Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

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

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Drug Safety

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This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to help sponsors and investigators comply with the requirements for investigational new drug (IND) safety reporting and safety reporting for bioavailability (BA) and bioequivalence (BE) studies under 21 CFR 312.32, 312.64(b), and 320.31(d)(3). This document provides guidance to sponsors and investigators on expedited safety reporting requirements for human drug and biological products[2] that are being investigated under an IND and for drugs that are the subjects of BA and BE studies that are exempt from the IND requirements. This guidance defines terms used for safety reporting, makes recommendations on when and how to submit a safety report, and provides advice on other safety reporting issues that have arisen from sponsors and investigators.

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

II. BACKGROUND AND BRIEF OVERVIEW OF THE REQUIREMENTS

On September 29, 2010, FDA published a final rule amending the 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.

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

[2] For the purposes of this document, unless otherwise specified, all references to "drugs" or "drug products" include human drug products and biological products that are also drugs.

A. IND Safety Reporting Requirements

Under the former 21 CFR 312.32(c)(1)(i)(A) and (B), sponsors investigating a drug under an IND were required to notify FDA and all participating investigators, in a written IND safety report, of any adverse experience associated with the use of the drug that was both serious and unexpected, and any finding from tests in laboratory animals that suggested a significant risk for human subjects. The phrase *associated with the use of the drug* was defined as "there is a reasonable possibility that the experience may have been caused by the drug" (former 21 CFR 312.32(a)). Notwithstanding this definition, sponsors frequently reported, as individual cases, serious adverse experiences for which there was little reason to believe that the drug caused the event. For example, sponsors often reported:

- Serious adverse experiences (e.g., mortality or major morbidity) that were likely to have been manifestations of the underlying disease
- Serious adverse experiences that commonly occurred in the study population independent of drug exposure (e.g., strokes or acute myocardial infarctions in an elderly population)
- Serious adverse experiences that were study endpoints (i.e., the study was evaluating whether the drug reduced the rate of these events)

These types of reports are generally uninformative when reported as single events (i.e., without a comparison of the incidence of the event in treated and untreated subjects), and they do not contribute meaningfully to the developing safety profile of an investigational drug or to human subject protection. Attempting to review and evaluate these reports without the necessary context was also a drain on resources for FDA, investigators, and institutional review boards (IRBs),[3] diverting them from other activities.

The tendency for sponsors to report such uninformative individual cases seems to have been primarily related to interpretation of the *reasonable possibility* standard in the definition of *associated with the use of the drug*. For an individual case of the types of adverse events described above, there would generally not be enough evidence to suggest that there was a reasonable possibility that the drug caused the adverse event. Such events would therefore not meet the definition of "associated with the use of the drug" and should not have been reported as IND safety reports.

Under 21 CFR 312.32, the amended requirements revise the definitions used for safety reporting and make clear when to submit expedited safety reports. The requirements distinguish circumstances in which it is appropriate to submit individual cases and circumstances in which cases should be aggregated and compared to cases in a control group and submitted only if the event occurs more frequently in the drug treatment group. Compliance with these requirements will increase 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. In addition, reducing the number of uninformative individual reports will enhance the ability of sponsors, FDA, investigators, and IRBs to focus on safety issues that affect public health.

[3] See section VI.F of this guidance for more information on safety reporting to IRBs.

Because the regulations require reporting certain adverse events in the aggregate rather than as individual cases, it is important for sponsors to collect and evaluate safety data systematically during product development, including accumulating safety data (see section V.A.3).

B. Safety Reporting Requirements for BA and BE Studies (21 CFR 320.31(d)(3))

Under former 21 CFR 320.31(d), certain in vivo BA and BE studies in humans were exempted from the IND requirements under part 312 if specific conditions were satisfied (i.e., samples of any test article and reference standard were reserved by the persons conducting the study and released to FDA upon request, studies were conducted in compliance with the requirements for institutional review set forth in 21 CFR part 56 and informed consent set forth in 21 CFR part 50). Although these studies were not subject to the IND safety reporting requirements under 21 CFR 312.32, FDA received safety information from these studies that provided important information about drugs under investigation. For this reason, the final rule contains safety reporting requirements under 21 CFR 320.31(d)(3) for persons conducting BA or BE studies that are exempt from the IND requirements. These requirements will help FDA monitor the safety of these drugs and better protect human subjects enrolled in BA or BE studies.

III. DEFINITIONS (21 CFR 312.32(a))

The IND safety reporting rule introduces terms and definitions that are meant to be clear and consistent. New definitions replace the definition of the phrase *associated with the use of the drug* in former 21 CFR 312.32(a), which, as previously discussed, has been a source of confusion. The definitions, followed by further explanation and examples, are provided in this section, and Appendix A provides a visual representation of the relationship between three of the terms.

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

> Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An *adverse event* (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, and does not imply any judgment about causality. An adverse event can arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose.

B. Suspected Adverse Reaction (21 CFR 312.32(a))

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Within the reporting requirement under 21 CFR 312.32(c)(1)(i), FDA makes clear the meaning of *reasonable possibility* by providing the following examples of types of evidence that would suggest 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 (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group

Suspected adverse reactions are the subset of all adverse events for which there is a reasonable possibility that the drug caused the event. Inherent in this definition, and in the requirement to report suspected adverse reactions, is the need for the sponsor to evaluate the available evidence and make a judgment about the likelihood that the drug actually caused the adverse event. We consider the application of the *reasonable possibility* causality standard to be consistent with the discussion about causality in the International Conference on Harmonization (ICH) E2A Guideline ("ICH E2A guidance").[4] However, the Agency notes there is a difference between this rule and the ICH E2A guidance with respect to who is responsible for making the causality judgment. The sponsor is responsible for making the causality judgment for this rule, whereas the ICH E2A guidance recommends that the judgment be based on either the investigator's or the sponsor's opinion. This is explained further in sections V.A and VI.D.1 of this document.

[4] *ICH E2A Guideline for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, March 1995, pages 6-7. CDER guidance documents can be found on the Internet at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web site. CBER guidance documents can be found at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

C. Adverse Reaction[5]

An adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

D. Unexpected (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

This definition relies entirely on the adverse events or suspected adverse reactions listed in the investigator brochure for the particular drug under investigation (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining whether newly acquired information generated from clinical trials or reported from other sources is *unexpected*.[6] This means that events not listed for the particular drug under investigation in the investigator brochure are considered "unexpected" and those listed are considered "expected." 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. In the clinical trial setting, there has been some confusion with the term "expected" as it has been used to mean "anticipated" for the disease being treated or population being studied rather than "listed in the investigator brochure." For example, some adverse events can be anticipated to occur as a result of a disease or in an older population (e.g., cancer-related deaths in a cancer trial, strokes or acute myocardial infarctions in an older population). However, for reporting purposes, these anticipated events are not "expected" because they are not listed in the investigator brochure (i.e., the test drug is not suspected or known to cause them). Monitoring and reporting these types of anticipated events are further discussed in section V.A.3 of this document.

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[5] 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)).

[6] For drugs marketed or approved in the United States, ordinarily FDA-approved prescription drug labeling is used as the basis for determining whether an event is unexpected for reporting purposes.

Adverse events listed in the investigator brochure as occurring with members of the same class of drugs, or as anticipated from the pharmacological properties of the drug, would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the angiotensin-converting enzyme (ACE) inhibitor class and angioedema would be described in the investigator brochure as a class effect, a case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes until it is included in the investigator brochure as occurring with the drug under investigation.

E. Serious (21 CFR 312.32(a))

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

This definition permits either the sponsor or the investigator to decide whether an event is *serious*. The investigator's perspective may be informed by having actually observed the event, while the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. Because serious adverse events are critically important for the identification of significant safety problems, FDA believes taking into account both the investigator's and the sponsor's assessment is important. Therefore, if either the sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the sponsor for expedited reporting (21 CFR 312.32(a) and 312.32(c)(1)).

We note that the definition of "serious" differs slightly from the ICH E2A guidance[7] (i.e., FDA definition uses "and" rather than "or" in the sentence "Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject ***and*** may require medical or surgical intervention to prevent one of the outcomes listed in this definition"). We will accept application of either the FDA definition (i.e., "and") or the ICH E2A guidance criteria (i.e., "or") in determining the seriousness of an event.

[7] *ICH E2A*, pages 4-5.

F. Life-Threatening (21 CFR 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.

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 it meets the definition of life-threatening, it must be considered life-threatening for reporting purposes (21 CFR 312.32(a)).

IV. REVIEW OF SAFETY INFORMATION (21 CFR 312.32(b))

The sponsor is required to review promptly all information relevant to the safety of the drug (21 CFR 312.32(b)). During the course of drug development, adverse event information is generally reported to a sponsor by investigators conducting clinical trials; however, a sponsor may become aware of new safety information from a variety of sources, both domestic and foreign. Some examples of sources are listed as follows, but safety information from any other source would also need to be reviewed and evaluated by the sponsor.

- Animal studies or in vitro studies
- Clinical or epidemiological investigations
- Reports in the scientific literature
- Unpublished scientific papers
- Information presented at scientific meetings
- Reports from foreign regulatory authorities
- Reports from commercial marketing experience
- Safety information presented at a professional meeting
- Foreign spontaneous reports

The sponsor's review should include examining data from all sources and deciding whether the information meets the criteria for expedited reporting (see section V), as well as evaluating all accumulating data at regular intervals to update safety information and to identify new safety signals. Some types of information should be sought by the sponsor as part of its continuous pharmacovigilance on the safety of the drug. For example, the sponsor should conduct literature searches regularly with a frequency appropriate to the drug or study design to seek safety information and report that information if necessary.

V. MONITORING THE SAFETY DATABASE AND SUBMITTING IND SAFETY REPORTS

Under 21 CFR 312.32(c), the sponsor is required to notify FDA and all participating investigators in 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 (see VII.C for a discussion of IND safety reporting time frames). *Participating investigators* include all investigators to whom the sponsor is providing drug under any of its INDs or under any investigator's IND (21 CFR 312.32(c)(1)). This includes, for example, all investigators participating in clinical trials under an IND, at U.S. and non-U.S. sites, for the investigational drug, and any investigators conducting a study under their own IND for whom the sponsor provides investigational drug.

In addition, 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 (21 CFR 312.32(c)(1)). The analysis must include similar reports from all INDs held by the sponsor and any other relevant information known to the sponsor (21 CFR 312.32(c)(1)). Sponsors should evaluate a suspected adverse reaction in the context of other related reports or adverse events, including those that occurred in the placebo or active comparator group and those that occurred in pre- and postmarketing studies.

Sponsors should conduct ongoing safety evaluations, including periodic review and analyses of their entire safety database, not only for IND safety reporting purposes, but also to update investigator brochures, protocols, and consent forms with new safety information (see section VI.B.2 for information about updating investigator brochures).

Sponsor-investigators, as defined in 21 CFR 312.3(b), are required to comply with both the sponsor and the investigator responsibilities under 21 CFR part 312. With respect to safety reporting under 21 CFR 312.32, this includes examining data from reports in the scientific literature and reports from foreign commercial marketing experience. The Agency 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. To protect human subjects, we recommend that entities that provide drug to or receive drug from other entities share safety information with each other.

The sponsor must submit an IND safety report when any of the following criteria are met:

A. Serious and Unexpected Suspected Adverse Reaction (21 CFR 312.32(c)(1)(i))

The sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected (21 CFR 312.32(c)(1)(i)). Before submitting an IND safety report, the sponsor needs to ensure that the event meets all three of the definitions:

- *Suspected adverse reaction*
- *Serious*
- *Unexpected*

If the adverse event does not meet all three of the definitions, it should not be submitted as an IND safety report.[8]

Deciding whether the adverse event meets the definition of a *suspected adverse reaction* is usually the most difficult determination, but this decision is critical to avoid the submission of uninformative IND safety reports. 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 meets the definition of a *suspected adverse reaction*. The suspected adverse reaction must then be reported expeditiously in an IND safety report if it also meets the definitions of *serious* and *unexpected* (21 CFR 312.32(c)(1)(i)).

Under 21 CFR 312.64, investigators are required to provide a causality assessment for each serious adverse event reported to the sponsor. For serious events that are unexpected, the sponsor considers the investigator's causality assessment but submits an IND safety report only for those events for which the sponsor determines there is a reasonable possibility that the drug caused the event, regardless of the investigator's causality assessment. (See Appendix B for a chart that clarifies sponsor and investigator responsibilities for reporting.)

For example:

- Sponsor would not report events for which the investigator's assessment is positive for causality, but where the sponsor's evaluation did not find evidence to suggest a causal relationship between the drug and the event.
- Sponsor would report events for which the investigator's assessment is negative for causality, but where the sponsor's evaluation found evidence to suggest a causal relationship between the drug and the event.

The investigator's assessment of causality should be included in the report submitted to the sponsor. If the investigator fails to provide a causality assessment and the sponsor is unable to obtain it, or if the investigator assesses the causality as unknown, the sponsor should evaluate the event without the investigator's assessment.

To assist sponsors with determining whether an adverse event meets the definition of suspected adverse reaction, the requirement under 21 CFR 312.32(c)(1)(i) specifies that sponsors are to report to FDA ***only*** if there is evidence to suggest a causal relationship between the drug and the adverse event and it provides examples of such evidence, described below.

1. Individual Occurrences (21 CFR 312.32(c)(1)(i)(A))

Certain serious adverse events are informative as single cases because they are uncommon and are known to be strongly associated with drug exposure. Some examples include angioedema, blood dyscrasias, rhabdomyolysis, hepatic injury, anaphylaxis, and Stevens-Johnson Syndrome. The occurrence of even one case of such adverse events

[8] 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., 21 CFR 312.33 IND annual report).

would meet the definition of *suspected adverse reaction* (i.e., there is a reasonable possibility that the drug caused the event).

2. One or More Occurrences (21 CFR 312.32(c)(1)(i)(B))

A single occurrence, or a small number of occurrences, of a serious adverse event that is uncommon in the study population, but not commonly associated with drug exposure may also be informative. 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.

3. Aggregate Analysis of Specific Events (21 CFR 312.32(c)(1)(i)(C))

Certain serious adverse events can be anticipated to occur in the study population independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population). An example of the former would be a non-acute death observed in a trial in cancer patients. An example of the latter would be an acute myocardial infarction observed in a long-duration trial in an elderly population with cancer. Although these serious adverse events meet the definition of *unexpected* at 21 CFR 312.32(a), as they are not listed in the investigator brochure (see sections III.D and VI.B), these events do not warrant expedited reporting as individual cases because it is not possible, based on a single case, to determine that there is a reasonable possibility that the drug caused the event. As a result, they do not meet the definition of a suspected adverse reaction.

Section 312.32(c)(1)(i)(C) requires reporting in an IND safety report when an aggregate analysis of specific events observed in a clinical trial indicates those events occur more frequently in the drug treatment group than in a concurrent control group. In cases where a randomized comparison is not available, the estimate of whether the rate is greater than in a control population would have to be based on some other group not receiving the drug, such as the general population or populations similar to the drug population with respect to demographics and disease state but not receiving the test drug (e.g., a historical control). An aggregate analysis of specific events should reflect information from all relevant studies. Therefore, it should be performed both for individual studies (if there are enough events to be informative) and across all studies, including across INDs of the drug, to determine whether they meet the criteria for expedited reporting.

The following recommendations are intended to assist sponsors with protocol development and monitoring the safety database.

a. Reporting Study Endpoints (21 CFR 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 study. The protocol would prespecify a monitoring plan for determining whether subjects receiving the drug treatment are at higher risk for the outcome (e.g., all-cause mortality), and such results would be reported according to the protocol. The study endpoints must be reported to FDA by the sponsor according to the protocol, and ordinarily would not be reported as IND safety reports, except when there is evidence suggesting a causal relationship between the drug and the event (21 CFR 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 drug treatment or a placebo. On the other hand, in the same trial with an all-cause mortality endpoint, if the death occurred as a result of an anaphylactic reaction that coincided with initial exposure to the drug, or as a result of fatal hepatic necrosis, the death must be reported as an individual case in an IND safety report because there would then be evidence suggesting a causal relationship between the drug and the event (21 CFR 312.32(c)(5)).

In addition to the study endpoints described above, some studies also evaluate the effect of the drug on several other specific adverse events, often called "safety endpoints" or "secondary endpoints." These safety endpoints or secondary endpoints should be identified in the protocol and monitored and reported by the sponsor as described in section V.A.3.b.

b. Serious Adverse Events That Are Not Study Endpoints

Other serious adverse events that are not study endpoints and are not "expected" (e.g., because they are not in the investigator's brochure), can be anticipated to occur with some frequency during the course of the trial, regardless of drug exposure, depending on the patient population and disease under study. Examples of such "anticipated" events include known consequences of the underlying disease or condition under investigation, events anticipated from any background regimen, events common in the study population, or re-emergence or worsening of a condition relative to pretreatment baseline. In general, a limited number of occurrences of such an adverse event in a study population in which occurrences of the event are anticipated is not an adequate basis to conclude that the event is a suspected adverse reaction (i.e., that there is a reasonable possibility that the drug caused the event). Such events should not be reported individually as they occur because they are uninformative as single cases. Such anticipated adverse events should nonetheless be monitored at appropriate intervals, and the numbers of events in each arm of a controlled study should be compared. The adverse event must be reported to FDA expeditiously as an IND safety report if there is an imbalance between arms suggesting there is a reasonable possibility that the drug

caused the adverse event (21 CFR 312.32(c)(1)(i)(C)). It is important to consider the entire clinical trial database in such analyses.

i. Identifying and monitoring protocol-specified serious adverse events

At the time of protocol development, the sponsor should identify in the protocol the serious adverse events that it does not plan to report individually in an expedited manner because they are anticipated to occur in the study population at some frequency independent of drug exposure. It is not possible or desirable to list in the protocol every adverse event that may occur in the study population. Factors to consider when deciding which adverse events to identify include, for example, characteristics of the study population, natural progression of the disease, background event rates, background regimens, co-morbid conditions, and past experience with similar populations. The list of the more common serious adverse events, based on past experience, could be used for all protocols (taking into account population differences) because the analyses of these adverse events should consider the entire safety database. Therefore, the sponsor should limit the list to those events that are common enough to make an overall analysis useful. For example, in a long-term osteoporosis trial in an elderly population, it would be reasonable to list myocardial infarction, but unreasonable to list acute narrow angle glaucoma, an event that can occur in this elderly population, but is relatively rare. The protocol should also describe how the protocol-specified serious adverse events will be monitored. The sponsor or an independent group should monitor the identified events during the conduct of the trial and submit an IND safety report if an aggregate analysis indicates that the events are occurring more frequently in the drug treatment group (see section V.A.3.c).

ii. Reporting serious adverse events that are not protocol-specified

The fact that an event is not identified in the protocol does not mean that the sponsor must report a single occurrence of the event expeditiously. The sponsor should use judgment in determining whether there is a reasonable possibility that the drug caused the event. Often, a single case will be unpersuasive. For example, in the osteoporosis trial previously described, a single case of acute narrow angle glaucoma would generally not be reported in an IND safety report because such cases are seen in an untreated elderly population, but if monitoring for subsequent cases revealed additional cases in the drug treatment group, the sponsor would consider the events to meet the definition of suspected adverse reactions at 21 CFR 312.32(a) and would report them expeditiously. However, FDA will accept expedited reports for individual cases of unexpected serious adverse events that are not study endpoints and are not specified in the protocol as "anticipated" (e.g., they are known consequences of the disease being treated or common in the study population) to address concerns expressed by sponsors about not expeditiously reporting such cases.

c. Safety Surveillance for Ongoing Clinical Trials[9]

Because it is critical that a drug product's risks be adequately assessed during development, sponsors should ensure that they have in place a systematic approach for safety surveillance. Such an approach should include a process for reviewing, evaluating, and managing accumulating safety data from the entire clinical trial database at appropriate intervals. In some cases, a specific independent committee with substantial external representation could be created to perform this function. In others, the sponsor may choose to create a safety team within the sponsor's organization. In either case, this independent group would oversee the evolving safety profile of the investigational drug and evaluate, at appropriate intervals, the accumulating data from individual and multiple clinical trials, as well as other available information.

B. Findings From Other Sources (21 CFR 312.32(c)(1)(ii) and (iii))

The sponsor must also report expeditiously any findings from clinical, epidemiological, or pooled analysis of multiple studies or any findings from animal or in vitro testing that suggest a significant risk in humans exposed to the drug (21 CFR 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 (21 CFR 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 immediate revision of the informed consent, intensification of subject monitoring, revised eligibility criteria or screening procedures, enrollment hold, or consideration of discontinuation of the trial. The sponsor is also required to submit protocol amendments that describe changes to the protocol or other documents (21 CFR 312.30(b)) in addition to the IND safety report.

1. Findings From Other Studies (21 CFR 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 21 CFR 312.32(c)(1)(i). For example, any clinically important finding from a drug interaction study, from a study evaluating the QT interval, or from a study of a marketed drug would be reported under this provision. An example of such a finding would be a prolongation of the QT interval in subjects receiving the investigational product.

[9] For more discussion of this subject, see FDA's guidances on *Establishment and Operation of Clinical Trial Data Monitoring Committees* and *Premarketing Risk Assessment* (see footnote 4 for location), and references 1-3.

2. Findings From Animal or In Vitro Testing (21 CFR 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 could 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.

C. Increased Occurrence of Serious Suspected Adverse Reactions (21 CFR 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 brochure (21 CFR 312.32(c)(1)(iv)). A baseline incidence rate may not always be available, but when one is available or can be inferred from data or analyses in the investigator brochure (e.g., from a table), a clinically important increase from that rate must be reported (21 CFR 312.32(c)(1)(iv)). 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 rate. For example, rhabdomyolysis is a recognized, infrequent adverse reaction that is known to occur in the HMG-CoA reductase inhibitor class of drugs (i.e., statins). A higher than expected rate would merit reporting.

VI. OTHER SAFETY REPORTING ISSUES

A. Alternative Reporting Arrangements (21 CFR 312.32(c)(3))

Title 21 of the CFR §§ 312.32(c)(1) and 312.32(c)(1)(v) specify the format and time frame for reporting suspected adverse reactions in an IND safety report (see section VII). Sponsors may request and adopt different reporting formats or frequencies if agreed to in advance by the director of the FDA review division that has responsibility for review of the IND (21 CFR 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 21 CFR 312.32(c)(1) and 312.32(c)(1)(v) (see 21 CFR 312.32(c)(3)). FDA may require a sponsor to continue to report expeditiously a medically significant suspected adverse reaction that is listed in the investigator brochure as observed with the drug (i.e., expected) so that its rate can be carefully monitored (21 CFR 312.32(c)(3)). For example, if a single occurrence of Stevens-Johnson Syndrome was observed in a subject receiving the investigational drug, FDA may 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 from clinical trials once a study or design has been identified as posing a potential or previously unforeseen risk to participants. See sections VI.D and VI.D.3 for information on investigator reporting arrangements.

B. Investigator Brochure

The purpose of the investigator brochure is to provide the investigator with information (clinical and nonclinical) about the investigational drug that is relevant to the study of the drug in human subjects. The investigator brochure should include the information that is important for the investigator, who is administering the drug to human subjects, to know and understand. The investigator brochure is required to include information about the following (see 21 CFR 312.23(a)(5)):

- Drug substance and formulation
- Pharmacological and toxicological effects of the drug in animals (and in humans, if known)
- Pharmacokinetics and biological disposition of the drug in animals (and in humans, if known)
- Information relating to safety and effectiveness in humans obtained from prior clinical studies
- Information about possible risks and side effects to be anticipated on the basis of prior experience with the drug under investigation or with related drugs
- Precautions or special monitoring to be done as part of the investigational use of the drug

The Agency accepts a variety of formats for the investigator brochure. Although the most important purpose of the investigator brochure is to provide the investigator with information about the investigational product, the investigator brochure is also used by the sponsor as the basis for determining whether a suspected adverse reaction is *unexpected* for purposes of IND safety reporting (see section III.D).

1. Clinical Risk Information

With respect to clinical risk information, the investigator brochure should specifically and accurately list those adverse events that have been observed with an investigational drug and for which a causal relationship with the drug is suspected or confirmed. In addition, the investigator brochure should list adverse events that commonly occur with the class of drugs or may be predicted to occur based on the pharmacological properties of the drug, even if not yet observed with the drug under investigation, to alert the investigator to the possibility of their occurrence. Sponsors should use judgment in determining which terms accurately reflect a particular adverse event, including syndrome names if applicable. The investigator brochure should not list adverse events that are unlikely to have been caused by the drug because such lists could dilute the importance of clinically meaningful risk information.

2. Updating the Investigator Brochure

During the course of the clinical trial, the sponsor must update the investigator brochure on an ongoing basis with new important safety information (21 CFR 312.55). Some updates to the investigator brochure should be made as soon as possible while others can be made on a routine basis. For example, a new safety finding that represents a

significant risk to study subjects (e.g., a finding that patients with renal impairment are likely to experience a serious adverse reaction) should be communicated to investigators immediately, along with an update to the investigator brochure and possibly to the protocol (e.g., a change in screening procedures and eligibility criteria). On the other hand, an update to reflect a minor change in a suspected adverse reaction rate could be done on an annual basis.

The sponsor should exercise judgment when deciding whether the threshold has been reached for adding a newly observed adverse event to the investigator brochure. Criteria to consider usually include the strength of the evidence from individual or multiple cases and previous knowledge about the drug or drug class.

Until the investigator brochure is updated to include a new serious, suspected adverse reaction, subsequent occurrences of similar serious, suspected adverse reactions must be submitted expeditiously in IND safety reports (21 CFR 312.32(c)(1)(i)) to FDA and all participating investigators.

There is more than one acceptable approach for updating the investigator brochure with new safety information. For example, adding a new serious and unexpected suspected adverse reaction to the investigator brochure as an addendum, rather than reissuing the entire brochure, is an acceptable approach for keeping investigators informed of new observations. Sponsors should ensure that any addenda are incorporated into the next full revision of the investigator brochure.

C. Unblinding

The blind should ordinarily be broken for IND safety reports submitted to FDA and all participating investigators. Knowledge of the treatment received is necessary for interpreting the event, 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). The Agency does not believe that unblinding single or small numbers of serious and unexpected adverse event cases will compromise the integrity of the study, in part because such unblinding should be infrequent. For example, because the requirement under § 312.32(c)(5) specifically describes different reporting requirements for study endpoints, in a trial evaluating death, myocardial infarctions, and strokes as endpoints, a case of liver injury, if unblinded, would have no effect on overall study integrity.

In general, 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 there is not a reasonable possibility 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 (21 CFR 312.32(c)(1)(i)(A)). For those adverse events that would not be reported unless an aggregate analysis indicated that they are occurring more frequently in the drug treatment group than in the placebo group, a determination that the adverse event is a suspected adverse reaction would require analysis and reporting of the event rates in both the drug-treatment and placebo groups.

To comply with the requirements for IND safety reports based on data in the aggregate, the sponsor should have in place a systematic approach for evaluating the accumulating safety data. A Data Monitoring Committee (DMC) or an independent sponsor safety team could perform this function (see sections V and V.A.3.c).

As described in section V.A.3.a, there should generally be no need to report unblinded study endpoints in an IND safety report. In many cases, an independent DMC would monitor the serious events that are study endpoints (see FDA's guidance document on *Establishment and Operation of Clinical Trial Data Monitoring Committees*).[10] If a sponsor has concerns that unblinding of adverse events will compromise the integrity of the study, the sponsor can propose in advance an alternative reporting format or frequency to maintain the blind that must be agreed to by the director of the review division in FDA with responsibility for review of the IND (21 CFR 312.32(c)(3)) (see section VI.A).

D. Investigator Reporting (21 CFR 312.64(b))

Most of the information about the safety of a drug prior to marketing comes from clinical trials. Therefore, adverse event reports from investigators are critically important, as they observe subjects' responses to the drug. Except for study endpoints, the investigator must immediately report to the sponsor all serious adverse events, regardless of whether the investigator believes that they are drug related, including those events listed in the protocol as anticipated to occur in the study population independent of drug exposure or in the investigator brochure as predicted to occur with the drug (21 CFR 312.64(b)). The Agency recognizes that it may take the investigator a short period of time (i.e., a day) to compile information about the event, but then expects the information to be immediately reported to the sponsor. Investigators are not required to determine whether an event is "unexpected," as defined in 312.32(a). This is a sponsor responsibility (see Appendix B).

Although it is the exception, immediate reporting of all serious adverse events to the sponsor may not be necessary in certain trials if the events are expected and well-defined. For example, many oncologic clinical trials use drugs with known serious hematologic adverse reactions and immediate reporting of each serious adverse event may not be useful. In these cases, the sponsor may propose an alternative reporting arrangement by identifying and describing the alternative reporting arrangement in the protocol or by requesting a waiver. The review division that has responsibility for the IND must agree to any alternative reporting arrangements (21 CFR 312.32(c)(3) and 312.10). Sponsor monitoring and reporting of these types of serious adverse events is discussed in section V.A.3.b.

[10] See footnote 4 for location.

1. Assessment of Causality

FDA believes that the sponsor is better positioned than the individual investigator to assess the overall safety of the investigational drug because the sponsor has access to serious adverse event reports from multiple study sites and multiple studies and is able to aggregate and analyze these reports (see section V.A). Moreover, the sponsor is more familiar with the drug's mechanism of action, class effects, and other information. For these reasons, investigators must immediately report any serious adverse event to the sponsor, whether or not the investigator considers the event to be drug related (21 CFR 312.64(b)).

In the report to the sponsor, the investigator must include an assessment of causality (i.e., whether there is a reasonable possibility that the drug caused the event) (21 CFR 312.64(b)). The investigator's view is important for the sponsor to consider when assessing the safety of the drug and determining whether to report an event expeditiously to FDA, because the investigator, who monitors the subject's response to the drug, is knowledgeable about the subject's clinical state (e.g., medical history, concomitant medications) and thus may be sensitive to distinctions between events that may be related to the drug versus those due to the underlying disease process and/or concomitant therapies. The sponsor should decide how to capture the investigator's causality assessment (e.g., rating scale, yes/no response to a question such as, "Was there a reasonable possibility that the drug caused the adverse event?").

2. Study Endpoints

The investigator must report study endpoints that are serious adverse events in accordance with the protocol (21 CFR 312.64(b)). Because endpoints are specifically defined in the protocol, they are often not collected on the adverse event pages of the case report form. The exception to this reporting requirement is when there is evidence suggesting a causal relationship between a drug and an event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the sponsor, even if the event is a component of the endpoint (e.g., all-cause mortality) (21 CFR 312.64(b)). "Safety endpoints" or "secondary endpoints," as described in section V.A.3.a, are not considered "study endpoints" and, therefore, must be reported to the sponsor immediately (21 CFR 312.64(b)).

3. Nonserious Adverse Events

The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol (21 CFR 312.64(b)). Generally, nonserious events are recorded on the case report forms and are submitted to the sponsor and reviewed at regular intervals during the course of the investigation. The

investigator's assessment of causality is not required for nonserious adverse events by the regulations, although many sponsors may require it in the protocol.[11]

For certain trials, such as a postmarketing outcome trial for a drug that has a well-established safety profile, it may be necessary for investigators to record only a subset of nonserious adverse events, or none at all. The sponsor can arrange that only specific types of adverse events be reported to the sponsor (e.g., those that resulted in withdrawal from the study or cessation of therapy, modification of dose, or addition of another drug) provided the director of the FDA review division that has responsibility for review of the IND has agreed to that arrangement in advance (21 CFR 312.32(c)(3)). Other nonserious adverse events would not need to be recorded by the investigator on the case report form.

E. Investigations of Marketed Drugs (21 CFR 312.32(c)(4))

According to 21 CFR 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 are observed in the study, at either domestic or foreign sites. The sponsor must also submit safety information from the clinical study as prescribed by the relevant postmarketing safety reporting requirements (e.g., under 21 CFR 310.305, 314.80, 600.80, 606.170, or under the Dietary Supplement and Nonprescription Drug Consumer Protection Act (Public Law 109-462)). Note that § 312.32(c)(1)(ii) requires the sponsor to report findings from other studies that suggest a significant risk in humans, whether or not conducted under an IND and whether or not conducted by the sponsor. Therefore, as long as the sponsor maintains an open IND for a drug marketed or approved in the United States, safety information from foreign and domestic studies, including non-IND studies, must be reported to the IND and in accordance with the postmarketing requirements, if it meets the criteria for reporting.

For example, if an applicant of a drug marketed or approved in the United States sponsors a multicenter, multinational clinical trial for a new indication, where the domestic sites are included in an IND, adverse events from the clinical trial, whether or not the foreign sites are also conducted under the IND, must be promptly evaluated and reported if they qualify for reporting under § 312.32 and the postmarketing requirements.

If the same applicant or sponsor receives a spontaneous report of an adverse event from U.S. or foreign commercial marketing experience for a drug that is also under investigation, the report would not need to be reported to the IND because it is not a suspected adverse reaction observed in a study, but would need to be reported in accordance with the postmarketing reporting requirements, if it meets the criteria for reporting.

[11] CIOMS VI recommends that collection of investigator's causality assessments are not needed for routine regulatory reporting, but "there may be circumstances when such assessments are useful and important, such as for non-serious adverse events of special interest" (CIOMS 2005, at 85).

F. Adverse Event Reporting to Institutional Review Boards (IRBs)

Investigators are required to promptly report "to the IRB … all unanticipated problems involving risk to human subjects or others," including adverse events that should be considered unanticipated problems (21 CFR 312.66). In 2009, FDA issued a guidance on *Adverse Event Reporting to IRBs – Improving Human Subject Protection* that makes recommendations on the types of adverse event information that should be reported to an IRB.[12] The term *unanticipated problem* used in the *Adverse Event Reporting to IRBs* guidance describes adverse events and other types of problems (i.e., adverse events are a subset of unanticipated problems) that investigators are required to report to IRBs.

Although the rule on IND safety reporting does not directly address safety reporting by investigators to IRBs, questions have arisen about its impact on adverse event reports to IRBs, particularly with respect to the specific adverse events considered to be "unanticipated problems" that must be reported to the IRB. In general, a report that meets the criteria for reporting in an IND safety report should also be considered an "unanticipated problem" and reported to the IRB by the investigator.

It is important to note that some events that would not meet the criteria for reporting in an IND safety report would be considered unanticipated problems involving risk to human subjects (e.g., informed consent or privacy issues, certain adverse events that could not be caused by the investigational drug, such as events that occur prior to test article administration as a result of a washout period or due to a screening procedure). As part of their clinical trial monitoring responsibility, sponsors generally require that investigators report such unanticipated problems to them. Sponsors should discuss any significant unanticipated problem with the applicable FDA review division, as the problem may affect trial conduct and subject monitoring.

G. Duration of Safety Reporting

The purpose of sending IND safety reports to investigators is to provide investigators with information they need to protect their patients participating in clinical trials. Once they are no longer enrolling or monitoring patients, 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. If the sponsor continues to send IND safety reports to the investigator and the investigator does not wish to continue receiving them, the investigator should contact the sponsor and request that the sponsor stop sending them.

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 that patients could be followed up if necessary.

[12] See footnote 4 for location.

H. IND Annual Reports and Labeling

The IND safety reporting requirements did not make any changes to the requirements for IND annual reports (21 CFR 312.33). FDA recently adopted the guidance for industry *E2F Development Safety Update Report*,[13] which describes a common standard for periodic reporting on drugs under development among the ICH regions and is intended to meet the IND annual reporting requirements. Questions have arisen about whether the Agency will accept the Development Safety Update Report (DSUR) because of the difference in the party responsible for making the causality judgment (see section III.C of this document). To promote global harmonization, FDA will accept the DSUR, as described in the *E2F Development Safety Update Report* guidance, to meet the IND annual report requirements.

The Agency does not expect the IND safety reporting requirements to have any impact on the adverse reaction information presented in prescription drug labeling.[14]

VII. SUBMITTING AN IND SAFETY REPORT (21 CFR 312.32(c)(1)(v))

A. Report Identification and Format

Each report must prominently identify its contents (21 CFR 312.32(c)(1)(v)).

- "IND safety report" for 15-day reports
- "Followup IND safety report" for followup information
- "7-day IND safety report" for unexpected fatal or life threatening adverse reaction reports

The type of report should be checked in box G7 on the FDA Form 3500A. The report can also be identified in box B5 and/or on a cover letter submitted with the FDA Form 3500A.

The format for IND safety reports is based on the type of expedited report.

1. Individual Cases

For reports of individual cases, a sponsor would ordinarily use FDA Form 3500A.[15] FDA will accept foreign suspected adverse reaction reports on a CIOMS I Form instead of FDA Form 3500A (21 CFR 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. If applicable, the narrative must also include identification of similar reports and an analysis of the significance of the suspected adverse reaction (21 CFR 312.32(c)(1)).

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[13] See footnote 4 for location.

[14] For more information, see 21 CFR 201.57(c)(7), 201.80(g) and the guidance for industry on *Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*. See footnote 4 for location.

[15] FDA Form 3500A can be found on the Internet at http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

2. Aggregate Reports

An IND safety report based on data in the aggregate must be in a narrative format (§ 312.32(c)(1)(v)). Sponsors should use judgment in deciding what to include in the narrative report. The report should include a description of the suspected adverse reaction, along with all relevant information, such as summary information about symptoms, concomitant medications, demographics, comorbid conditions, past history, pertinent laboratory test results, timing of events (onset and duration), and duration of treatment. Data from previously submitted individual case IND safety reports should be included, if applicable. Finally, the narrative report should describe the characteristics and results of the analysis, including a description of the databases, how the conclusion was reached, who reviewed the analysis, any planned changes in monitoring or to study documents (e.g., informed consent, investigator brochure), and any planned further analyses.

To evaluate the aggregated data in narrative format, FDA and participating investigators need the information on the individual cases that are summarized in the report. Therefore, at the same time that the narrative format IND safety report is submitted, the individual cases that were analyzed should also be submitted (e.g., a completed FDA Form 3500A for each case). If some individual cases were previously submitted as IND safety reports, they should be resubmitted and clearly identified as duplicates. Before submission, each individual case report should generally be unblinded. If a sponsor has concerns that unblinding will compromise the integrity of the study, the sponsor should discuss this in advance with the review division (see section VI.C).

If a sponsor is monitoring and evaluating the occurrence of a serious event in the aggregate (rather than submitting each case individually), FDA expects that records of each case will be complete (e.g., a completed FDA Form 3500A for each case), including a description of the suspected adverse reaction and any other relevant information, and that each case will be followed up for additional information, if necessary.

The sponsor should determine an appropriate approach for reporting subsequent occurrences of the same event to FDA and all participating investigators, and the sponsor should include a description of this approach in the initial expedited narrative IND safety report. For example, each subsequent occurrence of an infrequent event with immediate health implications or an event that is uncommon in a specific study population (e.g., stroke in young adults) should be reported in an expedited report. 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 once a certain number of additional cases are identified or after a specified period of time, as appropriate).

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 (21

CFR 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 report must be transmitted to the CDER or CBER review division that has responsibility for review of the IND (21 CFR 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, that should be reported to any IND under which the drug is being administered. The sponsor should reference all INDs to which the IND safety report is being submitted in the subject line of the cover letter. If applicable, the sponsor should also identify (e.g., with use of an underline) 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 accepts electronic submission of 15-day IND safety reports in eCTD format to the IND application 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 Web site, and assistance may be obtained by contacting ESUB@fda.hhs.gov.

We recommend that sponsors submit 7-day IND safety reports electronically in eCTD format. If the IND is not in eCTD format, other means of rapid communication (e.g., telephone, facsimile transmission, email) may be used. If the IND is not in eCTD format and the sponsor intends to submit 7-day IND safety reports by facsimile transmission or email, the sponsor should address the submissions to the Regulatory Project Manager and the Chief, Project Management Staff in the FDA review division that has responsibility for review of the IND. In addition, if the sponsor intends to submit 7-day IND safety reports by email, we recommend the sponsor obtain a secure email account with FDA.[16]

C. Reporting Time Frame

The time frame for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days after the sponsor determines that the suspected adverse reaction or other information qualifies for reporting (21 CFR 312.32(c)(1)). The language in the IND safety reporting regulations was modified to describe the reporting time frame applicable to aggregate reports (§ 312.32(c)(1)(i)(B) and (C)) and increases in rates of occurrence of serious suspected adverse reactions (§ 312.32(c)(1)(iv)), which 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 could be well before it was determined that the event must be reported.

Sponsors should have a predefined safety monitoring plan that includes processes and procedures for the review of safety information, including the frequency of review (see section V). FDA

[16] Refer to the following link for details on obtaining a secure email account with FDA: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm.

expects that events that are interpretable as single cases (i.e., uncommon and known to be strongly associated with drug exposure) should be reported to FDA within 15 days from initial receipt. For events that require more than one occurrence to assess causality and events evaluated in the aggregate, the time clock starts when the sponsor determines that the events qualify for expedited reporting. This means that, for example, incomplete cases should be immediately followed up for additional information so that a determination can be made about whether the event is reportable as an IND safety report.

Unexpected fatal or life-threatening suspected adverse reactions represent especially important safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)). The requirement for reporting any unexpected fatal or life-threatening suspected adverse reaction to FDA is no later than 7 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32(c)(2)). If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

The day of initial receipt for cases that are interpretable as single cases and the day the sponsor determines that multiple cases qualify for expedited reporting are considered day zero.

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 (21 CFR 312.32(c)(1)(v)). See section VIII for reporting time frames for followup information.

VIII. FOLLOWUP INFORMATION (21 CFR 312.32(d))

Most IND safety reports are derived from observations from clinical trials. In the setting of a clinical trial, information is 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 FDA Form 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. Any relevant additional information that the sponsor obtains that pertains to a previously submitted IND safety report must be submitted as a *Followup IND Safety Report* without delay, as soon as the information is available (21 CFR 312.32(d)(2)), but should be submitted no later than 15 calendar days after the sponsor receives the information. The sponsor should maintain records of its efforts to obtain additional information.

For example, if information on concomitant medications is obtained after the initial IND safety report is submitted, and such information is relevant to evaluating the suspected adverse reaction, a sponsor must submit a *Followup IND Safety Report* immediately (21 CFR 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 (21 CFR 312.31) or in an IND annual report (21 CFR 312.33).

IX. SAFETY REPORTING REQUIREMENTS FOR BA AND BE STUDIES

The IND safety reporting requirements under 21 CFR 312.32 apply to BA and BE studies that are conducted under an IND. However, BA and BE studies that meet the conditions for exemption under 21 CFR 320.31 are not conducted under an IND and are not subject to the IND safety reporting requirements. The rule contains safety reporting requirements under 21 CFR 320.31(d)(3) that apply to persons conducting BA or BE studies that are exempt from the IND requirements. The following information addresses these requirements.

FDA believes that BA and BE studies that meet the requirements for exemption are generally safe. The occurrence of a serious adverse event is very unusual because the number of subjects enrolled in such a study is small, subjects are usually healthy volunteers, and drug exposure is typically brief. However, FDA occasionally receives safety-related information associated with these types of studies, which could reflect either a problem with the drug product being evaluated or with the study design being used. For these reasons, the occurrence of any serious adverse event, whether or not it is considered drug related, is of interest. Timely review of this safety information is critical to ensuring the safety of study subjects.

A. BA/BE Study Safety Reporting Requirements (21 CFR 320.31(d)(3))

The person conducting a BA or BE study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event observed 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 (21 CFR 320.31(d)(3)). This includes, for example, serious adverse events listed in the reference listed product's approved labeling, the investigator brochure, and protocol. Serious adverse events, whether observed in the investigational drug group or in the approved drug group (e.g., reference listed drug), must be reported (21 CFR 320.31(d)(3)).

If any information necessary to evaluate the serious adverse event is missing or unknown, the person conducting the study should actively seek such information and maintain records of efforts made to obtain additional information. Any relevant additional information that is obtained that pertains to a previously submitted safety report must be submitted as a *Followup Bioavailability/Bioequivalence Safety Report* as soon as the information is available (21 CFR 320.31(d)(3)), but should be submitted no later than 15 calendar days after the sponsor receives the information. In addition, upon request from FDA, the person 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) (21 CFR 320.31(d)(3)).

If the adverse event is fatal or life-threatening, the person conducting the study must also notify the Clinical Safety Coordinator 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 (21 CFR 320.31(d)(3)). We recommend that these notifications be made by telephone, email, or facsimile transmission.

B. BA/BE Studies Conducted at Non-U.S. Sites

Under 21 CFR 320.31(d)(3), persons conducting human BA and BE studies in the United States that are exempt from the IND requirements under part 312 must report any serious adverse events from the study to FDA and to all participating investigators. The requirements under 21 CFR 320.31(d)(3) do not apply to human BA and BE studies that are exempt from the IND requirements and conducted outside of 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 abbreviated new drug application (ANDA) submission (see 21 CFR 314.94(a)(7)).

C. How and Where to Submit a Report (21 CFR 320.31(d)(3))

Each report must be submitted on FDA Form 3500A (21 CFR 320.31(d)(3)). The form should be completed with all the available information, including a brief narrative describing the serious adverse event, an assessment of causality, and any other relevant information. If applicable, the narrative should also include identification of other similar reports and an analysis of the significance of the serious adverse event. A summary of the study protocol should be submitted with the report.

Each report must prominently identify its contents (21 CFR 320.31(d)(3)).

- "Bioavailability/Bioequivalence safety report" for 15-day reports
- "Followup Bioavailability/Bioequivalence safety report" for followup information
- "7-day Bioavailability/Bioequivalence safety report" for unexpected fatal or life threatening adverse reaction reports

The type of report should be checked in box G7 on FDA Form 3500A. The report can also be identified in box B5 and/or in a cover letter submitted with the FDA Form 3500A.

The drug product should be listed in box C1 of FDA Form 3500A, and if the serious adverse event occurs in a subject receiving the investigational drug product, the drug administered during the BA/BE study should be identified as investigational and the established name of the reference listed drug should be identified.

Fifteen-day reports should be sent by email to OGD-PremarketSafetyReports@fda.hhs.gov. Paper reports may be sent to the Clinical Safety Coordinator, Office of Generic Drugs, in the Center for Drug Evaluation and Research at FDA.[17]

We recommend that 7-day notifications be made by telephone, email, or facsimile transmission. If the safety report submitted within 7 calendar days is complete, an additional submission within 15 days from day zero is not required.

[17] The address for the Office of Generic Drugs is available at http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm119100.htm. The phone and fax numbers (for fatal or life-threatening adverse event reports) are also available at this site.

X. REFERENCES

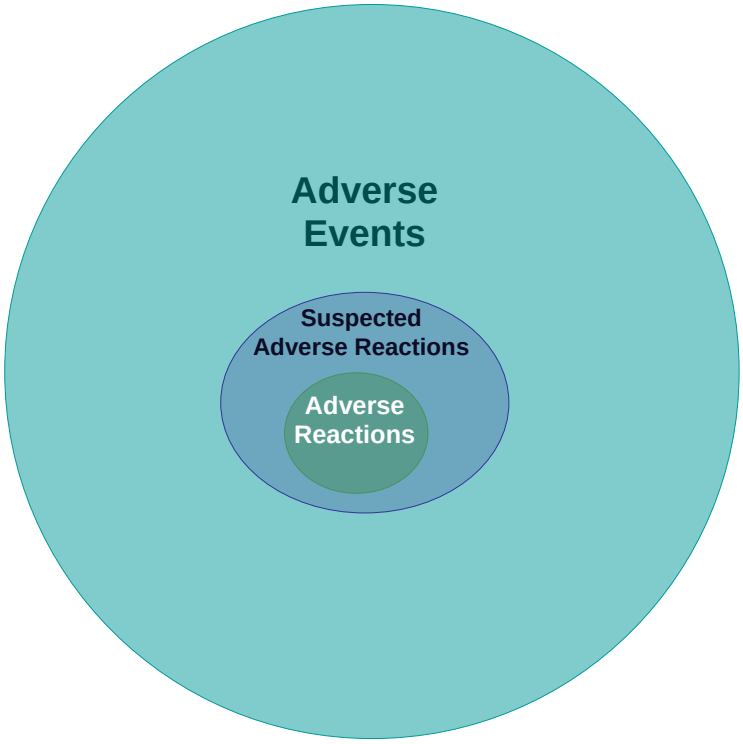
1. Crowe BJ, Xia HA, Berlin JA, et al. Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the Safety Planning, Evaluation and Reporting Team (SPERT). *Clin Trials* 2009: 6: 430-40.

2. Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI, 2005, *Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI*.

3. Xia HA, Crowe BJ, Schriver RC, et al. Planning and core analyses for periodic aggregate safety data reviews. *Clin Trials* 2011: 8: 175-182.

APPENDIX A: The Universe of Adverse Events

The diagram below depicts the relationship between adverse events, suspected adverse reactions, and adverse reactions.



APPENDIX B: Investigator and Sponsor Reporting Responsibilities

Reporting Responsibilities of Investigators under 21 CFR 312.64(b) and Sponsors under 21 CFR 312.32(c)(1)(i) for Serious and Unexpected Suspected Adverse Reactions

Term	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious (or life-threatening)	Yes (Investigator must report all serious adverse events to the sponsor immediately)	Yes	An event is considered serious or life-threatening, based on ***either*** the investigator's or sponsor's opinion.
Unexpected	No (No requirement to assess "expectedness")	Yes	The **sponsor** is responsible for determining whether event meets the definition of "unexpected," based on whether the event is listed in the investigator brochure; or if an investigator brochure is not required or available, is not consistent with the risk information described elsewhere in the general investigational plan or elsewhere in the current application.
Suspected Adverse Reaction – (causality assessment standard - "reasonable possibility")	Yes (Investigator must provide sponsor with an assessment of causality)	Yes (Sponsor's assessment determines reportability, regardless of investigator's assessment)	The ***sponsor*** is responsible for determining whether there is a reasonable possibility that the drug caused the adverse event, taking into consideration the investigator's assessment.

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The *sponsor* reports serious and unexpected suspected adverse reaction to the FDA and all participating investigators.