Is Our Current Approach to AE Safety Reporting Sensible and Efficient?

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Sensible Guidelines for the Conduct of Clinical Trials

Disclaimer

- The opinions and conclusions expressed in this presentation are those of the presenter and should not be interpreted as those of the FDA

Outline

- **What is our current approach to "AE Safety Reporting" and what additional changes will lead to a pre-market safety system optimized to detect valid safety signals as early as possible?**
  - **How did the FDA requirements for expedited reporting change on March 28, 2011?**
  - **How do current FDA regulations align with existing industry frameworks for expedited reporting?**
  - **How do current FDA regulations align with international guidelines for expedited reporting?**
  - **How did "AE Safety Reporting" become synonymous with expedited AE reporting and why is this so concerning?**

Problem: Submitting uninformative individual IND safety reports

- Sponsors often report serious adverse events as individual cases that are uninterpretable as single events (i.e., require evaluation in the aggregate to interpret) and/or
  - Are likely to have been manifestations of the underlying disease (e.g., mortality or major morbidity)
  - Commonly occur in the study population independent of drug exposure (e.g., strokes or acute myocardial infarctions in an elderly population)
  - Are study endpoints (i.e., the study was evaluating whether the drug reduced the rate of these events)

Why are sponsors submitting these uninformative reports?

- Previous guidance (including ICH E2A) indicating that reports should be sent for events where a relationship to medicinal product “cannot be ruled out”
- Previous guidance (including ICH E2A) indicating that either sponsor or local investigator can make this determination
- From both a practical and legal standpoint, it is expedient to send reports for any event that meets criteria of “unexpected” and “serious”

New IND safety reporting rule

- Final IND safety reporting rule published September 2010, effective March 28, 2011
  - Published guidance on period of enforcement discretion through September 28, 2011
- Goal
  - Improve the utility of premarket expedited safety reports, thereby enhancing human subject protection
    - Eliminate confusing terminology
    - Clarify sponsor and investigator responsibilities
    - Eliminate uninformative individual case reports

What Does the Rule Address?

- IND safety reports (21 CFR 312.32)
  - *Expedited* (7-day and 15-day) reports from the sponsor to FDA and all participating investigators
- Investigator reports (21 CFR 312.64(b))
  - Reports from the investigator to the sponsor
- Safety reports for bioavailability or bioequivalence studies (21 CFR 320.31(d))
  - *Expedited* reports from the person conducting the study to FDA and all participating investigators

The new rule seeks to reduce the number of uninformative reports:

- Report only suspected adverse reaction that is both serious and unexpected
  - *Suspected adverse reaction* means any adverse event for which there is a reasonable possibility that the drug caused the event
  - *Unexpected* means not listed in the investigator brochure…
  - *Serious* means results in death, is life-threatening, hospitalization…

Is the new rule perceived as sensible and efficient?

- Reporting **only** if there is evidence to suggest a causal relationship between the drug and the adverse event (sponsor judgment) will mitigate the problems caused by uninformative reports
- However, the new rule raised concerns among many stakeholders about issues related to compliance and harmonization

Existing framework efficiently meets old requirements of sponsor

(but they may not optimally serve subjects in clinical trials!!)

- Global safety database evolved to meet previous regulatory requirements
- Safety and legal teams have been trained to assess safety and risk, respectively, according to previous requirements
- Lack of international harmonization could require sponsors to have multiple reporting systems

CTTI IND Safety Assessment and Communication Project

- Clinical Trials Transformation Initiative (CTTI) is a public-private partnership founded by FDA and Duke University. Membership include industry, academia, government, patient advocates, etc…
- Conducted survey and held two-day meeting to better understand current pre-market safety practices

Survey Respondents

- Amgen
- Celgene
- Astellas
- Pfizer
- Eli Lilly
- Human Genome Sciences
- Novartis
- Vertex Pharmaceuticals
- Boehringer Ingelheim
- Astra Zeneca
- Bristol-Myers Squibb
- GlaxoSmithKline

Meeting participants also included representatives from FDA, CTTI, NIH, US Department of Veterans Affairs, patient advocates, and leaders in the field of biostatistics

Major Findings of CTTI Project

- Vast majority of sponsors are still following previous expedited reporting rules
- Sponsors do not to currently assess safety data of ongoing blinded studies in unblinded fashion
  - **Aggregate safety analyses instead evaluate at rates in overall population**
  - **Data Monitoring Committees (DMCs) and/or internal oversight groups sometimes (but not routinely) perform parallel review of unblinded safety data**
- Various stakeholders (sponsors, patients) have concerns about relying on sponsors to determine the thresholds for expedited reporting of an aggregate signal
- Sponsors concerned about lack of harmonization

International Harmonization

- ICH E2A states:
  - "All cases judged by either the reporting HCP or the sponsor as having reasonable suspected causal relationship to the medicinal product qualify as ADRs…"
    - "The expression 'reasonable causal relationship' is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship."
    - "…a reasonable possibility, i.e., the relationship cannot be ruled out."

While the new IND reporting rule is not harmonized with the role of the investigator in determining relatedness, it appears to be consistent with the E2A definition 'reasonable causal relationship'. However, E2A appears to have internal inconsistencies due to its definition of 'reasonable possibility'.

ICH E2A (continued)

- “It may be appropriate to reach agreement with regulatory authorities in advance concerning serious events that would be treated as disease-related and not subject to routine expedited reporting.”
- Draft FDA guidance on new reporting rule reflects this E2A position: events that are anticipated to occur in a trial should be monitored and reported according to protocol.
- Prospective monitoring of anticipated events combined with a more conservative approach to expedited aggregate reporting of unanticipated events may help with concerns about thresholds

Opportunities for Improving Expedited Safety Reporting

- Aggregate review of unblinded data is not only appropriate but necessary
  - Additional guidance from FDA
  - Use of internal oversight committees and/or expanded roles for DMCs
- Additional guidance from FDA on approaches to determining thresholds for expedited reporting of aggregate signals
- Improved international harmonization

More importantly: Opportunities for making pre-market safety sensible and efficient

- Elevate importance of IND annual report and periodic safety update report (PSUR)
- Promote concepts related to development safety update report (draft DSUR guidance published in August 2011)
- Develop systems and procedures (e.g., integrated clinical and safety databases; rationale approach to review of blinded data) designed to optimize both product development and patient safety
- Expedited reports should provide timely information about unanticipated safety signals, should not constitute foundation of pre-market safety system