Safety Data Collection in Late Stage Premarket and Postapproval Clinical Investigations

Patrick Archdeacon, MD
Medical Officer
Office of New Drugs
Center for Drug Evaluation and Research, FDA

November 12, 2013

Outline of Talk

- Review of FDA Guidance for Industry: Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations
- Implications of IND Safety Reporting Rule on Safety Data Collection
- Review of EMA's Clinical Trials Directive and Guidances – Areas of Overlap with FDA Guidance and Gaps in Harmonization

Investigator concerns related safety data collection for HABP/VABP: Big ticket and little ticket items

Non-serious AEs, lab data, other data not critical to evaluation of safety

Lack of international harmonization around collection and reporting of serious AEs

The Good News for HABP/VABP Investigators

FDA Guidance, IND regulations, and European Clinical Trials Directive appear to provide adequate mechanisms to address!!!

While harmonization between FDA and EMA has some gaps related to expedited reporting of SAEs, impact on HABP/VABP protocol and investigators limited.

IND Investigator Reports to Sponsor (21 CFR 312.64 (b))

- "Investigator must immediately report to the sponsor any SAE, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis)."
- "The investigator must record nonserious adverse events and report them to the sponsor according to the timetable for reporting specified in the protocol."

Guidance for Industry

Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations

DRAFT GUIDANCE

February, 2012

Background

- "In late stages of development or during the postmarket period, a selective, and better targeted, approach to safety data collection may be warranted."
- "Collection of data that are no longer useful for characterizing the safety profile of a drug may even have negative consequences. Arduous and excessive data collection may be a major disincentive to investigator participation in clinical trials."
- "There is also growing interest in and a need for larger, simpler trials to obtain outcome data, data on long-term effects of drugs, and comparative effectiveness and safety data, but excessive data collection requirements may deter the conduct of these types of trials."

Background (continued)

- "In such cases, more selective data collection may (1) improve the quality and utility of the safety database and safety assessment… (2) ease the burden on investigators conducing and patients participating in a study, and (3) lower costs, thereby facilitating increase use of large, simple trials and better use of clinical trial resources generally."
- "In the past, selective or specifically targeted data collection and reporting during clinical trials have been implemented on a case-by-case basis."
- "A sponsor considering a simplified data-collection approach should consult with the relevant FDA review division on the feasibility and acceptability of the plan before its implementation."

Circumstances in which targeted data collection may be appropriate

- Number of subjects exposed to the drug in previous studies is sufficient to characterize the safety profile for all but rare events
- The occurrence of adverse events has generally been similar across multiple studies
- There is a reasonable basis to conclude that occurrence of adverse events in the population to be studied will be similar to previously observed rates

These circumstances typically exist for…

- Postmarket studies
  - Studies of new indications (depends on nature of new study population, disease, dose, and duration of treatment)
  - Postmarketing requirements (typically enrolled population is similar to premarket safety database and purpose is to evaluate a specific safety concern)
  - Large outcome trials

- Late phase 3 trials

Types of safety data that may be appropriate for abbreviated collection or non-collection

- Non-serious adverse events not associated with drug discontinuation
- Routine lab monitoring
- Information on concomitant medications
- History and physical exams

Approach to Targeted Collection of Safety Data

- Include safety data collection plan in protocol
  - Specify the data that will not be collected at all
  - May also collect certain safety data only from a sample of the overall study population (e.g., selected patients at random, selected study sites at random, or only larger study sites)
  - Decreased frequency of data collection
- Discuss plan with relevant review division before starting the study

What about the ROW? Let's consider CT-3…

- Section 3 (Responsibilities of the investigator and sponsor as regards monitoring and safety reporting) of CT-3 guidance): "Investigator's responsibilities entail: reporting of serious adverse events to sponsor… and reporting of certain non-serious adverse events and/or laboratory abnormalities to the sponsor (see section 5)…"
- Section 5 (Reporting of non-serious adverse events and/or lab abnormalities by the investigator to the sponsor): "Article 16(2) of European Directive 2001/20/EC reads as follows: "Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reporting to the sponsor according to the reporting requirements and within the time periods specified by the protocol."
- By contrast, Section 5 makes clear that ALL SAEs must be reported by the investigator (some immediately, some non-immediately)

FDA and EMA have provisions that allow sponsors to target collection of non-serious AEs and other non-critical safety data when appropriate.

* Only FDA has stated this explicitly in guidance. However, EMA's CT-3 document logically implies this position. Certainly, EMA's clinical trial directive does not explicitly require complete collection all AEs and other non-critical safety data.

FDA and EMA are not perfectly harmonized around collection and reporting of SAE data. This has some impact on HABP/VABP protocols, but is likely a smaller ticket item.

IND Safety Reporting Rule (21 CFR 312.32 (c)(1))

- "Sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsors must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:
  - 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… that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."
- Note that this rule pertains only to expedited safety reports. All SAEs will be collected and ultimately reported in IND annual reports, DSURs, clinical study reports, and any ensuing NDAs.

IND Safety Reporting Rule : Implications for HABP/VABP Protocol

- Sponsor should submit expedited IND safety reports only for those SAEs where the evidence suggests a causal relationship with the drug (i.e., suspected adverse reaction)
- For most SAEs, this will require aggregate analysis of data. For instance, it would not be appropriate to submit an individual safety report of an event of C diff diarrhea. However, a report should be submitted if the aggregate data suggests a higher than expected rate of C diff diarrhea.
- The reporting by the sponsor to FDA and to investigators (21 CFR 312.32) is unrelated to the issue of safety data collection by the investigators in the HABP/VABP protocol (21 CFR 312.64)

European Directive 2001/20/EC

- "The investigator shall report all SAEs immediately to the sponsor except for those that the protocol or IB identifies as not requiring immediate reporting…" [Article 16(1)]
  - FDA regulations do not have such a provision to allow for flexibility regarding timing of reports by investigator to sponsor
  - However, CT-3 also makes clear that the investigator is responsible for reporting to the sponsor all SAEs either immediately or non-immediately (same as FDA).
  - Article 16 implies the use of an aggregated approach to SAE reporting for anticipated SAEs: as sponsor is not immediately collecting data on anticipated SAEs, this clearly implies that EMA has no expectation that sponsor must immediately report them to regulatory authorities (same as FDA)

European Directive 2001/20/EC and "CT-3"

- "… suspected serious unexpected adverse reactions shall be reported to the competent authorities concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen days of first knowledge by the sponsor." [Article 17 (1)(b)]
  - CT-3 guidance states that a SUSAR, by definition, means that there are facts (evidence) or arguments to suggest a causal relationship
  - Thus, FDA and EMA agree that sponsor need not report all SAEs in expedited fashion
  - However, EMA states that either investigator or sponsor can make determination that an SAE constitutes evidence of a SUSAR (FDA states only sponsor makes this determination)

Implications of SAE regulation on HABP/ VABP Protocol

- EMA and FDA agree that all SAEs should be collected by investigator and ultimately reported
- EMA and FDA agree that only serious unexpected suspected adverse reactions should be reported to authorities in expedited fashion
- However, despite similarities in principles, differences in international regulations regarding when SAEs must be reported to sponsor and who (investigator or sponsor) makes determination of causality introduce complexity for all international trials (not just HABP/VABP protocols)

Take Home Points

- Both FDA and EMA require the collection and reporting of all SAEs.
  - While some investigators and sponsors have suggested instances (e.g., comparative effectiveness research of marketed products using large simple trials) where such requirements represent barriers but do not improve safety, the conduct of HABP/VABP trials do not appear to represent such as case
- Recent FDA guidance clarifies FDA support of targeted collection of safety data in appropriate contexts and CT-3 appears to permit similar approaches.
  - However, some sponsors may rely on a very conservative reading of CT-3 in the absence of explicit guidance
- Lack of harmonization over expedited SAE reporting complicates the conduct of all international trials
  - However, likely not the big ticket barrier in context of HABP/VABP