



# **Safety Assessment for IND Safety Reporting Draft Guidance**

Robert Temple, MD

Deputy Center Director For Clinical Science

Center for Drug Evaluation and Research

Food and Drug Administration

# Outline

- Background
- Draft guidance recommendations
  - Safety assessment committee
  - Aggregate analyses of safety data
  - Planned unblinding of safety data
  - Reporting thresholds
  - Safety surveillance plan

## Regulation (21 CFR 312.32)

- Describes sponsors' responsibilities for reviewing safety information and for notifying FDA and all participating investigators of potential serious risks in an IND safety report
- Defines suspected adverse reaction (i.e., reasonable possibility that the drug caused the adverse event) and includes examples of evidence that suggest a causal relationship

## Regulation (21 CFR 312.32), cont.

- Examples of evidence that suggest a causal relationship:
  - Single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury)
  - 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 that indicates those events occur more frequently in the drug treatment group than in a control group (e.g., known consequences of underlying disease)

# 2012 Guidance

## 2012 guidance- *Safety Reporting Requirements for INDs and BA/BE Studies*

- Provides guidance on the implementation of the IND safety reporting requirements, with a focus on what should not be reported, as well as on what should be reported

# Rationale for Developing New Guidance

- Goal- Provide recommendations for how sponsors can identify and evaluate important safety information for IND safety reporting
- Critical that sponsors detect and report important safety information as early as possible (the point of 312.32)
- But reporting all serious adverse events as IND safety reports, including those where there is no ability to attribute any cause may obscure important safety information and is time-wasting (reports are sent to all investigators and institutional review boards)

## Rationale for Development New Guidance, cont.

- Concerns expressed by sponsors- new rule requires judgment
  - The guidance urges evaluating unblinded data; this raises concerns regarding preserving trial integrity
  - Judging when aggregate data should be reported
- Not stated, but real anxiety about not reporting serious events and possible disparity between US and Europe (causality assessment is made by sponsors for US reports)
- Need a systematic approach to safety surveillance, particularly for events that are interpretable only in the aggregate

## Background

- Reporting obvious drug-related events, such as agranulocytosis, acute liver injury, etc. is easy
- More difficult is serious adverse events that have a high background rate (MI, stroke)
  - Need a systematic approach to safety surveillance for these adverse events. Aggregate reporting provisions:
    - Requirement to report cases where an aggregate analysis indicates an event occurs more frequently in the test group than the control group (312.32(c)(1)(i)(C))
    - Requirement to report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (312.32(c)(1)(iv))



# Overview of Draft Guidance

Sponsors should have a systematic approach to safety surveillance to meet the IND safety reporting requirements and more generally to improve the quality of safety reporting

- Periodically review accumulating safety data across multiple studies, completed and ongoing, and other sources
- Analyze the data in the aggregate
- Make a judgment about the likelihood that the drug caused any serious adverse events



# **Draft Guidance Recommendations**

# Safety Assessment Committee

- Role- Review important safety information periodically and make a recommendation to the sponsor regarding whether the information meets the IND safety reporting criteria
- Information reviewed- all safety information, from all trials, including accumulating serious adverse events, that may qualify for IND safety reporting

## Safety Assessment Committee, cont.

- Meeting frequency- routine and ad-hoc; depends on multiple factors, including experience with the drug, the disease, the subject population, and enrollment rate
- Composition- multidisciplinary; internal, external, or both

# Anticipated Serious Adverse Events

Serious adverse events the sponsor can foresee occurring, independent of investigational drug exposure. For example, adverse events:

- That are known consequences of the condition under investigation
- Common in the study population
- Known to occur with the background regimen

# Anticipated Serious Adverse Events, cont.

- These events do not meet the criteria for reporting as individual cases (they are not unexpected)
- These events must be reported in the aggregate if analysis indicates the events occur more frequently in the drug treatment group
- Sponsors should prospectively identify these events and have a plan for monitoring these events

# Aggregate Analyses of Safety Data

## Aggregate reporting provisions:

- Requirement to report cases where an aggregate analysis indicates an event occurs more frequently in the test group than the control group (312.32(c)(1)(i)(C))
- Requirement to report any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure (312.32(c)(1)(iv))

## Aggregate Analyses of Safety Data, cont.

- Recommend regular unblinded comparisons of serious adverse event rates across treatment groups, for ongoing and completed trials, to detect numerical imbalances
- Sponsor judgment needed to determine if the aggregate data meets the reporting criteria. Decision may be informed by recommendations from the safety assessment committee.



# Unblinding Safety Data

- IND safety reports submitted to FDA and investigators should be unblinded (we do not think they are useful if treatment is unknown)
  - Single or small numbers of cases
  - Groups of events (to allow a comparison of event rates in treatment groups)
    - Reporting to investigators - may send narrative
- Controls to maintain trial integrity
  - Unblinding limited events
  - Unblinding limited data for those events
  - Unblinding limited individuals (safety assessment committee)

# Reporting Thresholds

- Individual and small numbers of events (312.32(c)(1)(i)(A) and (B))
  - Serious
  - Unexpected
  - Suspected adverse reaction
- Reasonably easy decision for events that are uncommon and known to be associated with drug exposure (e.g., Stevens-Johnson Syndrome) and for events that are not commonly associated with drug exposure but are uncommon in the population (e.g., tendon rupture)

# Reporting Thresholds

Aggregate data (312.32(c)(1)(i)(C), (c)(1)(iv))

- Clinical judgment
- Factors to consider
  - Size of the difference in frequency between groups
  - Consistent increase in multiple trials
  - Preclinical evidence
  - Evidence of a dose response
- Periodically re-evaluate updated rates of unblinded events to determine whether any new information impacts whether the events meet the reporting criteria

# Follow-up Information

Relevant follow-up information must be submitted as soon as it is available (312.32(d)(2)), for example

- Individual case
  - New information that significantly impacts the causality assessment
- Aggregate data
  - Additional occurrences that suggest a significant change in the rate of occurrence reported in the initial report

# Safety Surveillance Plan

- Sponsors should describe processes and procedures for assessing serious adverse events and other important safety information
- Recommended content
  - Roles and responsibilities
  - Anticipated serious adverse events
  - Previously recognized serious adverse reactions
  - Review processes
  - Guiding principles for periodic aggregate safety reviews

# References

- 21 CFR 312.32 and 2012 final guidance:  
<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm>
- Draft guidance: <http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm477584.pdf>
- Submitting comments on the draft guidance:
  - <http://www.regulations.gov>
  - Docket number FDA-2015-D-4562
  - Comments due by February 16, 2016