New Rules in FDA Safety Reporting: Are You Prepared?

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Bringing your projects to a higher level
IND Safety Reporting – Final Rule

Key Dates

• Date of Publication = September 29, 2010

• Original Enforcement Date = March 28, 2011

• New Enforcement Date = September 28, 2011
Definitions

• The definitions section for the IND Safety Reporting regulations now contains 7 terms
  – AE (adverse event)
  – SAR (suspected adverse reaction)
  – UAE (unexpected adverse event)
  – USAR (unexpected suspected adverse reaction)
  – SAE (serious adverse event)
  – SSAR (suspected serious adverse event)
  – SUSAR (serious unexpected suspected adverse reaction)
Level of Evidence of Causation

- “Association with the use of the drug” has been replaced with “adverse event” and “suspected adverse reaction”
- For SARs, “reasonable possibility” of causation replaces “associated with the use of the drug”
- SAR implies lesser degree of certainty about causality than “adverse reaction”
• Frequent misapplication of the “reasonable possibility” standard in the definition of “associated with the use of the drug”
  – Manifestations of underlying disease as SAEs
  – Common events in study population as SAEs
  – Occurrence of study endpoints as SAEs
• These events are NOT “associated with use of drug,” and should NOT have been reported as an IND safety report!
Definition of “Unexpected”

• “Unexpected” includes events:
  – Not mentioned in the Investigator Brochure
  – Not listed at the observed specificity or severity
  – Not consistent with risk information in the General Investigative Plan or in the current application
Definition of “Unexpected”

• Includes AEs or SARs that may be anticipated from the pharmacological properties of the drug, or that occur with members of the drug class, but that have not previously been observed with the drug under investigation.
SAR Reporting

• SAR is reportable ONLY if the sponsor has evidence to suggest causation

• Three evidentiary examples (of “reasonable possibility”) provided:
  – Individual uncommon usually drug-related occurrences
  – One or more otherwise uncommon occurrences
  – Aggregate analysis of specific events
Further Clarification of Definitions

• Definitions of “serious” and “life threatening” are updated to require more scrutiny by the sponsor
• Sponsors must now review all information, including accumulated data
• “That have not already been previously reported to the agency by the sponsor” language has been eliminated
Determination of Seriousness

- Determination of “life-threatening” or “serious” is based on the opinion of either the sponsor or the investigator
Determination of Day Zero

• Reporting time clock starts as soon as sponsor determines that the information qualifies for reporting (21 CFR 312.32(c))
• For a SUSAR, clock starts when sponsor receives info from investigator
• Sponsor must actively seek all info needed to evaluate and report the SUSAR
FDA Requests for More Data

• Sponsor has 15 calendar days for submission of additional data requested by FDA
• Same as required under 312.32(d) for submitting follow-up information to FDA (preferably “without delay as soon as the information is available”)
• Investigator safety notification within 15 days
Reporting Forms for FDA Submission

- MedWatch Form 3500A for domestic SARs
- Narrative Format for domestic SARs
- Only CIOMS I for foreign SARs
Heightened Scrutiny Requirement

- Sponsor must identify all safety reports previously submitted
- AND
- Sponsor must analyze the significance of SAR in light of previous reports
• IB lists those Adverse Events that have been observed with the investigational drug AND for which a causal relationship with the drug is suspected or confirmed

• Sponsors should NOT add long lists to IB of AEs that are unlikely to have been caused by the drug because such lists could dilute the importance of clinically meaningful risk information, and, as a result, put subjects at risk
Added Requirements

• Reports of findings from preclinical or clinical safety studies FROM ANY SOURCE must be filed
• Sponsor must expeditiously report any clinically important increase in the rate of SSARs exceeding rates in IB or protocol
• Changes in rates of most frequent non-serious AEs go in annual report
§ 312.32 IND safety reporting

• (ii) *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies (other than those reported under paragraph (c)(1)(i) of this section), whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
§ 312.32 IND safety reporting

• Ordinarily, such a finding would result in a safety related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.
§ 312.32 IND safety reporting

• (iii) *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or in vitro testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.
§ 312.32 IND safety reporting

• Ordinarily, any such findings would result in a safety-related change in the protocol, informed consent, investigator brochure (excluding routine updates of these documents), or other aspects of the overall conduct of the clinical investigation.
Breaking the Blind

• The FDA expects the blind to be broken for ALL expedited IND safety reports
• If placebo, event not typically reported
• If unblinding will compromise study integrity, sponsor and FDA must agree on alternative reporting format to maintain the blind
Study Endpoints as SAEs

• Study endpoints as SAEs that will *not be expedited individual safety reports* can and should be identified in the protocol
• Method of reporting those study endpoints as SAEs should be described in the protocol
Reporting Study Endpoints

• Study endpoints (e.g., mortality or major morbidity) must be reported according to protocol rather than as IND safety reports, except when there is evidence of SUSAR suggesting causality between study drug and event (e.g., death from anaphylaxis)

• Investigator still must report all AEs and SAEs to sponsor, but causality assessment only required for SAEs
Investigations of Marketed Drugs

• Sponsor of any approved drug being studied under IND must report all SUSARs from foreign or domestic sites (21 CFR 312.32)
• Sponsor must also report safety info as prescribed by postmarketing requirements (21 CFR 314.80)
Annual Reports

- Nothing in Final Rule changes IND annual reporting requirements
- If and when FDA implements ICH-E2F Developmental Safety Update Report (DSUR) Guidance, agency likely to revisit issue
- EMA-CHMP adopted ICH-E2F-DSUR guidance in September 2010
Acceptable Media for Reporting

- Can now report by:
  - Phone
  - Fax
  - E-Mail
  - Other alternatives
Bioavailability & Bioequivalence

• Sponsor of BA or BE studies exempted from IND but conducted in USA must report SAEs from BA or BE study to Office of Generic Drugs

• Revised §320.31(d)(3) does not apply to otherwise exempted BA/BE studies conducted outside the USA
Real life scenarios

Scenario #1: "How should regular review of safety data for trends and signal detection be performed now that it is required per the New Rule?"

Regular review of safety data for trend and signal detection was always required as per 312.32(b), and per the FDA, there are currently no rules or regulations in place which mandates how this is to be accomplished.
Real life scenarios

Scenario #2: "Is an integrated safety database required and if so, does our database comply with the New Rule for trend and signal detection?"

An integrated database is not required per the New Rule; a sponsor must be able to look across data to determine a basis for the need for expedited reporting and it is left up to them how they choose to accomplish this. It does make it infinitely easier to look at data across the lifecycle of a product if all safety data is housed in the same database. This will not, however, take into account data that is received from all sources, such as scientific papers, studies being conducted by other sponsors, etc.
Real life scenarios

Scenario #3: "How will we comply with the New Rule as it pertains to MedDRA coding and upgrading requirements?"

This New Rule does not address MedDRA coding in any manner. Currently, the FDA has no explicit rule or regulation that requires the use of MedDRA for pre-marketed studies. There is also no regulation in place that requires that MedDRA be upgraded on any specific schedule (NOTE: The MSSO issues an upgraded version of MedDRA semi-annually and the FDA implements this upgrade to their systems semi-annually as well.) It has been proposed to require MedDRA coding for post-marketed products, however this has not been approved (NOTE: The EMA has required the use of MedDRA since 2003).
Real life scenarios

**Scenario #4:** “Day 0 will be different for everyone if a trial is being run in a global capacity.”

**Example #1:** Event is reported to the investigator, so this is day 0.

   False.

**Example #2:** Event is reported to a ROW CRO on 30-Jun-2011. The sponsor is notified the next day. Day 0 is when the sponsor received the report.

   False.

**Example #3:** Event originated in the US and was reported to a US CRO on 30-Jun-2011. The sponsor and the ROW CRO are notified that same day. Due to time difference, the sponsor and ROW CRO receive the report on their next business day. Day 0 is when either the sponsor or ROW CRO picks up the notification.

   False.

Per the New Rule, day zero represents the day that the sponsor or any of their affiliates are notified of an event and determines that meets expedited reporting requirements. It does not matter that there is a time difference to consider. Once someone is notified of such an event, the regulatory clock starts ticking and all parties involved, even those located outside the US, must comply with regulatory reporting requirements.
Real life scenarios

Scenario #5: “Should all adverse events be reported by the investigator to the sponsor (or their affiliates) in the same manner as serious events and then entered into an integrated database for evaluation?”

No. For clinical trials, adverse events should not be entered into the integrated safety database. These events will be recorded within the CRF and will be retrieved by/submitted to the sponsor at regular intervals throughout the study (NOTE: Investigator causality assessment of non-serious events is not required).
Thank You for Attending!

These slides are now available for download on our blog:

– http://www.ask-cato.com