Safety Assessment in Clinical Trials and Beyond

Yuliya Yasinskaya, MD
Medical Team Leader
Division of Anti-Infective Products
Center for Drug Evaluation and Research

FDA Clinical Investigator Training Course
November 14, 2018
Outline

• Introduction
• Sources of safety information
• Safety monitoring/ Adverse Event ascertainment
• Safety Reporting
• Safety Assessment Committee
• Summary
Evaluation of Safety

• Evolving process
• Available data depend on the stage of development
• Safety information on approved products is reflected in product labeling (Package Insert)
• Up-to-date safety information on the products under investigation is found in the Investigator’s Brochure (IB)
  – In vitro testing Nonclinical pharmacology/toxicology studies
  – Clinical safety and pharmacokinetic data if available
  – For products under investigation, IB is equivalent to the Package Insert
Sources of Safety Information

• Clinical trial data for the indication
• Nonclinical data (CMC, in vitro, animals)
• Clinical Pharmacology studies
• Clinical trial safety data for other indications
• Postmarketing experience
• Medical literature
• Safety profile of other drugs in the same class
Nonclinical information

- Chemical structure/Drug class
  - Class toxicities
- In vitro toxicity evaluation
  - Genotoxicity
  - Cardiac repolarization
- Pharmacology-Toxicology studies in animals
  - Organ specific toxicities
  - Carcinogenicity
  - Teratogenicity
Clinical Studies/Trials

- Healthy subjects
- Patients
- Special populations
  - Renal impairment
  - Hepatic impairment
  - Pediatric and geriatric
  - Pregnant and lactating women
Adverse Event / Experience

• Any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related

(21 CFR 314.80)

– sign, symptom, or disease
– abnormal lab, vital signs, imaging, ECG, etc
– worsening of the above
– constellation of the above

ideally, prospectively established case definition (e.g., drug-induced parkinsonism)
Ascertainment of Adverse Events

• Spontaneously reported/observed symptoms and signs
• Symptoms/Signs reported as a result of a probe (checklist or questionnaire)
• Testing
  – Vital signs
  – Laboratory tests
  – Special safety assessments (visual, hearing)
AE Severity Grading Tables

• Provide general guidance on parameters for monitoring safety in clinical trials

• They are specific to:
  – Study population
  – Phase of product development (1-4)
  – Product evaluated (small molecule, therapeutic biologic, device, vaccine)

• Examples: NCI, DAIDS, DMID, FDA/CBER
Serious Adverse Event
(21 CFR 312.32(a))

Any Adverse Event that results in the opinion of the Investigator or Sponsor in:

– Death or is life-threatening
– Hospitalization
– Disability
– Congenital anomaly / birth defect
– Important medical events
Uncommon Serious AEs

- Anaphylaxis
- Aplastic anemia
- Blindness
- Deafness
- Bone marrow suppression
- Disseminated Intravascular Coagulation
- Hemolytic anemia
- Liver failure
- Liver necrosis
- Liver transplant
- Renal failure
- Seizure
- Stevens-Johnson
- Sudden death
- Torsades
- Thrombotic Thrombocytopenic Purpura
- Ventricular fibrillation
Evaluation of a Serious Adverse Event

- Is it of common occurrence in the population under study?
- Was it “treatment-emergent”?
- Did it respond to de-challenge?
- Did it recur on re-challenge?
- Were there concomitant medications?
- Were pertinent labs/other tests done?
- Was there an obvious alternative cause?
- Is SAE a study endpoint?
AE Reporting Requirements Investigator to Sponsor
(21 CFR 312.64(b))

- All Serious Adverse Events (SAE) regardless of causality
- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations
- Study endpoints that are SAEs ONLY if there is evidence of causal relationship to the drug
- Investigators provide causality assessment in the report
Discussion Case 1

You are the investigator for a clinical study evaluating whether antihypertensive Drug A is associated with a reduced risk of death, MI, or stroke. A 75 years old white male patient died on the study.

Do you have to report this case to the sponsor?
Coding of Adverse Events

• Process of converting investigators’ “verbatim” terms to standardized “Preferred Terms” (PT)
  – Standardization allows sorting of AEs and grouping of like events
  – PT used to calculate incidence of AE
• Currently most used: MedDRA (Medical Dictionary for Regulatory Activities)
Coding Problems

Coding problems may lead to missing safety signals

• Splitting same AE among similar PTs
  – Hypertension, high blood pressure, etc.

• Lumping different terms to same PT
  – Edema: leg edema, face edema, etc.

• Lack of adequate term/definition
  – Drug hypersensitivity, Metabolic syndrome, Serotonin syndrome
Unexpected Adverse Event
(21 CFR 312.32(a))

• Not listed in the Investigator’s Brochure (IB) or if IB not available or required
• Not listed at the specificity or severity observed
• Mentioned in IB as anticipated due to pharmacokinetic properties of the drug or occurred with other drugs in this class, but not with the study drug
You are the investigator for a clinical trial evaluating a new quinolone antibacterial Drug B for the treatment of pneumonia.

Investigator brochure lists a number of serious adverse events associated with use of quinolone drugs, including neurotoxicity.

Is a seizure in this trial considered an expected adverse event?
Suspected Adverse Reaction
(21 CFR 312.32(a))

Any adverse event for which there is a reasonable possibility that the drug caused the adverse event

- A single occurrence of an uncommon event that is known to be strongly associated with drug exposure (SJS)
- $\geq 1$ occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the exposed population (neutropenia in healthy subjects)
- An aggregate analysis of specific events observed in a clinical trial indicates that those events occur more frequently in the drug treatment group than in a concurrent or historical control group
Suspected Adverse Reaction
(21 CFR 312.32; 21 CFR 314.80)

Suspected Adverse Reaction: an Adverse Event with a reasonable possibility of drug related causality
Expedited Safety Reporting to FDA by Sponsor (Safety Reporting Rule) (21 CFR 312.32(c)(1)(i))

• Adverse Events that meet all three criteria are reported to FDA (SUSAR):
  – Serious (S)
  – Unexpected (U)
  – Suspected Adverse Reactions (SAR)

• Fatal or life-threatening SUSAR reported to FDA no later than 7 days

• Others SUSARs -- no later than 15 days
Discussion Case 3

In a study of a marketed HIV Drug C, an 8 month old infant enrolled at 1 month of age was noted at study month 4 to have a moderate hearing loss in clinic progress notes.

Should this event have been reported to the sponsor expeditiously?
Discussion Case 3 cont’d

The drugs used in the study are not labeled for ototoxicity based on adult trials.

Unblinded review of the safety data identified 3 cases of hearing loss in Drug C arm and 1 on the comparator.

Is this event reportable to FDA?
Expedited reporting by Sponsor (2)
21 CFR 312.32(c)

• (C)(1)(ii) Findings from other studies
• (C)(1)(iii) Findings from animal or in vitro testing
• (C)(1)(iv) Increased rate of occurrence of serious suspected adverse reactions
• Report not later than 15 days of sponsor becoming aware of the finding
Causality Assessment for Common AEs, Sponsor/FDA

• Individual assessment unlikely to help determine attribution for common AEs, i.e. headache, nausea, MI in elderly

• Such AEs require aggregate analyses using a population approach (risk or rate with study drug vs. control)
  – Placebo or active control
  – Dose response in dose-ranging studies
Safety Assessment Committee (SAC)

- Group of clinical trial experts
- Assesses whether AE(s) in an ongoing trial need to be reported to FDA in real time taking into account safety data for the whole IND
- Follows predefined Safety Surveillance Plan (SSP)
SAC: Safety Surveillance Plan (SSP)

- Identifies anticipated SAEs in the trial population and specifies their predicted rates
- Lists previously reported SUSARs and their predicted rates
- Identifies roles for members
- Specifies frequency of regular meetings and ad hoc procedures
- Outlines principles of unblinded review of aggregate data
- Available for FDA review
SAC: monitoring

- Whether a single occurrence of an SAE needs to be reported (did patient(s) received the drug)
- Whether an event needs to be reported based on an aggregate analysis
  - Data form the ongoing trial
  - Data from all trials under IND
- Whether study needs to be terminated or modified based on new safety finding
  - Enrollment criteria, informed consent, etc
Safety Reporting After Drug Approval

• Clinical trials for new indications
• Postmarketing safety trials
• Observational studies
• New non-clinical safety studies
• FAERS (FDA Adverse Event Reporting System repository) through MedWatch
• NDA safety reporting
  – Periodic Adverse Event Reporting (PADER)
  – Annual Reporting
MedWatch

• FDA’s reporting system for AE founded in 1993
• Voluntary reporting of any SAE regardless of causality
  – Healthcare professionals, consumers, patients
  – 1 page form
  – Online, by phone, mail or fax
• Also, provides subscribers with potential safety signals alerts
Summary

• Evaluation of safety spans drug’s life time
• Investigators play an integral part in assuring quality safety assessments by reporting:
  – relevant/complete AE information using the most scientific terms
  – clinical and lab AEs from unscheduled tests/visits
  – SAEs once drug approved
• Sponsor with help of SAC report expeditiously
  – SUSAR and increased SUSAR rates
  – Increased AE rates from aggregate analyses in clinical trials suggesting increased risk to study subjects
  – New safety findings in nonclinical studies
References

• 21 CFR 312.32, 21 CFR 314.80
• Safety Reporting Rule (Final Rule)
  – Safety Reporting Requirements for INDs and BA/BE Studies
  -- Draft guidance safety assessment for safety reporting

• Toxicity grading
  – FDA /CBER guidance
  – NCI
  http://evs.nci.nih.gov/ftp1/CTCAE/About.html
  – DAIDS
  – DMID

• MedWatch  http://www.fda.gov/Safety/MedWatch/default.htm