How Broad of an Assessment is Necessary When the Data are Sparse for Cardiovascular Events and Death in Non-Cardiac Studies

FDA Commentary

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The opinions expressed here are my own.

How Broad of an Assessment is Necessary When the Data are Sparse for Cardiovascular Events and Death in Non-Cardiovascular Studies

- Prevention
- Opportunities for Collaboration

Examples from Development Programs

- Positive cardiac biomarkers in a patient hospitalized for a non-cardiovascular event
  - If not considered serious by the investigator, these events never get referred for adjudication
  - Dataset does not record the "hospitalization" because patient is already hospitalized
  - Based on these findings, FDA knows that not all cardiovascular events have been referred for adjudication—questions about the quality of the data
  - All possible cardiovascular events, regardless of whether they are considered to be serious and regardless of attribution, should be referred for adjudication
- Chest Discomfort
  - Sponsor monitoring of serious and non-serious adverse events
- Adverse Event terms not used in a consistent way
  - Acute Coronary Syndrome (ACS) events
    - Myocardial infarction (STEMI, NSTEMI) versus unstable angina

Possible Options (per Dr. Sabol)

- Source documents only (Admission H&P and D/C Summary for each event)
- Source documents and narrative
- Comprehensive master document
- Individual event forms with specific questions and option to upload source documents

Solution

- Individual event forms with specific questions
- Source documents--upload at time of event
- Narrative

What do you do when prevention has failed and you still end up with sparse data for cardiovascular events and death?

- Mechanism of action of investigational drug product / class effect?
- Nonclinical study results
- Pharmacokinetic and pharmacodynamic effects of study drug and timing of events
- Risk / Benefit analysis

*If there is an imbalance in events and there is a high enough level of clinical suspicion, may need to do another randomized clinical trial

Palpitations, Dizziness / Presyncope etc.

- Drug Product (MOA, class effect?)
- History
  - Symptoms
    - Frequency
    - Duration
    - Timing of symptoms in relationship to drug product
    - Associated symptoms
    - At rest or on exertion
- Physical Examination with Vital Signs
- 12-lead ECG (consider other tests as appropriate)

Summary

- Prevention
- Collaboration
- Clinical Trials
  - Individual event forms with specific questions
  - Source documents—upload at time of event
  - Narrative
- Good Clinical Judgment