U.S. FOOD & DRUG ADMINISTRATION

Safety Assessment in Clinical Trials and Beyond

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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

Discussion Case 2

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?

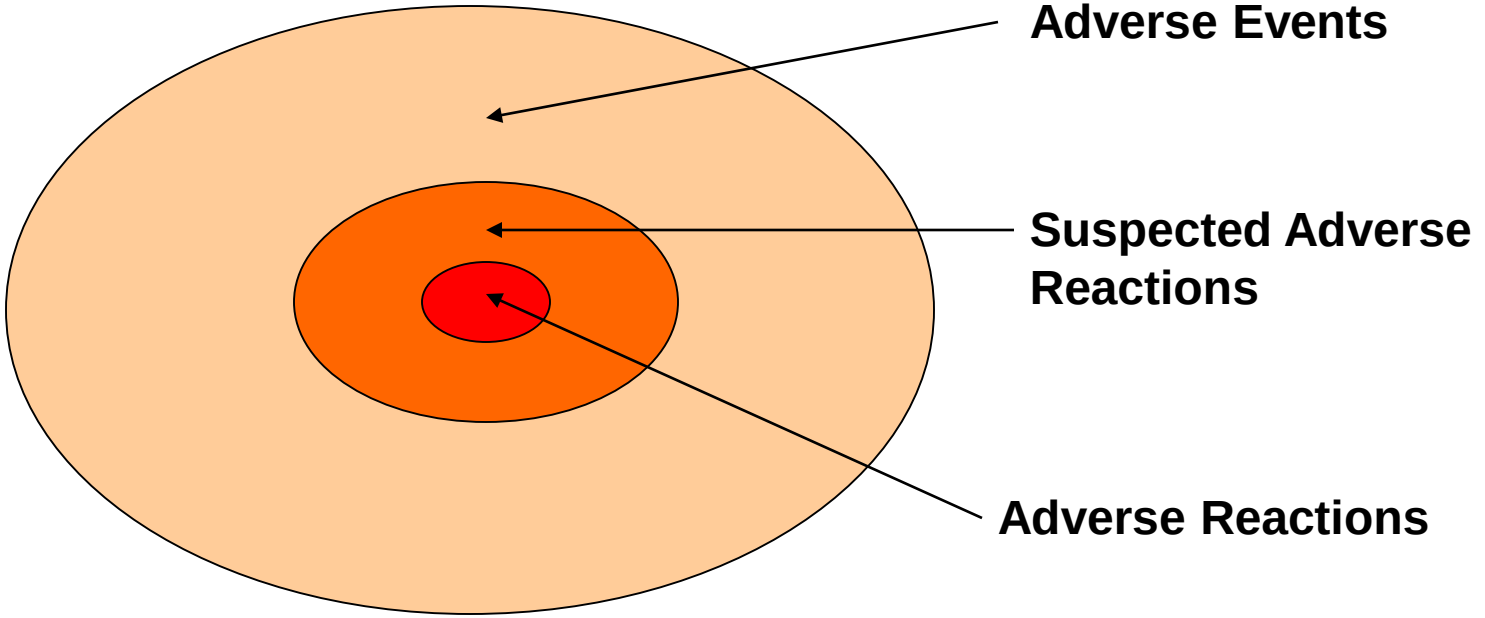
Suspected Adverse Reaction (21 CFR 312.32(a))

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)
- ≥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)
  http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf
  - Safety Reporting Requirements for INDs and BA/BE Studies
    http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf
    -- Draft guidance safety assessment for safety reporting
    https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm477584.pdf
- Toxicity grading
  - FDA /CBER guidance
    http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf
  - NCI
    http://evs.nci.nih.gov/ftp1/CTCAE/About.html
  - DAIDS
    http://rsc.tech-res.com/docs/default-source/safety/daids_ae_grading_table_v2_nov2014.pdf?sfvrsn=8
  - DMID
    https://www.niaid.nih.gov/sites/default/files/documents/dmidadulttox_0.pdf
- MedWatch *http://www.fda.gov/Safety/MedWatch/default.htm*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