets reporting criteria for IND safety reports (§ 312.32(c)(1)). Because the drug is not approved and is not marketed in the United States, 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 product.

D. Duration of Safety Reporting

The purpose of sending IND safety reports to investigators is to provide investigators with information they need to protect subjects participating in clinical trials. Once investigators are no longer enrolling or monitoring subjects 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 subjects who received the investigational drug, the investigator should be notified so subjects 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))[21]

A. Report Identification and Format

Each report must prominently identify its contents (§ 312.32(c)(1)(v)). Reports should be labeled as follows:

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

[21] Under section 745A(a) of the FD&C Act, 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 draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (October 2019). When final, this guidance will represent FDA's current thinking on this topic.)

For reports made on Form FDA 3500A, the type of report should be checked in box G6 on FDA Form 3500A.

The format for IND safety reports should be based on whether the report involves an individual case or events identified by aggregate analysis.

1. Individual Cases

For reports of individual cases, a sponsor should ordinarily use Form FDA 3500A.[22] FDA will accept foreign suspected adverse reaction reports on a CIOMS I Form instead of Form FDA 3500A (§ 312.32(c)(1)(v)). These forms should be completed with all available information, including a brief narrative describing the suspected adverse reaction and any other relevant information. Like all other IND safety reports, the narrative must also include identification of all previously submitted IND safety reports concerning a similar suspected adverse reaction and an analysis of the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information (§ 312.32(c)(1)). Sponsors should include the manufacturer report number for previously submitted IND safety reports for identification purposes.

2. Reports of Events Identified by Aggregate Analyses

IND safety reports required for submission based on aggregate analyses must be submitted to FDA in the format of a narrative summary report. See § 312.32(c)(v). The narrative summary report should include a summary of the analysis of the individual cases and should list the unique case identifiers for each case (or copies of such individual cases if they have not been previously submitted) 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's brochure), and any additional analyses planned.

Additionally, the narrative summary report must identify 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 (§ 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

[22] Form FDA 3500A is available at http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

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. Narrative summary reports and other reports required to be submitted in narrative format under § 312.32(c)(1)(v) (see section VIII.A.3 of this guidance) should not be submitted on Form FDA 3500A, which is for individual-case safety reports consisting of individual subject data.

At the time the narrative summary report is submitted, the sponsor should submit all reports for the individual cases that made up the analysis that were identified in the narrative summary report (e.g., a completed FDA Form 3500A for each case), if not previously submitted. If individual cases were previously submitted as IND safety reports in electronic common technical document (eCTD) format, the sponsor should list the eCTD sequence number[23] and date of submission with a hyperlink to the IND safety report to facilitate review. For INDs that are not in eCTD format, sponsors should attach previously submitted IND safety reports as PDF attachments to the narrative summary report and clearly identify them as duplicate submissions.[24] Before submission to FDA, each individual case report should be unblinded to include data that is necessary to evaluate the event. FDA considers sending only the narrative summary report to participating investigators without the individual unblinded case safety reports that are summarized in the narrative report to meet the requirement under § 312.32(c)(1) for a sponsor to notify all participating investigators in an IND safety report of potential serious risks.

For aggregate analysis, after an adverse event anticipated to occur in the study population 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's brochure, the protocol, 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's 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. 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's 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 subsequent occurrences of certain events in an IND safety report that the sponsor has added, as expected events, to the investigator's brochure, the protocol, and other safety related information. Although IND safety reporting is no longer required after an SAE is listed in the investigator

[23] The eCTD sequence number is the unique four-digit number for each IND submission the sponsor submits in the us-regional.xml file for the eCTD submission.

[24] For more information see the draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* and the technical specifications documents *Electronic Submissions of IND Safety Reports Technical Conformance Guide* (October 2019) and *Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments* (October 2019).

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 risk: benefit 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)).

3. Other Reports

For reports of overall findings or pooled analyses from published and unpublished in vitro, animal, epidemiological, or clinical studies, a narrative format must be used (§ 312.32(c)(1)(v)). If the findings are published, in full or in abstract form, the sponsor should include a copy of the publication.

B. Where and How to Submit

The IND safety report must be transmitted to the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation Research (CBER) review division responsible for reviewing the IND (§ 312.32(c)(1)(v)). IND safety reports should be submitted to all of the sponsor's INDs under which the drug is being administered. For example, if a drug is found to cause drug-induced liver injury, this should be reported to any IND under which the drug is being administered. The sponsor should reference in the subject line of the cover letter all INDs to which the IND safety report is being submitted. If applicable, the sponsor should also identify (e.g., by underlining) the specific IND under which the suspected adverse reaction occurred (e.g., "Suspected adverse reaction occurred under IND XXXX1, reference to INDs XXXX2, XXXX3").

FDA recommends that sponsors submit IND safety reports electronically in the eCTD[25] if the IND is in eCTD format or if the sponsor intends to convert the IND to eCTD format. Complete information on eCTD specifications and guidance can be found on the FDA eCTD website, and assistance may be obtained by contacting ESUB@fda.hhs.gov. If the IND is not in eCTD format, other means of rapid communication (e.g., telephone, fax, email) may be used. If the IND is not in eCTD format and the sponsor intends to submit IND safety reports by fax or email,

[25] Although FDA has exempted noncommercial INDs from the electronic submissions requirements under section 745A(a) of the FD&C Act, FDA also accepts electronic submissions from these INDs. For additional information on this subject, see the guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (February 2020).

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.[26]

C. 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) 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

[26] For details on obtaining a secure email account with FDA, visit https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm.

information (§ 312.32(c)(2)). If the safety report submitted within 7 calendar days is complete, an additional submission within 15 calendar days from day zero is not required.

Day zero 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)). See section IX of this guidance for reporting time frames for follow-up information.

Finally, because of the potential for delay between the occurrence of an adverse event and the reporting of the adverse event to the sponsor, the date of the event on Form FDA 3500A is not determined by the reporting time frames and is "the actual or best estimate of the date of first onset of the adverse event." FDA interprets the "date of first onset of the adverse event"[27] to be the date that the subject 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., information that would be contained in a narrative report or on Form FDA 3500A) 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 adverse event reports related to that subject 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 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 immediately submit a Follow-up IND Safety Report (§ 312.32(d)(2)). However, if the sponsor obtains other information that is not relevant to 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).

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

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) 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 312.32(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's 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 subjects enrolled in the study is small, the subjects are usually healthy volunteers, and drug exposure is typically brief."[28] 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).

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

[28] Final Rule, Investigational New Drug Safety Reporting Requirements for Human Drug and Biological roducts and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (75 FR 59953) published September 29, 2010.

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

The company 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's 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 subject 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 Clinical Safety Surveillance Staff 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 product, adverse event information from foreign clinical studies must be included in the NDA supplement or the abbreviated new drug application (ANDA) submission as appropriate, based on the purpose of the BA/BE study.[29]

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

For a BA/BE study conducted to support changes to an already approved NDA or abbreviated new drug application (ANDA), SAE reports must be submitted to FDA and should be submitted to the FDA Adverse Event Reporting System (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

[29] See 21 CFR 314.50(d)(5)(iv) and 75 FR 59935 at 59954 (September 29, 2010) (interpreting 21 CFR 314.97(a)(7) to require adverse event reports that occurred in foreign clinical studies to be included in the ANDA submission).

https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/ucm114027.htm. 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 BA/BE safety reports to FAERS. FDA provides two methods for electronically submitting safety reports from BA/BE studies conducted to support the approval of generic drugs:

1. FAERS Database-to-Database (E2B) Transmission

    - For more information about adverse event reporting via E2B submission, visit https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/ucm115894.htm.

2. HHS Safety Reporting Portal (SRP) submission, available at https://www.safetyreporting.hhs.gov/SRP2/en/Home.aspx?sid=3e955502-ce7f-4112-b379-87967ae2e4be.

    - 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, notifications generally submitted via E2B or SRP, FAERS will automatically route the submissions to the appropriate group in the Office of Generic Drugs for review. In situations when the E2B and SRP routes of submission are unavailable, sponsors should submit expedited reports of SAEs from BA/BE studies via email to OGD-PremarketSafetyReports@fda.hhs.gov.

SAE reports not submitted via E2B transmission or the SRP should be submitted to FDA via email using Form FDA 3500A 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. The type of report should be checked in box G6 on Form FDA 3500A. The report can also be identified in box B5 and/or in a cover letter 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 subject 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 subject'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.

REFERENCES

For additional information on a systematic approach to safety surveillance, please refer to the following:

Literature:

Council for International Organizations of Medical Sciences (CIOMS), Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI, Geneva 2005, ISBN 92 9036 079 8.

Crowe, BJ, HA Xia, JA Berlin, DJ Watson, H Shi, SL Lin, J Kuebler, RC Schriver, NC Santanello, G Rochester, JB Porter, M Oster, DV Mehrotra, Z Li, EC King, ES Harpur, and DB Hall, 2009, Recommendations for Safety Planning, Data Collection, Evaluation and Reporting During Drug, Biologic and Vaccine Development: A Report of the Safety Planning, Evaluation, and Reporting Team (SPERT), Clin Trials, 6(5):430–440.

Xia, HA, BJ Crowe, RC Schriver, M Oster, and DB Hall, 2011, Planning and Core Analyses for Periodic Aggregate Safety Data Reviews, Clin Trials, 8(2):175–182.

Guidances for Industry:

Guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees* (March 2006)

Guidance for industry *Premarketing Risk Assessment* (March 2005)

For additional information on topics related to aggregate analysis, please refer to the following:

Literature:

Wittes, J, B Crowe, C Chuang-Stein, A Guettner, D Hall, Q Jiang, D Odenheimer, HA Xia, and J Kramer, 2015, The FDA's Final Rule on Expedited Safety Reporting: Statistical Considerations, Stat Biophar Res, 7(3):174–190.

Guidance for Industry:

Draft guidance for industry *Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products* (November 2018)

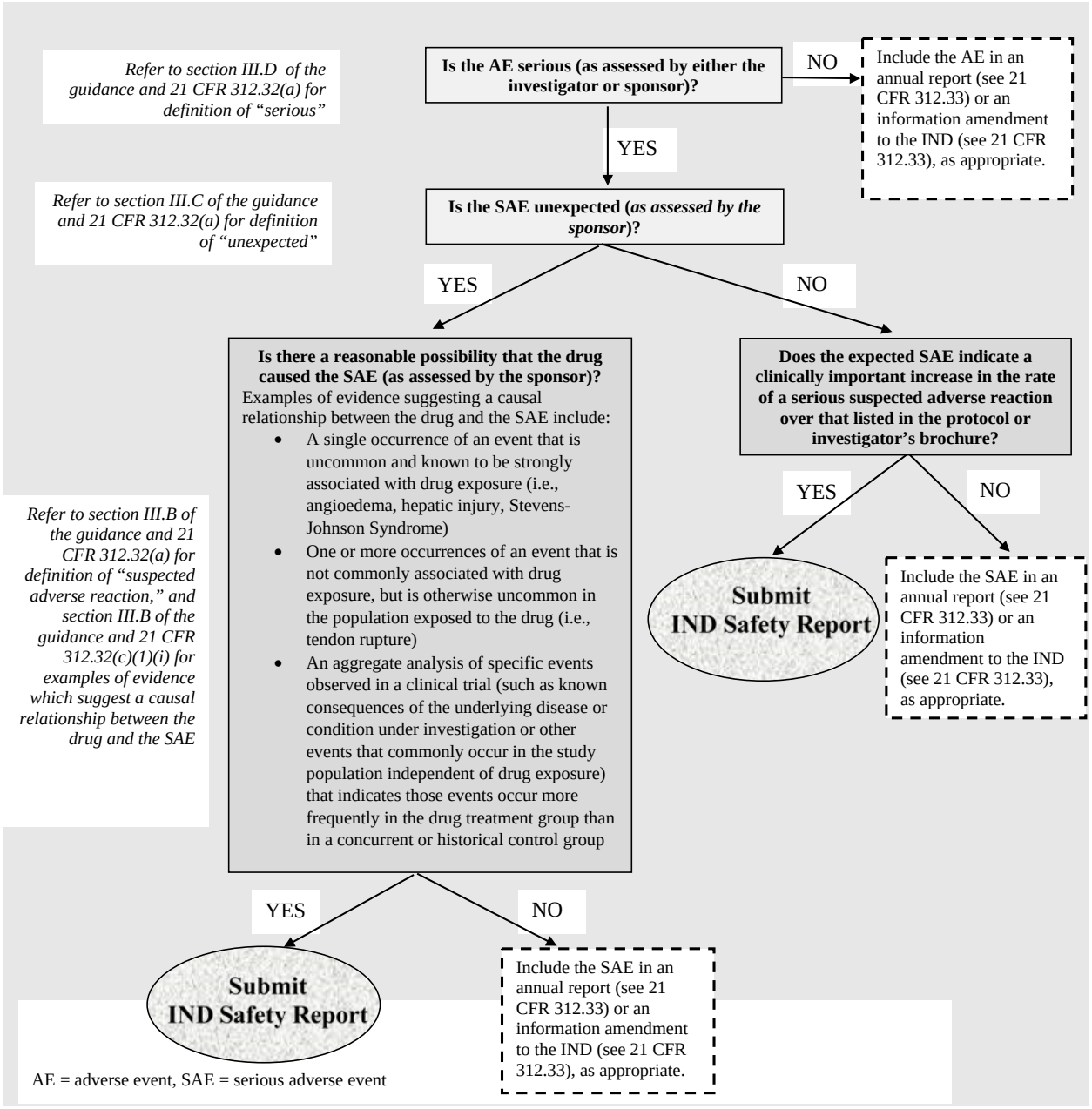
For additional information on submitting IND safety reports in electronic format, please refer to the following:

Guidances for Industry:

Draft guidance for industry *Providing Regulatory Submissions in Electronic Format: IND Safety Reports* (October 2019)

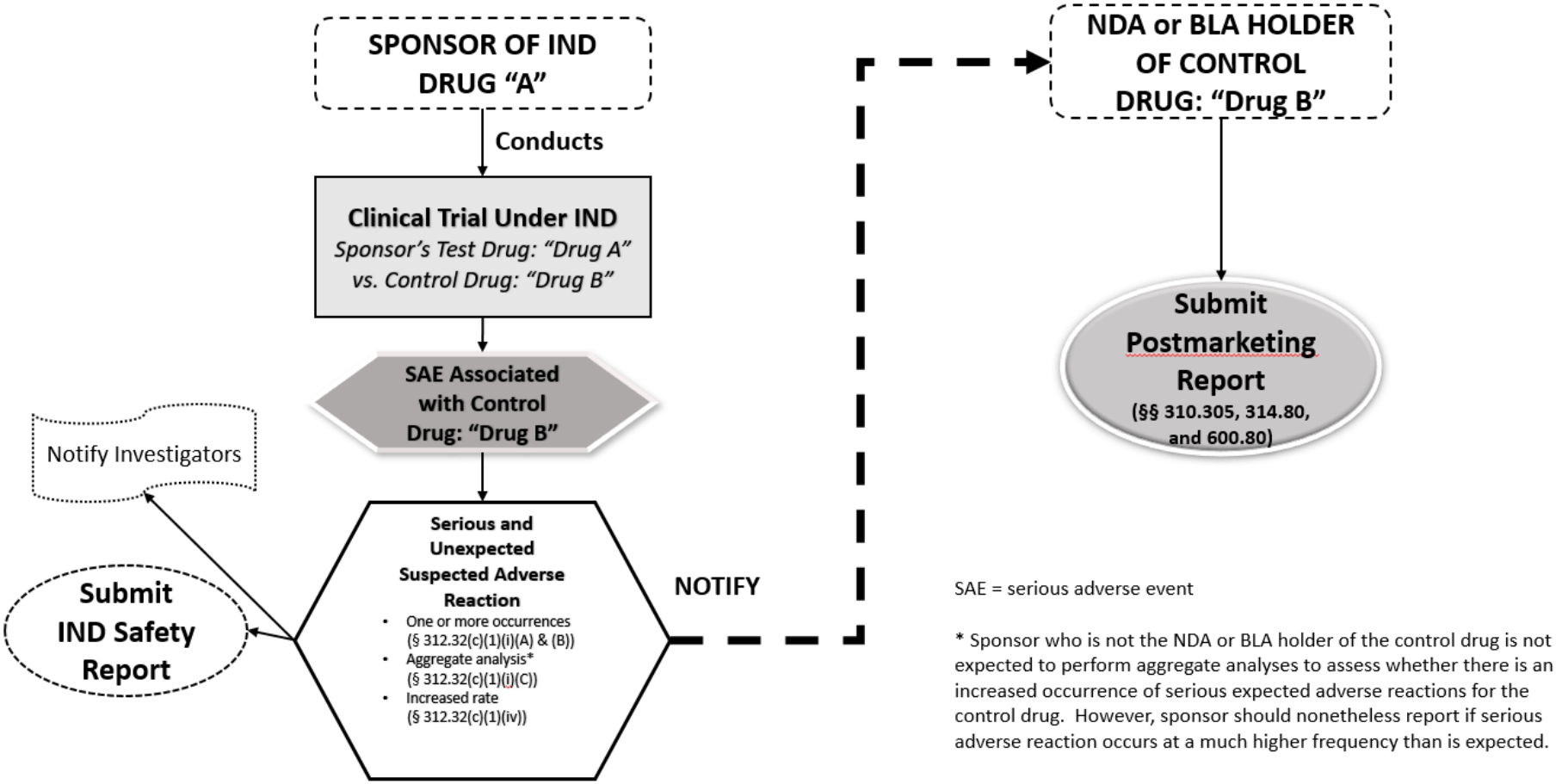
Technical Conformance Guide *Electronic Submission of IND Safety Reports* (October 2019)

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



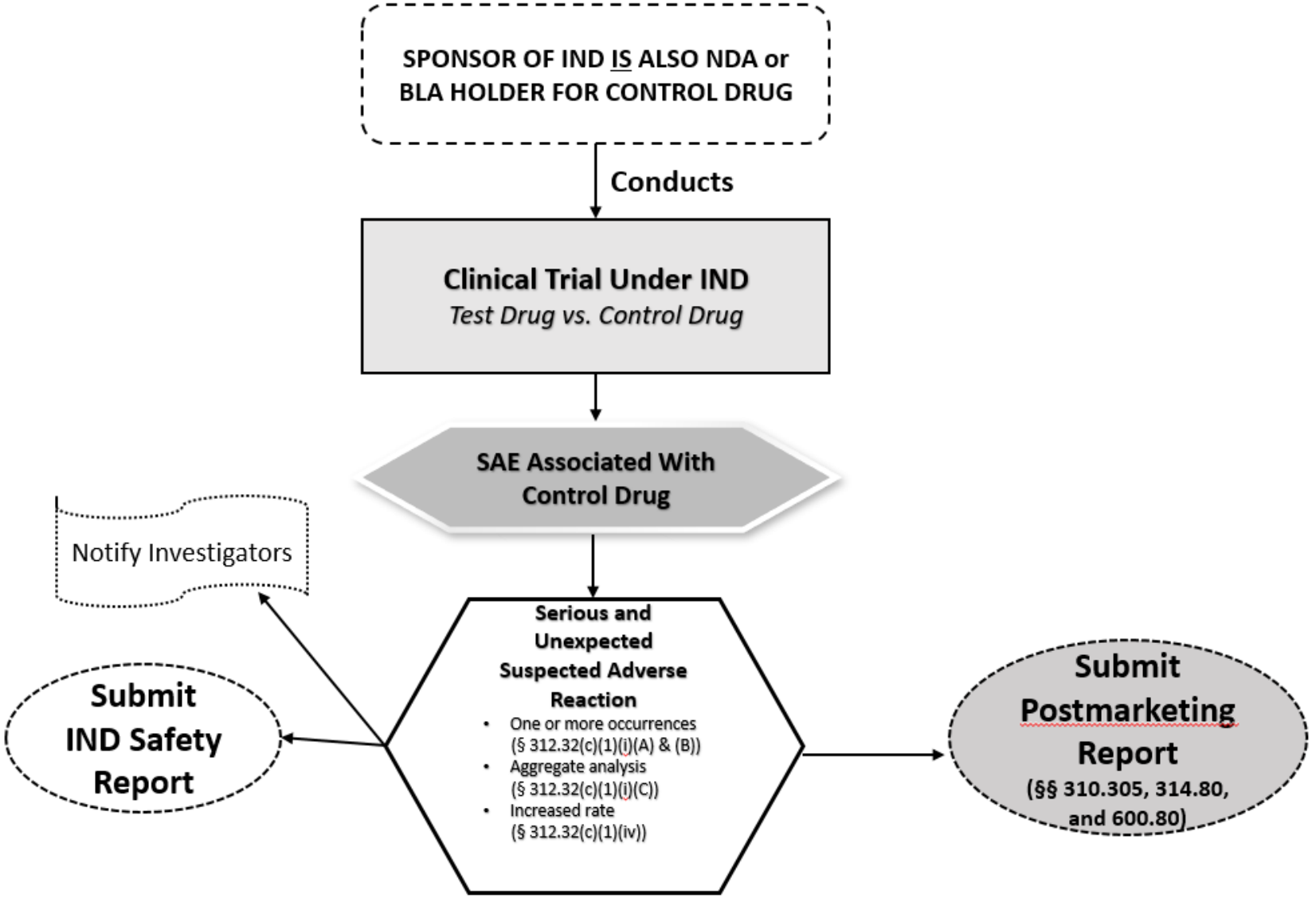
APPENDIX B: FLOWCHARTS FOR SUBMITTING SAFETY REPORTING FOR CONTROL DRUGS

Chart B.1: IND Sponsor is *NOT* the NDA or BLA Holder of the Control Drug



APPENDIX B (continued):

Chart B.2: IND Sponsor *IS* also the NDA or BLA Holder of the Control Drug



APPENDIX C: FLOWCHART FOR THE TWO APPROACHES TO AGGREGATE ANALYSES