Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

DRAFT GUIDANCE

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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)

September 2010
Drug Safety

Guidance for Industry and Investigators

Safety Reporting Requirements for INDs and BA/BE Studies

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Guidance for Industry and Investigators[1]

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This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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 document provides guidance to sponsors and investigators on safety reporting requirements for human drug and biological products[2] that are being investigated under an investigational new drug application (IND) and for drugs that are the subjects of bioavailability (BA) and bioequivalence (BE) studies that are exempt from the IND requirements. This guidance contains definitions 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 generated questions 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 OVERVIEW OF NEW 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. The new requirements are designed to improve the overall quality of safety reporting, strengthen FDA’s ability to review critical safety information, improve safety monitoring of human drug and biological products, and harmonize safety reporting internationally.

[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. Overall Changes to IND Safety Reporting Requirements

Under 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 to mean that "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, therefore, do not meaningfully contribute to the developing safety profile of an investigational drug. 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 default to reporting an uninformative individual case seems to have been primarily related to misapplication 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. Therefore, the event would not meet the definition of "associated with the use of the drug" and should not have been reported as an IND safety report.

The new requirements revise the definitions used for safety reporting and make clear when to submit expedited safety reports. The new requirements clearly distinguish circumstances in which it is appropriate to submit individual cases and circumstances in which cases should be aggregated and compared to a control group. These clarifications should increase the likelihood that submitted information will be interpretable and will meaningfully contribute to the

[3] 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 312.53(c)(1)(vii), 312.66, and 21 CFR 56.108(b)(1)). Investigators often submit to the IRB every individual case that they receive from the sponsor. For more information on when an unanticipated risk should be reported to an IRB, see FDA's *Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs – Improving Human Subject Protection.*
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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.

Because the new requirements specify reporting certain adverse events in the aggregate rather than as individual cases, it is important for sponsors to have in place a systematic approach to safety surveillance during product development that includes a process for evaluating accumulating safety data (see section V.A.3.).

B. New 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 has received safety information from these studies that has provided important information about drugs under investigation. For this reason, the final rule contains new 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 new 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 final IND safety reporting rule introduces new terms and definitions that are meant to be clear, consistent, and in harmony with those used internationally. New definitions replace the definition of the phrase *associated with the use of the drug* in former 21 CFR 312.32(a), which, as discussed above, has been a source of confusion. The new definitions are provided below, followed by further explanation or examples.

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, without any judgment about causality. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

B. Adverse reaction[4]

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

C. 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 them 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 definition of *suspected adverse reaction* and the application of the *reasonable possibility* causality standard to be consistent with the concepts and discussion about causality in the International Conference on Harmonization (ICH) E2A guidance.[5]

[4] 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)).

[5] *ICH E2A Guideline for Industry, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*, March 1995, pages 6-7.
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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. 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 a listing of the adverse events or suspected adverse reactions in the investigator brochure (or elsewhere in the general investigational plan if an investigator brochure is not required or available) as the basis for determining if newly acquired information generated from clinical trials or reported from other sources is *unexpected*. The suspected adverse reactions listed in the investigator brochure (i.e., "expected") are those observed with the investigational drug and for which a causal relationship between the event and the drug is suspected or confirmed. Thus, adverse events that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of reporting because they would not be listed in the investigator brochure. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the investigator brochure.

In addition, some adverse events are listed in the investigator brochure as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events 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 ACE inhibitor class and angioedema would be described in the investigator brochure as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

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 if an event is *serious*. 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. For example, the investigator's perspective may be informed by having actually observed the event, and the sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event. 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)).

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))

During the course of drug development, a sponsor becomes aware of new safety information from a variety of sources. In general, adverse event information will be reported to a sponsor by investigators conducting ongoing clinical trials. Safety information may come from domestic or foreign sources. In addition, some types of information should be sought by the sponsor as part of its continuous pharmacovigilance on the safety of the drug. The sponsor is required to promptly review all information relevant to the safety of the drug (21 CFR 312.32(b)). This review should include examining data from all sources and deciding if an individual case of a

serious and unexpected adverse event meets the criteria for reporting, as well as evaluating all accumulating data at regular intervals to identify new safety signals.

The regulation includes some examples of sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers. (See 21 CFR 312.32(b)). Reports may also come from foreign regulatory authorities and from foreign commercial marketing experience for drugs that are not marketed in the United States (21 CFR 312.32(b)). The sponsor should conduct literature searches at least annually, or at other appropriate intervals, to seek safety information and report it if necessary. Safety information from any other source would also need to be reviewed by the sponsor (e.g., safety information presented at a professional meeting) (21 CFR 312.32(b)).

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 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. *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)).

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)). Sponsors should evaluate a suspected adverse reaction in the context of other related reports or adverse events, including those that occurred in pre- and postmarket studies. Sponsors should have processes in place to periodically review and analyze their entire safety database, not only for IND safety reporting purposes, but also to update investigator brochures with new safety information.

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 that is both serious and unexpected. Before submitting this report, the sponsor needs to ensure that the event meets all three of the definitions contained in the requirement:

- Suspected adverse reaction
- Serious
- Unexpected

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

Appropriately deciding whether the adverse event meets the definition of a *suspected adverse reaction* is usually the most difficult determination, but it is critical to avoiding the submission of uninformative IND safety reports. The sponsor should evaluate the available information and decide if there is a reasonable possibility that the drug caused the adverse event and, therefore, 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)).

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 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 would meet the definition of *suspected adverse reaction* (i.e., that 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. In some investigations, serious adverse events that are consequences of the underlying disease may be study endpoints (e.g., mortality or major morbidity endpoints).

Because 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.), sponsors have often reported them individually in IND safety reports. However, 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. 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))

For trials that are 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 pre-specify a monitoring plan for determining if 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 not as IND safety reports, except in unusual cases (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)).

b) Serious adverse events that are not study endpoints

Other serious adverse events that are not study endpoints, such as known consequences of the underlying disease or condition under investigation or events common in the study population, are also anticipated to occur with some frequency during the course of the trial, regardless of drug exposure. In general, a limited number of occurrences of an adverse event in a study population in which occurrences of the event are anticipated independent of drug exposure 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. At appropriate intervals, the numbers of such events in each arm of a controlled study should be compared and 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. If an imbalance is noted in a study and the study is part of a larger drug development program, it will be important to evaluate the entire clinical trial database.

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 be common 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, co-morbid conditions, and past experience with similar populations. The sponsor should limit the list to those events that are common even in the absence of drug exposure. 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 course 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 should 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 described above, a single case of acute narrow angle glaucoma would generally not be reported in an expedited 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.

c) Safety surveillance for ongoing clinical trials[6]

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 committee, preferably independent 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 that 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 a protocol amendment that describes the change 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 or from a study evaluating QT interval would be reported under this provision.

[6] For more discussion of this subject, see the *Report of the Council for International Organizations of Medical Sciences (CIOMS) Working Group VI*'s discussion of a "multidisciplinary safety management team" (Management of Safety Information from Clinical Trials. Report of CIOMS Working Group VI (2005), pp. 55-67) and FDA's guidances, *Establishment and Operation of Clinical Trial Data Monitoring Committees* and *Premarketing Risk Assessment*. FDA's guidances are available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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 determine 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, 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 rate with one member of the class in a high-dose study 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 timeframe 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. For example, if an 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.

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 (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

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 if 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 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. 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 and as a result, may put subjects at risk.

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 renally impaired subjects are likely to experience a serious adverse reaction) should be communicated to the investigator 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.

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)). The sponsor should exercise judgment when deciding if 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. In some cases, the threshold for including an adverse event may be lower if it could result in a significant adverse outcome for trial participants.

C. Unblinding

The blind should ordinarily be broken for serious and unexpected adverse events that would meet the criteria for reporting as single occurrences or one or more occurrences (see sections V.A.1. and V.A.2). 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). In general, if the blind is broken and the subject 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 the subject was receiving drug treatment (test drug or active comparator), the suspected adverse reaction must be reported in an IND safety report (21 CFR 312.32(c)(1)(i)). Any similar occurrences in the placebo group would be described in the IND safety report as part of the analysis of the significance of the suspected adverse reaction in light of other relevant information, and subsequent occurrences submitted as followup information to the IND safety report. 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.

As described in section V.A.3.a. above, 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. If a sponsor has concerns that unblinding 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 that has responsibility for review of the IND (21 CFR 312.32(c)(3)). Any alternative arrangements would need to identify the serious adverse events in the protocol that will not be reported on an individual basis, and include the plan for monitoring and reporting results to FDA.

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 are monitoring the study subjects and making observations about the safety of the investigational 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)) unless an alternative reporting arrangement has been made under 21 CFR 312.32(c)(3). Study endpoints that are also serious adverse events are reported to the sponsor in accordance with the protocol.

1. Assessment of causality

Although the investigator's view of the causal relationship between an adverse event and the investigational drug is important, 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 is able to aggregate and analyze these reports. For this reason, investigators must immediately report any serious adverse event to the sponsor, without regard to causality (21 CFR 312.64(b)). However, it is also important for the sponsor to consider the investigator's view when assessing the safety of the drug and determining whether to report expeditiously to FDA because the investigator is knowledgeable about the human subject (e.g., medical history, concomitant medications), administers the investigational drug, monitors the subject's response to the drug, is aware of the subject's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be drug-related, and may have observed the event. Therefore, the investigator must include an assessment of causality (i.e., whether there is a reasonable possibility that the drug caused the event) in the report to the sponsor (21 CFR 312.64(b)). 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)).

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 retrieved by the sponsor, or submitted to the sponsor, at regular intervals during the course of the investigation. The investigator's assessment of causality is not required for nonserious adverse events.

For certain trials, such as a postmarket outcome trial for a drug that has a well-established safety profile, recording most nonserious adverse events may not be necessary. Under 21 CFR 312.32(c)(3), 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). Other nonserious adverse events would then 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), the only reports that must be submitted as IND safety reports for a drug marketed or approved in the United States are those arising from a study conducted under the IND (at domestic or foreign sites). The sponsor must also submit safety information from the clinical study as prescribed by the 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)). All other reports (e.g., marketing experience, studies not under an IND) would be reported in accordance with the relevant postmarket safety reporting requirements.

The table below[7] summarizes the reporting requirements for submitting safety reports from a clinical study.

Drug marketed or approved* in U.S.?	Under U.S. IND?	Trial site location	Must report to IND?	Must report per postmarket requirements?
Yes	Yes	U.S. or Foreign	Yes	Yes
Yes	No	U.S. or Foreign	No	Yes
No	Yes	U.S. or Foreign	Yes	
No	No	Foreign		

*If a drug is approved in the United States, but is not currently being marketed in the United States, the postmarket requirements would still apply.

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

A. Format

The format for IND safety reports is based on the type of expedited report. For reports of individual cases, a sponsor would ordinarily use FDA Form 3500A. 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)).

[7] Reporting requirements for BA and BE studies that are not conducted under an IND and subject to the requirements under 21 CFR part 320 are not addressed in the table, but are addressed in section IX of this document. Areas in the table are left blank when an IND or marketing application would not exist.

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, the sponsor should include a copy of the publication. FDA will typically also request information on the individual cases from aggregated data from a clinical study.

Each report must prominently identify its contents (21 CFR 312.32(c)(1)(v)). For example, an IND safety report would be identified in box A5 of FDA Form 3500A as an "IND Safety Report," and submission of follow-up information would be identified as a "Followup IND Safety Report." Currently, FDA is not able to accept electronic submission of these reports.

B. Where to submit

The report must be transmitted to the review division in CDER or CBER that has responsibility for review of the IND (21 CFR 312.32(c)(1)(v)). If there are INDs in different review divisions, the report should cross-reference all open INDs.

C. Reporting timeframe

The timeframe 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)). 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)).

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)). Any unexpected fatal or life-threatening suspected adverse reaction must be reported to FDA no later than 7 calendar days after the sponsor's initial receipt of the information (21 CFR 312.32(c)(2)). We recommend that sponsors notify FDA by telephone or facsimile transmission. Other means of rapid communication (e.g., email) may also be used, if prior to transmission, the sponsor contacts the Project Manager in the FDA review division that has responsibility for review of the IND and ascertains that other means of rapid transmission are acceptable.

VIII. FOLLOW-UP 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 to FDA as a *Followup IND Safety Report* without delay, as soon as the

information is available (21 CFR 312.32(d)(2)). 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 should submit a *Followup IND Safety Report* immediately. 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 final rule contains new 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 new 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. New 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, regardless of whether the event is considered drug-related, observed during conduct of the study, 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)). Serious adverse events observed in the investigational drug group and 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 to FDA as a *Followup Bioavailability/Bioequivalence Safety Report* as soon as the information is available (21 CFR 320.31(d)(3)). 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 (21 CFR 320.31(d)(3)).

If the adverse event is fatal or life-threatening, the person conducting the study must also notify the Office of Generic Drugs within CDER 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 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 bear prominent identification of its contents (21 CFR 320.31(d)(3)). For example, a report would be identified in box A5 of FDA Form 3500A as a *Bioavailability/Bioequivalence Safety Report* or a *Followup Bioavailability/Bioequivalence Safety Report*, as applicable. 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 established name of the reference listed drug should be listed and identified as investigational.

Because FDA is not currently able to accept email or electronic submission of these reports, send them in paper form to the Director, Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA.[8]

X. IMPLEMENTATION

The effective date for the final rule is March 28, 2011. Many of the requirements in the final rule are not new, but have been clarified to promote submission of meaningful safety information. Because many sponsors already have processes in place for ongoing surveillance of

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

accumulating safety information, FDA does not anticipate that implementation of these new requirements will require sponsors to make major changes to their current practices or ongoing clinical trials. However, sponsors should review their ongoing clinical trials and if a sponsor has any questions about whether changes are necessary to meet the new requirements (e.g., aggregating certain serious adverse events, not reporting study endpoints as IND safety reports), the sponsor should contact the FDA review division responsible for the IND.