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# *Updated FDA Guidance on Sponsor Responsibilities for IND Safety Assessments*

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In a recently released draft guidance document, the U.S. Food and Drug Administration (the "FDA") has proposed updated recommendations related to IND safety reporting.[1] Revised recommendations relate to: (1) planned unblinding of safety data and implications for trial integrity, (2) increased flexibility about who reviews safety information for IND safety reporting purposes, (3) clarification regarding the scope and methodology for aggregate analyses, and (4) clarification regarding the plan for safety surveillance, including elements to be included in the plan.

The FDA previously issued a 2015 draft guidance on this topic.[2] The agency received multiple comments and revised its recommendations in the current draft. Generally, the updated guidance provides sponsors greater flexibility in determining who will conduct the safety assessments and no longer focuses on the implementation of a Safety Assessment Committee, which some saw as redundant to existing processes. The FDA is withdrawing the 2015 draft, and is accepting comments on the updated draft document for 90 days.

## Planned Unblinding of Safety Data and Implications for Trial Integrity

The FDA continues to recommend two approaches for assessing serious adverse events that are interpretable only based on aggregate data: (1) to estimate and prespecify the background rate of the event in the population and then utilize an unblinding trigger rate resulting in an unblinded analysis; and (2) to regularly analyze unblinded safety data on serious adverse events by treatment group to assess whether there is a meaningful increase in a particular event in the intervention group compared to the control group.

Unlike the 2015 draft guidance, the current draft guidance document does not make an overall recommendation that the second approach is preferable. Rather, the 2021 draft notes that it may be challenging to use a trigger approach when the rates of some anticipated events in the specific trial population are not available. The FDA indicates that the second approach is preferable when it is not possible to accurately predict rates of anticipated serious adverse events. The FDA cautions, however, that the second approach requires "scrupulous, thoroughly planned and well-documented efforts to protect data integrity, assuring that the entity carrying out the review is completely firewalled from the staff conducting the trial and assessing efficacy."

## Increased Flexibility Regarding Who Reviews Safety Information

Although sponsors are responsible for promptly reviewing relevant safety information and making IND safety reports, sponsors may designate an individual or group of individuals (such as CROs) to review the accumulating safety information in a drug development program. This designated entity may recommend whether safety information is reportable. Sponsors may also elect to use multiple entities to make such recommendations. For example, one entity might assess individual occurrences and another might evaluate aggregate adverse events. Regardless of who is used, the entity reviewing aggregate safety information should be qualified to make clinical judgments about the safety of the drug and include an individual(s) with knowledge about the investigational drug, the disease being treated, and the characteristics of the study population. The roles and responsibilities of any designated entity should be clearly defined in the plan for safety surveillance.

The FDA's draft guidance suggests sponsors have greater flexibility in structuring entities reviewing safety information. For example, sponsors may elect to use individuals within the sponsor's own organization, a Data Monitoring Committee ("DMC"), or a combination of these entities to conduct aggregate safety analyses. The FDA highlights the advantage of using a DMC, which routinely sees unblinded data and can utilize existing controls for maintaining trial integrity. This would be a new role, however, for most DMCs. DMC processes would likely require additional updates to assess whether IND safety reporting criteria have been met after reviewing safety data across trials, across INDs, and, if applicable, from other sources.

Sponsors may also identify other entities within or outside of their own organization to review safety data. Regardless of the entity, care must be taken to ensure no unblinded effectiveness data is revealed to personnel participating in the conduct or analysis of an ongoing clinical trial program (except for those appropriately firewalled and designated to conduct unblinded safety analyses). A hybrid or "triage" approach is also possible where sponsor personnel conduct a blinded review because they are most familiar with the product and clinical program to see if the data meet certain criteria that would trigger an unblinded comparison of event rates in the treatment and control groups.

## Clarification on the Scope and Methodology for Aggregate Analyses

When the sponsor is using an unblinding trigger approach, the FDA indicates that the sponsor may choose to predict rates of certain anticipated serious adverse events and to not predict rates of others. Some of these background events are not interpretable as single events, but may be expected to occur relatively infrequently. Unblinding to assess incidence by treatment group may be specified for such less common events when, for example, only four or five events are reported. The sponsor should document its rationale for the selection of the events and its determination of the threshold.

The FDA notes that, absent a specific concern, it is reasonable to conduct aggregate analyses at intervals based on volume of safety data collected, subject accrual into the trial, or event rates. It is likely that the need to conduct such analyses will happen at regular intervals (e.g., six months, or more frequently, as appropriate). The frequency and its rationale should be documented in the safety surveillance plan.

## Clarification on the Plan for Safety Surveillance, including Plan Elements

The FDA has also clarified the information that it expects to be within the safety surveillance or safety monitoring plan. The updated guidance emphasizes the need to document the decision-making process and rationale for reviewing aggregate safety data and determining when the data is reportable. Elements of the safety surveillance plan should include, among other things:

- Processes for conducting aggregate safety reviews including a list of anticipated adverse events that the sponsor does not expect to report individually, regardless of the investigator's assessment of causality;
- Pre-planned assessments of the trial and program safety database when trials within the program are completed and unblinded, when safety information from trials of other drugs in the same class are reported, or when any information relevant to safety is presented;
- Methods that may be used to evaluate events, including graphical, tabular, or statistical approaches; and
- Unblinding practices and controls and processes for maintaining trial integrity.

Clinical trial programs should review and potentially revise their processes in light of the updated guidance, particularly their processes for evaluating aggregate safety data. Rationales and controls for unblinding data should be considered carefully and appropriately documented.

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*If you have any questions concerning these developing issues, please do not hesitate to contact either of the following Paul Hastings Washington, D.C. lawyers:*

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[1] See, Guidance for Industry: Sponsor Responsibilities – Safety Reporting Requirements and Safety Assessment for IND and Bioavailability/Bioequivalence Studies (June 2021), available at https://www.fda.gov/media/150356/download

[2] See, Guidance for Industry: Safety Assessment for IND Safety Reporting (Dec. 2015), available at https://www.fda.gov/files/drugs/published/Safety-Assessment-for-IND-Safety-Reporting-Guidance-for-Industry.pdf