



U.S. Food and Drug Administration

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# FDA's Clinical Investigator Course

*Cosponsored by  
FDA's Office of Critical Path Programs (OCCPP)  
and  
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**FDA**

U.S. Department of Health and Human Services

**Food and Drug Administration**





# Safety assessment in Clinical Trials and Beyond

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# Outline

- Introduction
- Sources of safety information
- Is your patient right for the trial?
- Safety monitoring/ AE ascertainment
- AE Coding
- Safety Reporting
- Postmarketing safety (MedWatch) reporting
- 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

## ■ ■ ■ Phase 1/Pharmacokinetic Trials

- Absorption, metabolism,  $C_{\max}$ , AUC,  $T_{1/2}$ 
  - in healthy subjects
  - in patients
  - in special populations
- Drug safety profile in dose escalation trials
  - Healthy volunteers
  - Safety signals supporting nonclinical findings
  - New safety signals in humans only

# ■■■ Is your patient fit for the trial?

Apply IB findings to the protocol and a prospective subject

- Inclusion/Exclusion criteria
  - medical history
  - lab values
  - concomitant medications
- Dosing regimen, duration (examine the potential for drug accumulation/ toxicities) – monitoring implications
  - PK parameters single versus multiple doses
  - Linearity of exposure with dose escalation



# Safety Monitoring

Unexpected Adverse Events

Common Adverse Events

Laboratory abnormalities

**Adverse Events**

Rare Adverse Events

Adverse Events of Special Interest

Serious Adverse Events

Adverse Reactions

# ■ ■ ■ Ascertainment of Adverse Events

- Spontaneously reported/observed symptoms and signs
- Symptoms/Signs reported as a result of a probe
  - Checklist
  - Questionnaire
- Both

## ■ ■ ■ Other Safety Assessments/Monitoring

- Vital signs
- Laboratory evaluations
  - CBC
  - LFTs
  - CPK
  - Renal Function Tests
  - Pancreatic enzymes
- Special safety assessments, for example:
  - Visual, Hearing
  - Neurological exam
  - ECG



# 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, VS, imaging, ECG, etc
  - worsening of the above
  - constellation of the above

ideally, prospectively established case definition (e.g., drug-induced parkinsonism)

# ■ ■ ■ AE Severity Grading Scales

- 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
  - WHO
  - DMID

# ■ ■ ■ AE Severity Grading Scale (NCI)

Common Terminology Criteria for Adverse Events (CTCAE) used for oncology drugs, generally not appropriate for otherwise healthy subjects.

- Grade refers to the severity of the AE
  - **Grade 1** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated
  - **Grade 2** Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
  - **Grade 3** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL
  - **Grade 4** Life-threatening consequences; urgent intervention indicated.
  - **Grade 5** Death related to AE.



# AE Severity Grading Scale (FDA/CBER)

- Healthy adult and adolescent volunteers in vaccine trials
  - Grade 1 Mild
  - Grade 2 Moderate
  - Grade 3 Severe
  - Grade 4 Potentially Life-threatening

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>



# 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 (immediate risk of death)
  - Hospitalization or prolongation of existing hospitalization
  - Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (aka disability)
  - Congenital anomaly / birth defect



# Uncommon Serious AEs

- Anaphylaxis
- Aplastic anemia
- Blindness
- Deafness
- Bone marrow suppression/pancytopenia
- DIC
- Hemolytic anemia
- Liver failure
- Liver necrosis
- Liver transplant
- Renal failure
- Seizure
- Stevens-Johnson/TEN
- Sudden death
- Torsades
- TTP
- Vfib



# 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?

*Note to Investigators: provide enough relevant information in CRF to allow for good quality narratives*



# AE Reporting requirements for the Investigator to the Sponsor (21 CFR 312.64(b))

- All Serious Adverse Events with causality assessment
- Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations.

*Note to Investigators: Report all SAEs regardless of causality. Include in your report results of relevant lab tests performed outside protocol scheduled visits*

## ■ ■ ■ 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)



# MedDRA Structure – Hierarchy

Highest level of terminology, least specific



SOC - System Organ Class (26)

HLGT - High Level Group Term (335)

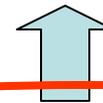
HLT - High Level Term (1,709)

Represents a single specific medical concept



PT - Preferred Term (18,786)

LLT - Lowest Level Term (68,258)



**AE as reported on CRF  
“Verbatim”**





# 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
    - Leg edema, face edema, etc.
  - Lack of adequate term/definition
    - Drug hypersensitivity, Metabolic syndrome, Serotonin syndrome

*Note to Investigators: Be consistent and use scientific terminology when reporting AEs*



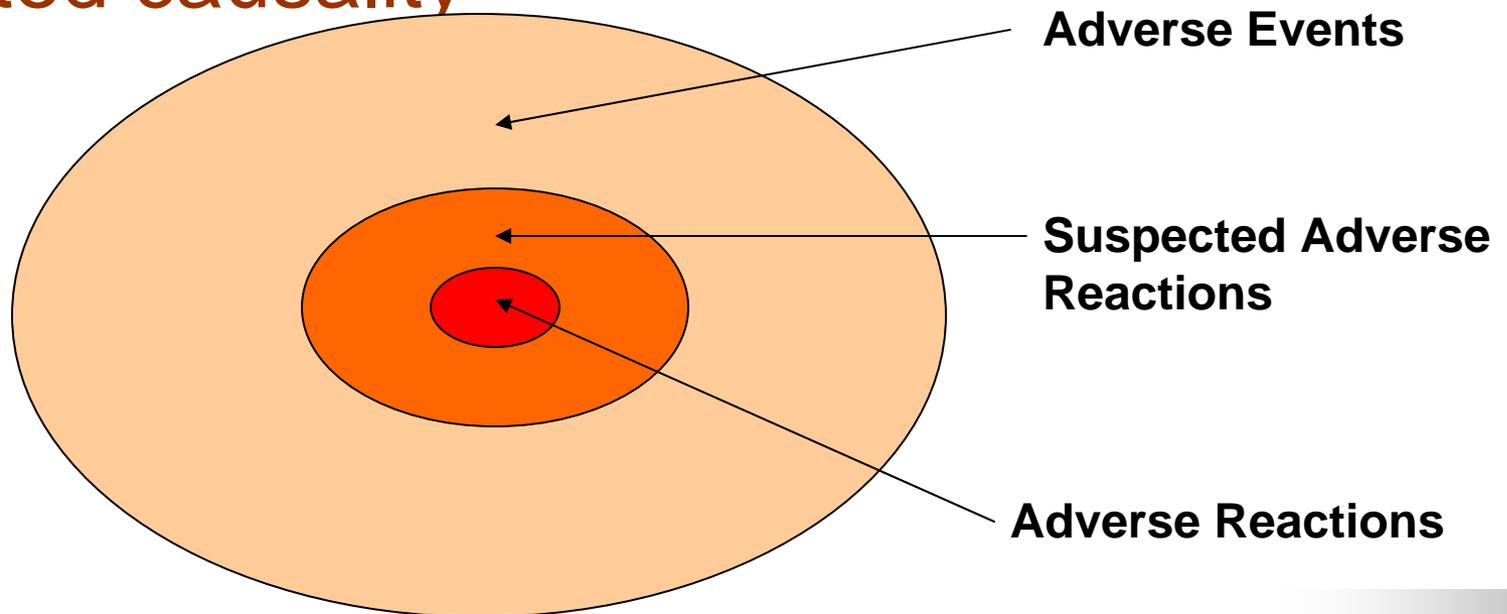
## Unexpected Adverse Event (21 CFR 312.32(a))

- 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

# 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 (New 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 should be reported to FDA no later than 7 days
- Others SUSAR should be reported to FDA no later than 15 days

## ■ ■ ■ 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 you 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
  - Other doses in multiple dose studies

# ■■■ Postmarketing Safety

- Postmarketing studies
  - Nonclinical studies
  - Clinical trials
  - Observational studies
  - Registries
- FDA AERS (Adverse Event Reporting System repository) through MedWatch
- VAERS (Vaccine Adverse Event Reporting System)
- Sentinel Initiative
  - Active surveillance system to query diverse automated healthcare data

## ■ ■ ■ 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
  - Provide relevant/complete AE information
  - Use the most scientific term when reporting
  - Report clinical and lab AEs from unscheduled tests/visits
  - Continue to report SAE once drug approved

# ■ ■ ■ References

- 21 CFR 312.32, 21 CFR 314.80
- New Safety Reporting Rule

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm226358.htm>

- Guidance
- Final rule
- NEJM perspective

(<http://www.nejm.org/doi/pdf/10.1056/NEJMp1103464>)

- FDA /CBER toxicity grading guidance

<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf>

- MedWatch

<http://www.fda.gov/Safety/MedWatch/default.htm>