Safety Assessment for IND Safety Reporting

Guidance for Industry

DRAFT GUIDANCE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)

December 2015
Drug Safety

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Safety Assessment for IND Safety Reporting Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document provides guidance to sponsors on developing a systematic approach for investigational new drug application (IND) safety reporting for human drugs and biological products[2] developed under an IND. See section II.A of this guidance for an overview of the IND safety reporting requirements. This guidance is a follow-on to the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies*[3] and provides recommendations for how sponsors of INDs can identify and evaluate important safety information that must be submitted to FDA and all participating investigators under the IND safety reporting regulations at § 312.32 (21 CFR 312.32). This guidance is most applicable to sponsors managing a drug development program that has multiple studies. This guidance contains recommendations on the following: (1) the composition and role of a safety assessment committee, (2) aggregate analyses for comparison of adverse event rates across treatment groups, (3) planned unblinding of safety data, (4) reporting thresholds for IND safety reporting, and (5) the development of a safety surveillance plan.

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

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in conjunction with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

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

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Web page. The guidances mentioned in this document are available on the Drugs guidance Web Page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm and the Biologics guidance Web page at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

II. BACKGROUND

The IND safety reporting requirements for human drugs and biological products being studied under an IND are stated in § 312.32, and the guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* describes and provides recommendations for complying with the requirements. During the evaluation of comments to the draft guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* (Docket No. FDA–2010–D–0482) and at meetings with stakeholders, FDA identified the need for additional guidance on IND safety reporting.

A. Overview of Safety Reporting Requirements

The regulation on IND safety reporting[4] describes, among other things, sponsors' responsibilities for reviewing information relevant to the safety of an investigational drug and responsibilities for notifying FDA and all participating investigators of potential serious risks in an IND safety report (§ 312.32). Among other things, the regulation requires sponsors to submit reports of serious and unexpected suspected adverse reactions (§ 312.32(c)(1)(i)). It identifies circumstances under which single and small numbers of serious and unexpected adverse events must be reported as serious and unexpected suspected adverse reactions (§ 312.32(c)(1)(i)(A) and (c)(1)(i)(B)) and illustrates the types of serious adverse events that are interpretable based on single or small numbers of events. Some examples include angioedema, hepatic injury, Stevens-Johnson Syndrome, tendon rupture, agranulocytosis, and acute liver failure. Most serious adverse events, however, will not be readily interpretable as single events. A suspected adverse reaction is defined as one in which there is a reasonable possibility that the drug caused the adverse event (§ 312.32(a)). Serious adverse events that are not likely to represent suspected adverse reactions or that are study endpoints should generally not be submitted to FDA as IND safety reports.

To meet the requirements of the IND safety reporting regulation, sponsors should periodically review accumulating safety data collected across multiple studies (completed and ongoing) and other sources, analyze the data in the aggregate, and make a judgment about the likelihood that the drug caused any serious adverse events. The following provisions of the IND safety reporting regulation for events that are not interpretable as single or small numbers of events are particularly dependent on a systematic approach to safety surveillance for IND safety reporting:

- Requirement to report in an IND safety report cases where an aggregate analysis of specific events observed in a clinical trial indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group (see § 312.32(c)(1)(i)(C))

[4] Food and Drug Administration, Final Rule, Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans (75 FR 59935, September 29, 2010).

- Requirement to report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or the investigator brochure (see § 312.32(c)(1)(iv))[5]

The guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies* recommends that sponsors have a systematic approach to safety surveillance to comply with the IND safety reporting requirements and to improve the overall quality of safety reporting. Such an approach should include a process for reviewing, evaluating, and managing accumulating data on serious adverse events from the entire clinical trial database. The process should include a method for comparing event rates across treatment groups, as needed, to detect serious and unexpected suspected adverse reactions and clinically important increased rates of previously recognized serious adverse reactions. An important component of such an approach is prospective identification of serious adverse events that the sponsor can foresee occurring with some frequency independent of drug exposure in the patient population, disease under study, or both (i.e., anticipated serious adverse events). For additional discussion, see section IV.A of this guidance.

Although not the focus of this guidance, sponsors should also have processes for evaluating and managing, and must report as soon as possible but no later than 15 calendar days after determining that the information qualifies for reporting, any findings from:

- Epidemiological studies, pooled analyses of multiple studies or clinical studies (other than those already reported under § 312.32(c)(1)(i)), whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug (§ 312.32(c)(1)(ii))

- Animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug (§ 312.32(c)(1)(iii))

Sponsors of clinical studies of a drug marketed or approved in the United States that are conducted under an IND must also submit safety information from clinical studies 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, see also § 312.32(c)(4)).

For vaccine trials, which typically enroll healthy subjects (each of whom receives a single dose or a small number of doses) the majority of serious adverse events are likely to meet the criteria for IND safety reporting under § 312.32(c)(1)(i)(B). Sponsors should discuss their approach to IND safety reporting for such trials with CBER.

Sponsors should conduct ongoing safety evaluations. The evaluations should include 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

[5] For the purposes of this guidance, we will refer to events reportable under this provision as previously recognized serious adverse reactions because they are included in the protocol or investigator the brochure (i.e., they are expected events).

information. In addition, if necessary, sponsors should take action, as required, to eliminate an unreasonable and significant risk to subjects (see § 312.56(d)).

B. Rationale for Developing Guidance

It is critical for sponsors to detect and report, as early as possible, serious and unexpected suspected adverse reactions and clinically important increased rates of previously recognized serious adverse reactions (see § 312.32(c)(1)(i) and (c)(1)(iv)). Early detection of such occurrences will enable sponsors to carry out their obligation to monitor the progress of the investigation (see § 312.56(a)) and, when necessary, to take steps to protect subjects (e.g., modifying dosing, selecting subjects, monitoring subjects) to allow an investigational drug to be safely developed despite potential risks. Early detection also allows sponsors to report meaningful safety information to FDA and all participating investigators in an IND safety report as soon as possible.

Timely reporting of meaningful safety information allows FDA to consider whether any changes in study conduct should be made beyond those initiated by the sponsor and allows investigators to make any needed changes to protect subjects. Simply reporting all serious adverse events, however, including those where there is little reason to consider them suspected adverse reactions (i.e., those with a reasonable possibility of having been caused by the drug), does not serve this purpose because it may obscure safety information that is relevant to the investigational drug. Sponsors' effective processes for a systematic approach to safety surveillance, coupled with IND safety reporting to FDA and all participating investigators (and subsequent reporting to involved institutional review boards), allows all parties to focus on important safety issues and to take actions to minimize the risks of clinical trial participation to human subjects.

For these reasons, this guidance provides recommendations intended to help sponsors meet their obligations under § 312.32. We recommend that sponsors develop a safety assessment committee and a safety surveillance plan as key elements of a systematic approach to safety surveillance. A safety assessment committee would be a group of individuals chosen by the sponsor to review safety information in a development program and tasked with making a recommendation to the sponsor regarding whether the safety information must be reported in an IND safety report (see section III of this guidance). A safety surveillance plan should describe processes and procedures for assessing serious adverse events and other important safety information (see section V of this guidance).

A Clinical Trials Transformation Initiative (CTTI)[6] project conducted in 2011 and 2012 found that sponsors' processes for reviewing serious adverse event data from ongoing trials often were limited by concerns about protecting trial integrity.[7] We understand that sponsors have typically

[6] Initiated in 2008, CTTI is a public-private partnership involving FDA, academia, industry representatives, patient and consumer representatives, professional societies, investigator groups, and other Government Agencies. CTTI's mission is to identify and promote practices that will increase the quality and efficiency of clinical trials.

[7] Archdeacon P, Grandinetti C, Vega JM, et. al., 2013, Optimizing Expedited Safety Reporting for Drugs and Biologics Subject to an Investigational New Drug Application, *Therapeutic Innovation and Regulatory Science*, doi:10.177/2168479013509382.

evaluated individual case study reports from ongoing trials in a blinded fashion or only unblinded the safety reviewer to the treatment assignment for particular individual cases. This type of evaluation allows assessment of adverse events interpretable as single events but not of adverse events that can be assessed only by considering aggregate data, usually across studies. Sponsors have shared with FDA their challenges in developing procedures for performing analyses of safety information from ongoing trials. In particular, sponsors identified the following two concerns: (1) as noted previously, the balance between the need to develop processes for evaluating unblinded data from ongoing trials (when necessary) and the need to preserve the scientific integrity of trial data and (2) the need to judge when aggregate data have met a threshold for IND safety reporting. Although we recognize these challenges, the need for a premarket safety system optimized to detect and evaluate important safety information as early as possible remains paramount. We believe that using a safety assessment committee and developing a safety surveillance plan will help sponsors resolve these concerns.

III. SAFETY ASSESSMENT ORGANIZATIONAL STRUCTURE

As noted previously, we recommend that sponsors use a safety assessment committee. For the purposes of this guidance, we will focus our recommendations on this group of individuals chosen by the sponsor to review safety information in a development program (i.e., across trials, INDs, and other sources) for IND safety reporting purposes. The extent of the sponsor's organizational structure necessary to support and carry out a prespecified safety surveillance plan (discussed in section V of this guidance) will vary by development program.

The recommendations apply to safety assessment committees managed by sponsors as well as safety assessment committees managed by contract research organizations.

A. Role of the Safety Assessment Committee

The safety assessment committee should oversee the evolving safety profile of the investigational drug by evaluating, at appropriate intervals, the cumulative serious adverse events from all of the trials in the development program, as well as other available important safety information (e.g., findings from epidemiological studies and from animal or in vitro testing) and performing unblinded comparisons of event rates in investigational and control groups, as needed, so the sponsor may meet its obligations under § 312.32(b) and (c). The safety assessment committee's primary role should be to review important safety information on a regular basis, with additional reviews as needed, and make a recommendation to the sponsor to help the sponsor determine whether an event or group of events meets the criteria for IND safety reporting. The safety assessment committee, possibly together with other parties (e.g., steering committees, data monitoring committees [DMCs]), can also participate in decisions about whether the conduct of the study should be revised (e.g., change in eligibility criteria, revision of informed consent). The roles and responsibilities of both the safety assessment committee and the individuals on the safety assessment committee should be clearly defined and distinguished from the roles of other groups.

205 *1. Information the Safety Assessment Committee Reviews*
206
207 The safety assessment committee should periodically review the accumulating serious adverse
208 events across all trials. The safety assessment committee should also review findings from any
209 clinical studies other than those reported under § 312.32(c)(1)(i), epidemiological studies, and
210 pooled analyses of multiple studies (§ 312.32(c)(1)(ii)). Similarly, the safety assessment
211 committee should review any findings from animal or in vitro testing that may suggest a
212 significant risk in humans exposed to the investigational drug (§ 312.32(c)(1)(iii)). The safety
213 assessment committee will need access to the totality of safety information in the development
214 program (i.e., completed and ongoing) because these data may contribute to the evaluation of
215 serious adverse events.
216
217 *2. Recommendations the Safety Assessment Committee Makes*
218
219 The sponsor must decide, considering recommendations from the safety assessment committee
220 or another group (when applicable), whether single and small numbers of events meet the IND
221 safety reporting criteria under § 312.32(c)(1)(i)(A) and (c)(1)(i)(B). For single and small
222 numbers of events, the sponsor may prefer to refer questions regarding whether the IND safety
223 reporting criteria have been met to a group other than the safety assessment committee. The
224 safety assessment committee should analyze aggregate data, as appropriate, if serious adverse
225 events not anticipated and prespecified in the safety surveillance plan are observed (see section V
226 of this guidance for a discussion of a safety surveillance plan). The safety assessment committee
227 should then make a recommendation to the sponsor regarding whether any numerical imbalance
228 in the unblinded rates meets the criteria for IND safety reporting (see section IV.D of this
229 guidance for a discussion of reporting thresholds).
230
231 For serious adverse events that are prespecified in the safety surveillance plan as anticipated or
232 previously recognized serious adverse reactions listed in the protocol or the investigator
233 brochure, the safety assessment committee should analyze the data in the aggregate and make a
234 recommendation to the sponsor regarding whether the events meet the IND safety reporting
235 criteria under § 312.32(c)(1)(i)(C) and (c)(1)(iv). See section IV.B of this guidance for
236 recommendations for performing aggregate analyses. The safety assessment committee should
237 also make a recommendation to the sponsor regarding whether findings from clinical studies
238 other than those reported under § 312.32(c)(1)(i), epidemiological studies, pooled analyses of
239 multiple studies, or animal or in vitro testing, suggest a significant risk in humans exposed to the
240 investigational drug and require IND safety reporting under § 312.32(c)(1)(ii) and (c)(1)(iii).
241
242 *3. Frequency of Safety Assessment Committee Meetings*
243
244 The sponsor must deal promptly, considering recommendations from the safety assessment
245 committee or another group (when applicable), with serious and unexpected suspected adverse
246 reactions that are interpretable as single events or small numbers of events so the sponsor can
247 fulfill its duty to report these potential serious risks as soon as possible but no later than 15
248 calendar days after determining that the information qualifies for IND safety reporting
249 (§ 312.32(c)(1)(i)(A) and (c)(1)(i)(B)). The frequency of routine safety assessment committee
250 meetings to evaluate serious adverse events that require aggregate analysis will likely depend on

several factors, including experience with the investigational drug, the disease being studied, the subject population, and the enrollment and data acquisition rates. For example, more frequent meetings to review accumulating safety data may be important early in development, when a safety concern arises, or when there is a high enrollment rate. Less frequent meetings to review accumulating safety data will usually be appropriate for studies of an approved product with a well-established safety profile. Sponsors should establish a process for ad hoc meetings to review important safety information in a timely manner.

4. Differences Between a Safety Assessment Committee and a DMC

The safety assessment committee described in this guidance is distinct from a DMC and has different roles and operational practices (see FDA's guidance for clinical trial sponsors *Establishment and Operation of Clinical Trial Data Monitoring Committees*). A sponsor may choose to use the DMC's expertise and reports generated for the DMC's use or created by the DMC to facilitate the operations of the safety assessment committee. However, we recommend that the sponsor implement a process in advance to limit the unblinded data to those data that are necessary to evaluate the event (e.g., the reports are modified to exclude efficacy data and controls are in place to prevent unintentional unblinding of sponsors' staff).

It is recognized that, in most cases, an existing DMC, without modification, will not be able to function as a safety assessment committee because a DMC may meet too infrequently and is usually focused on a single trial, rather than on the entire safety database. The DMCs also recommend to the sponsor when to modify or stop the study because the investigational drug is not effective or clearly demonstrates an adverse effect on an important safety endpoint. In contrast, the role of the safety assessment committee would be to review accumulating safety data to determine when to recommend that the sponsor submit an IND safety report to FDA and all participating investigators. The threshold DMCs traditionally used for reporting safety concerns to the sponsor is generally higher than the threshold for reporting potential serious risks obtained from aggregate data in an IND safety report.

B. Composition of Safety Assessment Committees

Safety assessment committees are expected to be of variable size and structure, depending on the characteristics of the investigational drug, the subject population, the characteristics of the clinical trial, and the size of the development program. FDA recognizes that a variety of safety assessment committee compositions and organizational structures could provide the ongoing safety assessments described in this guidance. Recommendations and considerations for the composition of a safety assessment committee are discussed in this section.

1. Disciplines

A safety assessment committee should be multidisciplinary. It should include at least one physician who is familiar with the therapeutic area for which the investigational drug is being developed as well as clinicians who have general or specific (e.g., cardiology, hepatology, neurology) safety experience. Other disciplines should be considered on a regular or an ad hoc basis (e.g., epidemiology, clinical pharmacology, toxicology, chemistry, biostatistics).

Identification of new safety information may warrant additional expertise within the safety assessment committee (e.g., ocular toxicity, renal toxicity). For studies of a marketed drug, an individual involved in evaluating the postmarket safety of the drug should be included. In general, the safety assessment committee should not include individuals directly responsible for the conduct or analysis of the trials in the development program.

Members of the safety assessment committee should have knowledge about the investigational drug, the epidemiology of the disease, and the characteristics of the subject population (e.g., natural history of the disease being treated, background rates of anticipated serious adverse events, placebo experience). Members of the safety assessment committee should be qualified by training and experience to participate in making safety assessments and should be available to review safety information on a regular or ad hoc basis.

2. Affiliation

A safety assessment committee could be a group within the sponsor's organization, a specific independent committee with both sponsor representation and substantial external representation, or an external group that may be used to evaluate many different investigational drugs for multiple sponsors. The sponsor should consider the need for specific external expertise or external perspectives on the safety assessment committee. Note that, regardless of the makeup of the safety assessment committee, the sponsor holds the responsibility for IND safety reporting described in § 312.32 as well as other responsibilities described elsewhere in FDA regulations (see, e.g., § 312.50).

IV. SAFETY ASSESSMENT PRACTICES

A. Anticipated Serious Adverse Events

An important component of a systematic approach to safety surveillance is prospective identification of anticipated serious adverse events. For the purposes of IND safety reporting, anticipated serious adverse events are serious adverse events that the sponsor can foresee occurring with some frequency, independent of investigational drug exposure, in the general patient population under study, in patients with the disease under study, or both. Examples of anticipated serious adverse events include the following:

- Known consequences of the underlying disease or condition under investigation (e.g., nonacute death observed in a trial in cancer patients, pneumonia in patients with chronic obstructive lung disease, diabetic ketoacidosis in a trial of diabetes management)

- Events common in the study population that are unlikely to be related to the underlying disease or condition under investigation (e.g., cardiovascular events in an elderly population, hip fracture in an elderly population, volume overload or pulmonary edema in a dialysis population)

- Events known to occur with drugs administered as part of a background regimen (e.g., neutropenia with a myelosuppressive chemotherapeutic agent, intracerebral hemorrhage with an anticoagulant, cytomegalovirus colitis with an immunosuppressive regimen)

In addition to anticipated serious adverse events that can be identified for the entire study population, some serious adverse events may be anticipated in a subset of the study population (e.g., predefined elderly population, subjects from a specific geographic region). For example, in a trial with a population of subjects between the ages of 18 and 75 years, a sponsor may identify stroke in subjects over the age of 65 years as an anticipated serious adverse event that will not be reported as an individual event. A stroke occurring in a subject that is not included in the identified subset (e.g., a 30-year-old subject), in contrast, would be reported as an individual case if the sponsor determined the event was a serious and unexpected suspected adverse reaction under § 312.32(c)(1)(i).

Anticipated serious adverse events that are consequences of the underlying disease or are events common in the study population meet the definition of *unexpected adverse event* under § 312.32(a) because they are not listed in the investigator brochure or elsewhere as specified by § 312.32(a). However, these events do not warrant IND safety reporting as individual cases because it is not possible, based on a single case, to conclude that there is a reasonable possibility that the investigational drug caused the event. As a result, these events do not meet the definition of a *suspected adverse reaction*. They would be reportable under § 312.32(c)(1)(i)(C), however, if an aggregate analysis indicated that the events were occurring more frequently in the drug treatment group than in a control group (see section IV.D of this guidance for a discussion of reporting thresholds).

At the time of protocol development, the sponsor should identify, in the safety surveillance plan, the anticipated serious adverse events that it does not plan to report individually in an IND safety report under § 312.32(c)(1), together with a plan for monitoring the events (see section V of this guidance for a discussion of a safety surveillance plan).

Examples of factors to consider when deciding which serious adverse events to identify as anticipated events include the following: (1) characteristics of the study population, (2) natural progression of the disease, (3) background event rates, (4) background drug regimens, (5) comorbid conditions, and (6) past experience with similar populations. The sponsor should limit the identified anticipated serious adverse events to those events for which individual occurrences are uninterpretable and an overall analysis is needed. The safety assessment committee should monitor the identified anticipated events at appropriate intervals during development of the investigational drug and make a recommendation to the sponsor regarding submitting an IND safety report if an aggregate analysis indicates the events are occurring more frequently in the drug treatment group than in the control group (§ 312.32(c)(1)(i)(C)).

B. Aggregate Analyses of Safety Data

Section 312.32(c)(1)(i)(C) requires reporting of a serious and unexpected suspected adverse reaction in an IND safety report if there is evidence to suggest a causal relationship between the drug and the adverse event, including 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 or historical control group. In addition, § 312.32(c)(1)(iv) requires reporting in an IND safety report of a clinically important increase in the rate of a previously recognized serious adverse reaction. The aggregate analysis should generally be performed across multiple studies under the IND and, as appropriate, across other INDs held by the same sponsor to determine whether the criteria for IND safety reporting have been met. Furthermore, evaluation of individual studies will help the sponsor look for consistency and possible differences related to the characteristics of subjects and for deciding whether there is, in fact, an increased rate of such events.

As discussed in section IV.A of this guidance, sponsors should not submit IND safety reports for those serious adverse events that were prospectively identified as anticipated to occur in the study population unless the evidence suggests a causal relationship between the drug and the event (see § 312.32(c)(1)(i)(C))— which is a matter of judgment. Although a basis for individual IND safety reports (e.g., Stevens-Johnson Syndrome, agranulocytosis) can sometimes arise early in clinical development, the types of safety information that are based on aggregate data become more informative as development progresses and the database size increases.

Determining when the aggregate safety data provide evidence to suggest a causal relationship between the drug and a serious and unexpected adverse event or show that there has been a clinically important increase in the rate of a previously recognized serious adverse reaction over the rate listed in the protocol or the investigator brochure is a complex judgment that is, in most cases, not a simple application of a planned statistical analysis.

1. Performing Aggregate Analyses of Safety Data

Unlike efficacy determinations, for which a hypothesis is tested with prespecified endpoints and planned analyses, safety determinations almost invariably involve multiple endpoints of potential interest, except when there is an existing safety concern based, for example, on related drugs, preclinical findings, or previous clinical trials.

In 2011, CTTI conducted a survey on safety reporting practices. The results indicated that the majority of sponsor safety teams surveyed compared overall adverse event rates in the entire study population of ongoing trials to historical comparators, presumably reporting adverse events that occur at a rate greater than in the historical norm in the overall population. When performing aggregate analyses, sponsors rely on previous experience and external controls (e.g., historical data, existing registries, class labeling) to establish comparators for the observed adverse event rates.

Some sponsors reported use of specific tools to perform such aggregate analyses (e.g., fractional reporting ratios, standardized incidence ratios, network meta analyses, data visualization tools, Multi-Item Gamma Poisson Shrinker, disproportionality analyses), yet other sponsors rely on descriptive statistics in making comparisons between incidence rates predicted from external populations and those in the trial. The majority of sponsors reported not reviewing unblinded data for imbalances in event rates across treatment groups for ongoing blinded studies.

We recommend unblinding to allow a comparison of event rates and detection of numerical imbalances across treatment groups to identify important safety information. The safety assessment committee should regularly perform unblinded comparisons of rates across treatment groups for serious adverse events that are prespecified in the premarket safety surveillance plan as anticipated serious adverse events or as previously recognized serious adverse reactions listed in the protocol or the investigator brochure, as long as appropriate steps to maintain the overall study blinding are taken (see section IV.C of this guidance for unblinding considerations). Such an approach could identify important safety information more rapidly.

An alternative approach used by some sponsors, as noted previously, is to perform the unblinded comparison of event rates across treatment groups (for serious adverse events that are prespecified in the safety surveillance plan as anticipated serious adverse events or as previously recognized serious adverse reactions listed in the protocol or the investigator brochure) when the overall rate for all treatment groups of a specific serious adverse event is substantially higher than a predicted rate. Given the uncertainty of the predicted rate in any given population, however, and the substantial challenges of specifying a predicted rate for all events, the preferred approach is to regularly perform unblinded comparisons.

To follow the alternative approach, sponsors should prespecify, in the safety surveillance plan, the predicted rates of anticipated serious adverse events and previously recognized serious adverse reactions listed in the protocol or the investigator brochure and provide guidelines for determining that an observed rate exceeds the predicted rate and informs a determination that the event is causally related (see section IV.D of this guidance). Sponsors should use all available data, including placebo databases, class information, historical data, literature, external epidemiological databases,[8] and disease-specific registries, to estimate predicted rates of anticipated serious adverse events. The predicted rates of the serious adverse reactions previously recognized as caused by the investigational drug should be based on prior experience with the investigational drug.

The majority of the serious adverse events that are not interpretable as individual or small numbers of events will generally be serious adverse events that are anticipated or are previously recognized serious adverse reactions. However, unexpected serious adverse events not specified in the safety surveillance plan, but not interpretable as single events, are likely to be observed and will require evaluation to determine whether the events must be reported as serious and unexpected suspected adverse reactions under § 312.32(c)(1). In some cases, failure to have identified the events as anticipated may have been in error. In addition to aggregate analyses of anticipated serious adverse events and previously recognized serious adverse reactions, the safety assessment committee should therefore perform aggregate analyses (as appropriate) of any such observed unexpected serious adverse events unless they already qualify for reporting under § 312.32(c)(1)(i)(A) and (c)(1)(i)(B). Unblinding of these events to allow a comparison of event rates across treatment groups may be necessary to determine whether the events qualify for IND safety reporting under § 312.32(c)(1)(i)(C).

[8] For example, see the Centers for Disease Control and Prevention's National Center for Health Statistics. The National Cancer Institute's Surveillance, Epidemiology, and End Results Program provides information on cancer statistics.

The principal aggregate analyses should be pooled analyses[9] of serious adverse events from completed and ongoing trials, but examination of individual studies will often be of interest to determine whether or not there is consistency of findings across studies and differences related to the characteristics of subjects. The most pertinent data for aggregate analyses will be from controlled trials, generally including both placebo and active control trials (presuming that the active control does not cause the adverse event of interest). The frequency of periodic aggregate analyses should be prospectively determined and depend on several factors, including the following: (1) experience with the investigational drug, (2) the disease being studied, (3) the subject population, and (4) enrollment and data acquisition rates.

2. Importance of Standardized Coding

Accurate and standardized coding of serious adverse events allows events to be analyzed and maximizes the likelihood that important safety information will be detected. As part of the sponsor's responsibility to promptly review all obtained information relevant to the safety of the drug (§ 312.32(b)), sponsors should review serious adverse events submitted by the investigator and verify the accuracy and severity of the event. Sponsors should document any changes they make to the terms used by investigators. FDA recommends that sponsors ensure that each investigator's verbatim terms for serious adverse events are coded to standardized, preferred terms that are specified in a coding convention or dictionary to allow appropriate grouping of similar events that were reported using different verbatim language. See FDA's premarketing risk assessment guidance for additional discussion of coding.

C. Unblinding Safety Data

IND safety reports submitted to FDA and all participating investigators should be unblinded. Two distinct cases should be considered.

First, as implicitly acknowledged by the IND safety reporting regulations, some serious and unexpected adverse events are interpretable as single or small numbers of adverse events (§ 312.32(c)(1)(i)(A) and (c)(1)(i)(B)). For these events, 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 an investigational drug that could have implications for the ongoing conduct of the trial (e.g., monitoring, informed consent). It is also critical for IND safety reporting purposes to know whether a serious and unexpected adverse event (e.g., agranulocytosis, Stevens-Johnson Syndrome) occurred in a drug- or placebo-treated subject.

FDA does not believe that unblinding single or small numbers of serious and unexpected suspected adverse event cases will compromise the integrity of the study, in part because unblinding outside of the safety assessment committee should be infrequent based on the specific

[9] Data pooling is the integration of patient-level data from several clinical studies to assess important safety information. Generally, data pooling is performed to achieve larger data sets because individual clinical studies are not designed with sufficient sample size to estimate the frequency of low incidence events or to compare differences in rates or relative rates between the test drug and the control. See FDA's guidance for industry *Premarketing Risk Assessment* (premarketing risk assessment guidance) for additional discussion on data pooling.

criteria that must be met to submit the serious and unexpected suspected adverse reactions in an IND safety report. In addition, unblinding these single and small numbers of serious and unexpected adverse events should not compromise the integrity of the study because the subjects that experience such events will often be withdrawn from the study at the time of the event, and most of their data will have been collected with complete blinding.

The second case is where the adverse event is interpretable only by examining rates of events in treated and control groups to determine whether a specific serious adverse event is occurring more frequently in the drug treatment group (§ 312.32(c)(1)(i)(C)) or whether there is a clinically important increase in the rate of a specific previously recognized serious adverse reaction (§ 312.32(c)(1)(iv)). For these events that are not interpretable as individual cases, with appropriate controls to limit unblinding, there should be minimal concerns with the integrity of the study because only the data required to evaluate the serious adverse event would need to be unblinded. There is, moreover, a long history of accessing trial databases to prepare materials for the DMCs to monitor study endpoints (the events of greatest concern with respect to unblinding) in clinical trials; analogous processes to prepare materials for review by the safety assessment committee should pose no risk to the integrity of the study.

We recognize that, because of concerns that the perception of the integrity of trials may be adversely affected, there may be variability in how sponsors unblind safety data for the safety assessment committee. Sponsors should have appropriate procedural controls and processes for unblinding safety data for evaluation for IND safety reporting purposes described in the safety surveillance plan (see section V of this guidance). Such controls should include a mechanism for restricting the number of individuals who have access to unblinded data (i.e., the safety assessment committee) as well as a plan to unblind only those data that are necessary to evaluate the event (i.e., treatment assignment of the subjects who experienced the serious adverse event under review, clinical data that may correlate with the event [e.g., serum creatinine for the serious adverse event of acute kidney injury]). Study endpoints, efficacy data, and other data collected for the study that do not pertain to the adverse event should not be unblinded. In addition, unblinding should be limited to serious adverse events that would be reportable as IND safety reports, i.e., those under § 312.32(c)(1)(i) (i.e., serious and unexpected suspected adverse reactions) and § 312.32(c)(1)(iv) (i.e., clinically important increased rate of occurrence of previously recognized serious adverse reactions) if the IND safety reporting criteria are met. Furthermore, sponsors should have procedures for any needed emergency unblinding by the sponsor or its representative and procedures for any accidental unblinding.

FDA recommends that those participating in the conduct or analysis of the study (e.g., study clinicians, statisticians, chief medical officers, clinical research associates) remain blinded to overall data, although in individual serious adverse event cases, appropriate medical care may require unblinding.

Provisions of § 312.32 that already minimize the impact of unblinding on trial integrity include requirements to report only a subset of serious adverse events (§ 312.32(c)(1)(i) and (c)(1)(iv)) and given that study endpoints are generally not reported as IND safety reports (§ 312.32(c)(5)). In addition, compliance with the sponsor's plan for monitoring anticipated serious adverse events is an important part of minimizing the impact of unblinding on trial integrity.

If a sponsor has concerns about unblinding serious adverse events for a specific study, the sponsor may propose an alternative reporting format to maintain the blind. If the sponsor proposes and follows a different reporting format than that required in § 312.32(c), it must be agreed to in advance by the director of the review division in FDA with responsibility for review of the IND (§ 312.32(c)(3)).

To address a sponsor's concerns with unblinding large numbers of subjects to investigators when submitting aggregate reports, FDA considers it acceptable to send all participating investigators the narrative portion of the IND safety report based on data in the aggregate, without sending a completed Form FDA 3500A for each case.

D. Reporting Thresholds for IND Safety Reporting

As noted previously, 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 (§ 312.32(a)). This determination must be made before a serious and unexpected adverse event is reported as a serious and unexpected suspected adverse reaction under § 312.32(c)(1)(i). The decision about the nature of the evidence requires clinical judgment, particularly for cases in which:

- Aggregate analyses of specific events observed in a clinical trial indicate that those events occur more frequently in the drug treatment group (§ 312.32(c)(1)(i)(C))

- An increase in the rate of a serious suspected adverse reaction over that listed in the protocol or the investigator brochure that is determined to be clinically important is observed (§ 312.32(c)(1)(iv))

Factors to consider when making the judgment include the following:

- The size of the difference in frequency between the test and control groups

- Consistent increase in multiple trials

- Preclinical evidence to support the finding

- Evidence of a dose response

- Plausible mechanism of action

- Known class effect

- Occurrence of other related adverse events (e.g., both strokes and transient ischemic attacks)

Because we recommend that the safety assessment committee review safety information on a regular basis so that the sponsor may meet its obligations under § 312.32(b) and (c), we expect

that the safety assessment committee's view that certain adverse events do not trigger the requirement that the sponsor report the events as serious and unexpected suspected adverse reactions (§ 312.32(c)(1)(i)) or as a clinically important increase in the rate of a previously recognized serious adverse reaction (§ 312.32(c)(1)(iv)), based on aggregate analyses, may change over time as data accumulate. At each meeting, the safety assessment committee should re-evaluate updated rates of unblinded events that the safety assessment committee recommended to the sponsor as not requiring reporting under § 312.32 to determine whether any new information suggests that an event warrants IND safety reporting.

Generally, study endpoints refer to outcomes that sponsors are measuring to evaluate efficacy. Sponsors must report study endpoints to FDA according to the protocol and ordinarily would not report study endpoints as IND safety reports, except where the event is a serious and unexpected adverse event and there is evidence suggesting a causal relationship between the drug and the event (§ 312.32(c)(5)). For example, a death ordinarily would not be reported as an individual case in an IND safety report from a trial designed to compare all-cause mortality in subjects receiving either drug treatment or a placebo. On the other hand, in such a trial, 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, in these cases, the evidence would suggest a causal relationship between the drug and the event (§ 312.32(c)(5)). A DMC, rather than a safety assessment committee, should be used (when necessary) to collect, track, and monitor endpoint information.[10]

E. Follow-Up Information (§ 312.32(d))

FDA's guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE studies* describes the content of an IND safety report based on an individual case, aggregate data, and other sources (i.e., findings from other studies, findings from animal or in vitro testing) and also describes information that warrants a follow-up IND safety report under § 312.32(d).

Relevant follow-up information to an IND safety report must be submitted as soon as the information is available (§ 312.32(d)(2)). To assist sponsors with determining whether follow-up information is relevant to an IND safety report, in this section, FDA provides additional guidance on the types of information that generally would require a follow-up IND safety report.

For an individual case that was submitted as an IND safety report under § 312.32(c)(1)(i)(A) and (c)(1)(i)(B), examples of the types of information that trigger the follow-up IND safety reporting requirements include the following: (1) a change in diagnosis of the adverse event, (2) death as a result of the adverse event, (3) autopsy findings, and (4) other new information that significantly impacts the assessment of causality. For aggregate data that were submitted as an IND safety report under § 312.32(c)(1)(i)(C), examples of the type of information that trigger follow-up IND safety reporting requirements include the following: (1) additional occurrences of the adverse event that, in the aggregate, suggest a significant change in the rate of occurrence from the initial aggregate report and (2) information about individual events that comprise the aggregate report

[10] See section V.A.3.a of FDA's guidance for industry and investigators *Safety Reporting Requirements for INDs and BA/BE Studies*.

that significantly impact the assessment of causality. The following information generally would not trigger the requirement for a follow-up IND safety report: (1) noninvestigational treatment changes, (2) nonresolving adverse event updates, and (3) additional medical or treatment history that is not relevant to the assessment of causality.

V. PROSPECTIVE PLANNING: DEVELOPING SAFETY SURVEILLANCE PLANS

Prospective development of a plan for assessing serious adverse events and other important safety information is a critical component of a premarket safety system for IND safety reporting. Sponsors should develop a safety surveillance plan that describes processes and procedures for assessing serious adverse events and other important safety information.

Matters to consider in the development of a safety surveillance plan for IND safety reporting include:

- Determining needed expertise for the safety assessment committee (e.g., cardiologists, hepatologists, clinical pharmacologists)
- Planning for the safety assessment committee's review of serious adverse events and other important safety information (e.g., nonclinical, epidemiologic, observational data) as needed
- Ensuring that all serious adverse events from all ongoing studies and other important safety information are provided to the safety assessment committee for routine reviews and for timely ad hoc reviews as needed
- Unblinding practices

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

- Clearly defined roles and responsibilities of the safety assessment committee and participating individuals as well as any parties that have responsibility for reporting safety information to the safety assessment committee or conducting any analyses of the data
- List of serious adverse events that the sponsor does not plan to report individually in an expedited manner because the events are anticipated to occur in the study population or in a subset of the study population
- List of previously recognized serious adverse reactions (or a reference to these expected events in the protocol or the investigator brochure) that the sponsor is monitoring for a clinically important increase in the rate over that listed in the protocol or the investigator brochure

- A process for routine and timely review of serious adverse events and other important safety information by the safety assessment committee, including the frequency of routine reviews and the process for ad hoc reviews

- Guiding principles for periodic aggregate safety reviews, specifically describing when the safety assessment committee will perform unblinded comparisons of event rates across treatment groups

- Any predefined reporting thresholds and the process for evaluating whether a group of events qualify for IND safety reporting

- Predicted rates of anticipated serious adverse events and previously recognized serious adverse reactions (i.e., expected events) if unblinding of the safety assessment committee is triggered by a comparison of overall observed serious adverse event rates to predicted rates

The safety surveillance plan should be maintained by the sponsor and, if created, must be available for FDA inspection as required under § 312.58(a). Before initiating phase 2 or 3 studies, we recommend that the sponsor submit a portion of the safety surveillance plan to the IND. Specifically, the sponsor should submit the list of anticipated serious adverse events and previously recognized serious adverse reactions and guiding principles for periodic aggregate safety reviews.

We recommend that sponsors include in the protocol a summary of and reference to their safety surveillance plan. The protocol should include any study-specific differences from the safety surveillance plan, including any study-specific plans for monitoring specific anticipated serious adverse events in the aggregate.