CTTI IND Safety Assessment and Communication Project

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Disclaimer

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

Background on IND Safety Assessment and Communication Project

- In 2009, CTTI undertook the "Improving Unexpected SAE Reporting to IND Investigators" project which found that:
  - Aggregate reports prepared for FDA are infrequently sent to investigators
  - Processing of SAEs are time consuming and expensive
  - Individual SAE reports received by investigators do not lead to protocol amendments, improved informed consent, changes to Investigator Brochure, or otherwise improve patient safety

Background on IND Safety Assessment and Communication Project (continued)

- Concurrently with original CTTI project, the new IND Safety Reporting Rule was 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

Background on IND Safety Assessment and Communication Project (continued)

The new IND reporting rule seeks to address the issue of uninformative individual SAE reports:

- Report any suspected adverse reaction that is both serious and unexpected – **must meet all three definitions**
  - *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…

Background on IND Safety Assessment and Communication Project (continued)

- 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

IND Safety Assessment and Communication Project

Goal: To promote responsible oversight of safety for pre-market products

1. To obtain a deeper understanding of sponsors' current practices:
   - For assessing safety of a pre-market product across all trials and sources of safety information
   - For communicating potential safety signals
2. To facilitate an informed discussion of practices and challenges in assessing and communicating IND safety information
3. To issue recommendations for future approaches that will support the intent of the IND safety reporting rule

IND Safety Assessment and Communication Project

- Project leads created and distributed a survey to 14 small, medium, and large pharmaceutical companies
- Drawing on the survey results, background materials were prepared and distributed to all meeting attendees
- A two day meeting was held Feb 28-29, 2012
- A group of biostatisticians who participated in the meeting continue to meet and will produce recommendations

IND Safety Survey Background

- 54 question survey assembled by the CTTI IND safety assessment and communication working group
- Completed by 12 of the 14 sponsors who were solicited for their input
- Two CTTI staffers removed all identifiers from the collated responses before they were reviewed by the working group

Survey Respondents

- Amgen
- Astellas
- AstraZeneca
- Bristol-Myers Squibb
- Celgene
- GlaxoSmithKline
- Human Genome Sciences
- Janssen Research & Development/ Johnson & Johnson
- Novartis
- Pfizer
- The Medicines Company
- Vertex

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

Areas for Discussion

I. Organization of Personnel and Data

II. Methods and Processes Developed to Conducting Aggregate Product Safety Assessments

III. Confirmation and Escalation of Potential Safety Signals

IV. Analysis of Blinded Studies

Major Survey Findings Related to Organization of Personnel and Data

- 11 out of 12 respondents indicated they use Safety Management Teams (SMTs) to coordinate efforts of individual safety teams related to a given product
- Product data are maintained in parallel safety and clinical databases. Each product typically has a single global safety database, but separate clinical databases for each trial
- Data Monitoring Committees (DMCs) are sometimes relied upon to complement the individual safety team in detecting safety signals, in addition to protecting subject safety in a trial

Major Survey Findings Related to Methods for Aggregate Reviews of Safety Data

- Sponsors generally rely on aggregate analysis of the entire safety population (rather than imbalances across treatment groups) to detect potential safety signals in ongoing blinded trials
- Refinement of potential signals through analysis of the global safety database typically relies on customized queries rather than standardized queries

Major Survey Findings Related to Signal Thresholds and Escalations

- 6 of 12 responses specifically stated that individual case reports are still being submitted based on investigator's determination of causality
- Clinical judgment rather than quantitative thresholds serve as the basis for decisions
- A range of practices exist regarding thresholds for update reference safety information versus thresholds for sending IND safety reports based on aggregate data analysis

Major Findings Regarding Analysis of Blinded Data

- 11 of 12 respondents stated that primary review of safety data of ongoing studies is blinded, except for the unblinding of a single reviewer for SAEs meeting individual case reports to requirements for expedited reporting
- Some sponsors use DMCs to review unblinded or stratified safety data
- A few sponsors indicated experience with internal oversight committees and/or “alternate” safety teams to review aggregate data in unblinded or stratified fashion

Gaps Identified by Attendees

- **Unblinding (n=33)**
- **Lack of methods for meaningful analysis (n=21)**
- **Thresholds for reporting (n=19)**
- **Lack of global harmonization (n=11)**
- **Expanding role of DMCs (n=4)**
- **Avoiding false signals (n=3)**
- **Public perception of new IND rule (n=2)**
- **MEDRA coding (n=2)**
- **Increased sponsor resources to assess causality (n=1)**
- **Planning (n=1)**

Gap 1: Analysis of Blinded Safety Data in Ongoing Clinical Trials

- ***Gap: "Inability to unblind treatment status makes it impossible to assess incremental risk"***
- **Potential solutions:**
  - **For companies of sufficient size: set up internal safety review committee in a way that adequately addresses concerns regarding the potential for bias**
  - **Develop draft guidance from FDA/ICH on use of internal DMCs and/or allowable unblinding of safety data**
  - **Industry-wide, firewalled third-party consortium**
  - **Possible hybrid internal-external model**
  - **Use of Type 2 DMC (looking at unblinded data across whole development program)**

Gap 2: Limitations of Current Methodologies

- **Elevate safety as study objective to optimize design**
- **Database issues**
  - **Develop unified database to satisfy regulatory needs with comprehensive clinical dataset**
  - **Have all safety data in an accessible, standard format so they can be mined and queried**
- **Create clearinghouse for best practices for complying with new IND Safety Reporting rule (e.g., encourage Lilly to share their approach to)**
- **Develop best practices for meta-analysis of premarketing safety data**

Gap 3: 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."
  - "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."

Gap 4: Difficulty Defining Thresholds

- Most discussed issue other than unblinding, but fewer solutions proposed
- New reporting rule implies the need to exercise appropriate clinical judgment – cause for concern?
- Could one combine the use of DMCs to monitor "anticipated" events with a conservative reporting of "unanticipated" events to address this concern?
- Biostatistics follow-up report pending

Next Steps for the IND Safety Assessment and Communication Project…

- A report from a group of biostatisticians who participated in the meeting will be forthcoming this summer (Dr Wittes to discuss further)
- CTTI staff are reviewing SAE reports previously generated by clinical trials conducted at the DCRI to field test impact and practicality of new reporting rule

Next Steps for FDA to consider

- Additional guidance about handling blinding data in ongoing trials
- Additional guidance about use of internal oversight and program-level DMCs to assist with safety assessments
- Develop “anticipated event” concept for assessing and reporting certain data according to protocol
- Elevate importance of annual report, PSUR, and DSUR