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Client Alert

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FDA Issues New Draft Guidance for Sponsors on Safety Event Analysis and Reporting for IND and Bioavailability/Bioequivalence Studies

Focuses on Aggregate Safety Data Analysis and Expedited Reports; Expectation for Prospective Safety Surveillance Plan

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The Food and Drug Administration (FDA) has issued a new draft guidance[1] (the Draft Guidance) that provides updated recommendations for Sponsors and Sponsor-Investigators to comply with the safety assessment and reporting requirements for clinical investigations of drugs and biological products conducted under Investigational New Drug (IND) applications, as well as bioavailability (BA) and bioequivalence (BE) studies. This Draft Guidance merges some content from a 2012 final guidance[2] on safety reporting (which FDA intends to withdraw when this new guidance is finalized), and some content from a 2015 draft guidance on IND safety event assessment (which was withdrawn upon publication of this new draft guidance).[3] It does not include any updated recommendations for investigators. FDA intends to issue separate draft guidance with revised recommendations for investigators about safety reporting. Comments on the Draft Guidance should be submitted by **September 24, 2021**.[4]

The Draft Guidance provides an extensive overview of sponsors' safety reporting requirements. However, in addition to general IND safety reporting requirements, a major focus is updated recommendations regarding the analysis of aggregate safety data to determine if expedited safety reporting is required. FDA presents its current concerns and provides new recommendations regarding:

- planned unblinding of safety data and maintaining trial integrity;

- the person who reviews safety data for reporting purposes during an ongoing clinical investigation;
- the scope and methodology for aggregate safety data analysis; and
- the sponsor's plan for safety surveillance, including elements that should be included.

BACKGROUND

On September 29, 2010, FDA issued a final rule that amended the IND safety reporting requirements in 21 CFR Part 312. It also separately amended 21 CFR Part 320 to add safety reporting requirements for parties conducting BA and BE studies that are exempt from the IND requirements. The 2010 IND rule made major changes in safety event definitions and reporting requirements applicable to expedited reporting. Prior to the amendment, sponsors were required to conduct expedited reporting of any adverse event (also referred to as adverse experience) associated with the use of a drug that was both serious and unexpected. FDA amended the regulatory provisions because the Agency was concerned that a lack of clarity between when individual safety events should be reported, versus when reports should be based on aggregate analysis, resulted in overreporting of uninformative individual adverse events and underreporting of aggregate adverse events. The 2010 rule also revised the safety reporting requirements to clarify when expedited reporting should be used to submit adverse events.

Under 21 CFR 312.32(c), as it currently exists, a sponsor must provide expedited reporting to FDA and to all participating investigators of any "suspected adverse reaction that is both serious and unexpected" (a serious and unexpected suspected adverse reaction (SUSAR)). The regulation clarifies the separate definitions of serious and unexpected; in addition, it requires that classification of an adverse event as a suspected adverse reaction be supported by evidence to "suggest a causal relationship" between the adverse event and the drug. The regulation also requires expedited reports related to certain serious suspected adverse reactions.

- **Single adverse events.** The regulation identifies two specific categories of adverse events in which there could be evidence to suggest a causal relationship between a single adverse event or a small number of events and the investigational drug (21 CFR 312.32(c)(1)(i)(A) and (B)).
- **Aggregate adverse events**. It also specifies two categories of adverse events in which an aggregate analysis of adverse events, including comparison of the incidence of the event in the drug treatment group versus a concomitant or historical control group, would be needed to suggest a causal relationship of the drug.

  (1) Aggregate analysis is needed when an event is a known consequence of the underlying disease or condition under investigation or the event occurs commonly in the study population independent of drug therapy (21 CFR 312.32(c)(1)(i)(C)).

  (2) In addition, aggregate data analysis may be needed to determine if there is a clinically important increase in the rate of serious suspected adverse reactions over the rate listed in the protocol or investigator's brochure (21 CFR 312.32(c)(1)(iv)).

In the 2021 Draft Guidance, FDA explains its appreciation that the assessment of a possible causal relationship between a drug and an adverse event – an adverse reaction or suspected adverse reaction – is very challenging for sponsors. The issuance of this Draft Guidance suggests that FDA perceives continued uncertainty and confusion among sponsors regarding when and how aggregate analysis of adverse events should be conducted during an ongoing clinical investigation to make this determination. It also suggests current concern by the Agency that unblinding an ongoing randomized controlled clinical trial for safety reporting purposes has the potential to bias the conduct of the trial and raise issues of data integrity unless safeguards are in place.

The Draft Guidance does not provide substantive new recommendations regarding the requirements in 21 CFR Part 320 that require reporting of SAEs as a condition whereby certain BA and BE studies are exempt from the IND safety reporting requirements (21 CFR 320.31(d)).

EXPEDITED IND SAFETY REPORTING: KEY RECOMMENDATIONS IN THE DRAFT GUIDANCE

- **Identification of a suspected adverse reaction: the responsibility of only the sponsor.** FDA recognizes that the process for identification of a SUSAR usually begins with a three-step decision tree of first identifying whether an adverse event is *serious*. If the event is identified as *serious* by either the investigator or sponsor, the next step is identifying whether it is *unexpected* because it is not listed in the investigator's brochure or not listed at the specificity or severity observed in the study population. If an adverse event is both serious and unexpected, the third step is making a determination of whether the event is a "suspected adverse reaction" based on a judgment of definite causality (*adverse reaction*) or a reasonable possibility of a causal relationship between the drug and the event *(suspected adverse reaction*). FDA cautions that the ICH E2A guidance[5] (which is incorporated as guidance by FDA and adopted by many IND sponsors as company policy) allows the causality judgment to be based on either the investigator's or sponsor's opinion. In the Draft Guidance, FDA emphasizes that, although the IND sponsor should consider the investigator's assessment of causality, the regulations at 21 CFR Part 312 impute the sponsor with responsibility for making the final causality judgment for reporting purposes.
- **Planned unblinding of the safety data and implications for trial integrity.** If an adverse event is a well-known consequence of the study population's underlying condition or otherwise occurs commonly in the study population, unblinding may be necessary to conduct an aggregate analysis of all instances of the event and compare the rates of the event in the treatment group versus the control group. Unblinding may also be needed to determine if there is an excess of a serious suspected adverse reaction in comparison with the rate cited in the investigator's brochure. To protect the integrity of an ongoing trial related to unblinding of safety data, FDA advises three specific, overarching steps. First, internal personnel conducting unblinded safety reviews should not participate in the conduct of the trial or in other analyses of the trial or trials. Second, and more generally, sponsors should ensure that procedural controls and processes are prospectively specified in the safety surveillance plan to prevent sponsor personnel involved in the conduct of the trial or other analyses from being unblinded to the treatment assignment of individual subjects. FDA notes its longstanding opinion that a serious suspected adverse reaction in an individual subject should be unblinded by the site investigator if "knowledge of the treatment received is assessed as necessary for the medical management of the subject." Third, to avoid unblinding large numbers of subjects' treatment assignments to investigators, FDA recommends that sponsors comply with the requirement for expedited reporting by providing the narrative portion of the IND safety report to all participating investigators rather than providing a completed Form FDA 3500A for each individual event to all investigators.
- **The party reviewing aggregate safety data for IND safety reporting purposes.** Although FDA stresses flexibility for sponsors in identifying the party(ies) that will review accumulating safety data and conduct aggregate analyses of potentially unblinded data, the Draft Guidance essentially identifies three approaches. The first approach would rely on an independent Data Monitoring Committee (DMC) to conduct periodic aggregate analyses of serious adverse events to determine if reporting criteria have been met. An advantage of the use of a DMC for this purpose is that a DMC usually operates under a charter with strict controls for maintaining data integrity if it analyzes unblinded data. If a DMC is assigned this role, it should be specified in the charter. An alternative is the identification of a team within the sponsor's organization or an external entity for this purpose. FDA emphasizes that any internal or external personnel charged with conducting aggregate safety data analyses during the trial for which unblinding of data may be necessary, should be completely "firewalled" from personnel responsible for conducting the trial or conducting other analyses of the trial. The third option is a triage approach where individuals who are firewalled from personnel

conducting the trial conduct blinded analyses of aggregate events in the treatment and control groups and, if there is a trigger of a prespecified imbalance between the groups, this team would triage the events to a separate firewalled entity responsible for determining if the threshold for IND reporting is met (which may include unblinding). A variation on this model is that a single firewalled individual would conduct an unblinded analysis to determine if an imbalance in event rates is present and then triage the events to a separate firewalled entity to determine if the threshold for expedited reporting is met.

- **The scope and methodology of aggregate safety data analyses.** The Draft Guidance emphasizes that determining if there is a possible causal relationship between the drug and a serious adverse event is "almost never a simple application of a planned statistical analysis." To make the judgment that the threshold of reasonable possibility of causality has been met, FDA advises consideration of nine factors but does not recommend that all or the majority of these factors must be met for a reasonable possibility of causality to be found:

    1. Magnitude of the increase in incidence of the adverse event in the investigational drug group compared to the control group; notably, FDA does not advise that nominal statistical significance be met
    2. Evidence of a dose response
    3. Consistency of the increase in incidence in other clinical trials investigating the drug
    4. Presence of a plausible mechanism of action
    5. Nonclinical evidence; for example, evidence from toxicology or pharmacology animal studies, genetic animal models, or human genetic data
    6. Pharmacology of the drug and known class effects
    7. Occurrence of the event in individual subjects likely to be more susceptible to experience the adverse event; for example, subjects with an underlying condition or concomitant use of a background drug that could increase susceptibility
    8. Occurrence of other adverse events that are potentially clinically related; for example, strokes and transient ischemic attacks

For determining if there is an increased rate of occurrence of serious suspected adverse reactions, FDA recommends aggregate analysis of the incidence in comparison with the rate provided in the investigator's brochure or elsewhere in the current IND application. In addition, clinical judgment is needed to determine if the magnitude of the numerical increase in the rate is "clinically important." FDA advises that sponsors should consider the consistency of the increase in frequency over time and across multiple trials, if applicable.

The Draft Guidance also addresses the determination of possible causality regarding a control group with an active comparator drug. FDA emphasizes that, if aggregate data comparisons of the group receiving the investigational drug treatment and the group receiving an active comparator drug (rather than a placebo) indicate a substantially higher rate in the control group, the sponsor should report this imbalance to the Agency in an IND safety report.

- **The sponsor's plan for safety surveillance, and what elements should be included.** In the Draft Guidance, FDA affirms that sponsors of clinical investigations conducted under an IND should have a systematic approach for safety surveillance to ensure compliance with IND safety reporting requirements and to enhance the overall quality of safety reporting, including adverse events reported by investigators and information from other sources (21 CFR 312(c)(1)(ii) and (iii)). Newly emphasized in this Draft Guidance, FDA strongly recommends that a sponsor develop a formal written *prospective plan for safety surveillance* that is specific to the premarket development program for the investigational drug. Further, the Draft Guidance emphasizes that the prospective plan for safety surveillance should be maintained and available for FDA inspection in the sponsor's records and reports (21 CFR 312.56(a)). FDA advises that the plan should contain the following elements:

    1. The defined roles and responsibilities of all entities and individuals that have responsibility for any aspect of IND safety event analysis and reporting
    2. A plan for regular review of SAEs and "other important safety information," with appropriate unblinding as necessary
    3. A process for aggregate data safety reviews, including a list of adverse events that are anticipated in the study population and that the sponsor does not intend to report as individual events
    4. Whether the sponsor will use a trigger (threshold) approach to decide when SAEs should be unblinded, and if this approach will be used, a listing of the "predicted rates of anticipated SAEs and the basis for the predicted rates"
    5. A plan to monitor the incidences of all events, other than those that do not require aggregate analysis (which would be reported without aggregate analysis), including anticipated events and expected events (those listed in the investigator's brochure)
    6. The frequency for performing aggregate reviews of safety data
    7. Pre-planned assessments of the trial's safety database and the drug's safety database when a) trials of the drug are completed and unblinded, b) safety data from trials of other drugs in the same class are reported, or c) when "any information relevant to safety is presented"
    8. Methods to be used to evaluate adverse events, including graphical, tabular, or statistical approaches
    9. Processes for unblinding, including the controls and processes for maintaining data integrity

The Draft Guidance also emphasizes that FDA may disagree with sponsor decisions critical to expedited reporting, including the determination of a potential causal relationship between the drug and the adverse event. "Waiting for a statistically significant difference in event rates, when other evidence points to a potential causal association, may unduly delay reporting serious events of concern.… Recognizing the complexity of the judgments, FDA will focus on the sponsor's process and reasoning underlying the sponsor's decision in the event the FDA and sponsor reach different conclusions regarding whether SAEs evaluated by analyses of aggregate data meet IND safety reporting criteria." Thus, sponsors should consider including in the plan the method for documentation of the process and reasoning for decisions related to potential causality.

KEY TAKEAWAYS

This Draft Guidance signals FDA's current attention on the IND sponsor's analysis of adverse events that may require expedited reporting to FDA and to all participating investigators. In particular, it emphasizes FDA's current focus on *aggregate* analysis of safety events, including comparison of the incidence of the event in the investigational drug group and the control group, for the determination of a possible causal relationship between the investigational drug and event. Although this analysis of a possible causal relationship may require unblinding, the Draft Guidance extensively discusses the risk of the unblinding of safety data on the trial's integrity and potential safeguards to mitigate this risk. Sponsors may wish to carefully review the recommendations related to aggregate safety data analyses and crosswalk FDA's recommendations to current processes within the company for safety surveillance, including unblinding for analysis of safety events, in IND investigations.

In addition, FDA proposes that sponsors develop a formal written *prospective plan for safety surveillance* that is specific to the premarket development program for the investigational drug and subject to FDA inspection. The recommendations regarding the construction and contents of the plan in the Draft Guidance are complex and may differ from current approaches by many sponsors. Thus, to inform FDA's development of final guidance, sponsors may consider submitting comments to the open docket regarding this recommendation, including alternative approaches.

If you have questions regarding this Draft Guidance or would like assistance in preparing comments to the open docket, please contact Beverly Lorell, Chris Markus, Gary Messplay, Eva Temkin, or Elaine Tseng for more information.

[1] "Sponsor Responsibilities—Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies. Draft Guidance for Industry" (June 2021), https://www.fda.gov/media/150356/download. Also see Federal Register notice 86 Fed. Reg. 34,020 (June 28, 2021) accessed at https://www.federalregister.gov/documents/2021/06/28/2021-13684/sponsor-responsibilities-safety-reporting-requirements-and-safety-assessment-for-investigational-new.
[2] "Safety Assessment for IND Safety Reporting. Draft Guidance for Industry" (published December 2015; withdrawn June 25, 2021).
[3] "Guidance for Industry and Investigators. Safety Reporting Requirements for INDs and BA/BE Studies. Final Guidance" (December 2012) accessed at https://www.fda.gov/media/79394/download.
[4] Comments may be submitted electronically under docket number FDA-2020-D-2099 via the federal portal https://www.regulations.gov.

[5] International Conference on Harmonisation, "Guidance for industry (ICH E2A) Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (March 1995), accessed at https://www.fda.gov/media/71188/download.