# Safety Considerations in Clinical Drug Development

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# Learning Objectives

- To understand that protection of subjects should always be the first priority when designing early clinical studies
- To learn key safety considerations in the conduct of phase 1 trials
- To understand the principles of safety monitoring and reporting in clinical trials

# Phase 1 Trials

- Objectives
  - Assess safety and tolerability
  - Characterize dose-limiting adverse reactions
  - Determine maximum dose associated with acceptable safety profile
  - Characterize pharmacokinetic parameters
  - Explore drug metabolism and drug interactions

# Phase 1 Trials

- Subjects
  - Healthy volunteers
    - Less confounding factors
  - Patients: Enrolled when drug is known or expected to be toxic as with cytotoxic agents
    - Confounding factors
    - Difficulty in separating disease-related manifestations from adverse reactions
  - Special populations (e.g., renal or hepatic impairment)

# General Considerations

- Consider evidence from nonclinical studies:
  - Duration and total exposure proposed in humans
  - Characteristics of the test drug (biologic, long half-life)
  - Disease targeted for treatment
  - Populations in which drug will be used (women of child-bearing potential, pediatrics)
  - Route of administration (systemic, topical)

# General Considerations

- Do nonclinical studies provide sufficient safety support for the proposed clinical trials?
  - Choice or relevance of species
  - Potential target organs of toxicity
  - Duration, dose, route of exposure
  - Pharmacokinetic and pharmacodynamic assessments
  - Identifying dose response
  - Safety in special populations (pediatrics, pregnant women)

# General Considerations

- Some toxicities noted in nonclinical studies translate into adverse events noted in humans, while some do not
- Both predictable and unpredictable toxicities can appear in any phase of development or sometimes only post-marketing
- Certain subjective adverse events or hypersensitivity reactions cannot be assessed in nonclinical testing

# Example of Predictable Toxicity: Linezolid

- In nonclinical studies: dose-and time-dependent myelosuppression
- Phase 3 trials: Increased frequency of thrombocytopenia
- At the time of initial approval, labeling included:
  - Precautions: thrombocytopenia
  - Animal Pharmacology: hematopoietic effects noted in animals
- Postmarketing: Myelosuppression (e.g., leukopenia, anemia, pancytopenia, and thrombocytopenia)
  - Labeling updated to reflect a warning regarding myelosuppression

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021130s023s024,021131s021s022,021132s022s023lbl.pdf

# Example of Unpredictable Toxicity

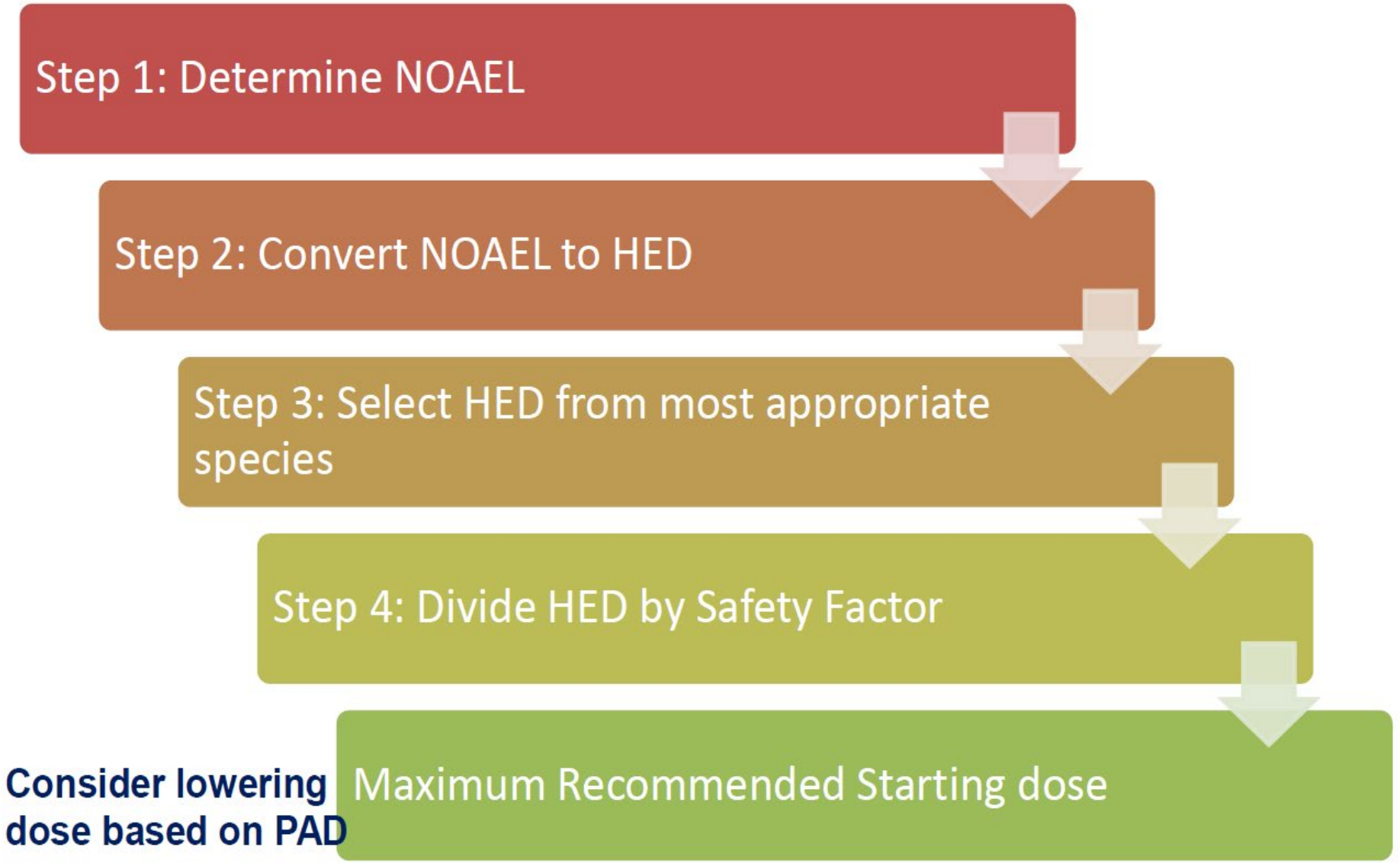
- Two products; both members of beta-lactam class; structure modified to enhance spectrum of activity
  - No unexpected toxicities seen in animals – NOAEL established
  - Proceeded to Phase 1 trials
    - Single-dose well tolerated
    - In multiple-dose trials, subjects developed moderate-severe skin reactions
    - Product development halted

# Maximum Recommended Starting Dose (MRSD)

- Principles in selecting an MRSD
  - avoid toxicity at the initial clinical dose
  - allow reasonably rapid attainment of the trial objectives (tolerability and PK)
- Algorithmic approach based on administered doses and observed toxicities
- Alternate approaches based on animal pharmacokinetics and modeling

# MRSD: Key Concepts

- No Observed Adverse Effect Levels (NOAEL): The highest dose tested in animal species that does not produce a significant increase in adverse effects compared to control group
- Human Equivalent Dose (HED): Conversion factor applied that converts mg/kg dose for each animal species to a mg/kg dose in humans
- Selection of animal species
  - The most sensitive species is chosen (i.e., the species in which the lowest HED can be identified)
  - Some instances, especially with biologics, appropriate animal species used based on *in vitro* binding and functional studies




Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers

# Safety Factor

- The safety factor provides a margin of safety for protection of human subjects receiving the initial clinical dose
- The default safety factor is usually 10
- Allows for variability in extrapolating from animal toxicity studies to studies in humans
  - Uncertainties due to enhanced sensitivity in humans vs. animals
  - Difficulty in detecting certain toxicities in animals (headache, myalgia)
  - Differences in receptor densities or affinities
  - Unexpected toxicities
  - Interspecies difference in absorption, distribution, metabolism, excretion (ADME)

# Increasing Safety Factor

- Novel therapeutic class
- Toxicities:
  - Severe or irreversible
  - Nonmonitorable toxicity- e.g., histopathologic changes in animals, not readily monitored clinically/markers
- Steep dose response curve
  - May indicate a greater risk in humans
- Non-linear pharmacokinetics:
  - Limits the ability to predict dose-related toxicity
- Variable bioavailability
  - Poor bioavailability in test species may underestimate toxicity in humans

# Decreasing Safety Factor

- Members of a well-characterized class
- Toxicities produced by the therapeutic agent are easily monitored, reversible, predictable with relatively shallow dose-response relationship
- If the NOAEL was determined based on toxicity studies of longer duration
  - assuming toxicities are cumulative
  - are not associated with acute peaks in therapeutic concentration, and
  - did not occur early in the repeat dose study

# Example of MRSD calculation

- HEDs derived from rats was ~ 400 mg
- Starting dose of 100 mg was proposed
  - Safety factor of 4
- Rationale provided
  - member of a well-characterized class of drugs
  - toxicity studies in both rats and monkeys were of appreciably longer duration than the proposed clinical trial
  - potential toxicities were readily monitorable and reversible

# Example of MRSD Calculation

- Members of the class had exhibited more toxicity than the parent class from which it was derived
- Bioavailability in animals was low
  - Human bioavailability could be greater, leading to greater than anticipated exposure
- The agreed upon starting dose was lowered to 50 mg (safety factor ~8)

# Safety Considerations

- Are the clinical trial protocols designed appropriately to ensure safety and meet stated objectives?
- Is there information regarding quality of investigational products?
- Are the route and rate of administration appropriate?
  - Slow infusion vs. bolus dose
- What is the mode of action?
  - Is it a novel mechanism?
  - What is the nature and intensity of the effect on the specific target and non-targets? Especially cautious if
    - mode of action involves a target which is connected to multiple signaling pathways
    - effects a biologic cascade or cytokine release

Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products

http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf

# Safety Considerations: Dosing

- Ideally, single subject should receive a single dose, followed by sequential administration within each cohort
- Adequate period of observation between dosing to observe and interpret adverse reactions
- Duration of observation will depend on product properties and PK/PD characteristics.
- Prior knowledge from trials of similar products must also be considered
- When the adverse event is delayed, repeated administration can lead to accumulated toxicity

# Safety Considerations: Dose Escalation

- Is the dose escalation scheme appropriate?
  - Are the dose increments appropriate?
  - Cautious rate of dose escalation if small therapeutic window seen in preclinical data, poor animal models, or concerns about toxicity
- Is the amount of information and follow up before each dose escalation appropriate?
- Are the number of subjects at each dose appropriate?

# Safety Monitoring

- Appropriate monitoring scheme to assess for clinical signs or symptoms of adverse events likely to be associated with the drug
- Duration of clinical observation should be adequate with respect to
  - Sometimes need for prolonged observation of the subject in a hospital setting following initial dosing
  - Follow up should be long enough to preclude the possibility of undetected serious toxicity

# Safety Monitoring

- Frequency of monitoring
  - Need for more frequent observation within the first week following initial dosing
  - More frequent clinic visits for subjects found to have developed adverse events or laboratory abnormalities
- Laboratory test data collected should be appropriate and adequate
  - Do they include routine assessment of all organ systems?
  - Are they sufficiently detailed and complete for organs more likely or known to be affected by the agent?
  - Are there stopping rules for patients whose laboratory test abnormalities reach a certain threshold?

# Safety Stopping Rules

- Rules established for stopping the drug or  enrollment or dose escalation, and termination of the trial
- Protocol changes that are to be implemented when toxicity is observed
- To generate stopping rules, develop
  - a list of acceptable toxicities (i.e., toxicities that, if observed, will not result in changes to subject enrollment and dosing)
  - a procedure for the occurrence of other toxicities (i.e., not on the list of acceptable toxicities)

# Challenge Question 1

**Which of the following is used to calculate the MRSD?**

A. NOAEL

B. LOAEL

C. MTD

# Evaluation of Safety

- Safety evaluation is a central component in all stages of drug development
  - Evolving process
  - Available data depend on the stage of development
- Safety information for approved products is reflected in product labeling (Prescribing Information, PI)
- Up-to-date safety information on the investigational product is found in the Investigator Brochure (IB)

# Sources of Safety Information

- Nonclinical Data [Chemical, Manufacturing, Controls (CMC), In vitro, animal data]
- Clinical Pharmacology studies (PK/PD)
- Early Clinical trial data in HV, patients
- Clinical trial data for the same indication
- Post-marketing experience
- Medical literature
- Safety profile of other drugs in the same class

# Safety Monitoring

**Why is safety monitoring required in all clinical trials?**

To Ensure Subject Safety

# Adverse Events (AE) (21 CFR 312.32(a))

- Any untoward medical occurrence associated with the use of a drug in humans, whether or not, considered drug related
  - sign, symptom, or disease temporally associated with use of a drug
  - abnormal laboratory finding, vital signs, imaging, ECG, etc
  - worsening of the above
  - constellation of the above

# Examples of Adverse Event Ascertainment

- Spontaneously reported or observed symptoms or signs
- Symptoms or signs reported as a result of a probe (e.g., checklist or questionnaire)
- Testing
  - Vital signs
  - Laboratory tests (CBC, liver tests, CPK, renal function tests, pancreatic enzymes)
  - Special safety assessments (e.g., visual, hearing, neurologic exam, ECG)

# AE Severity Grading/Classification Systems

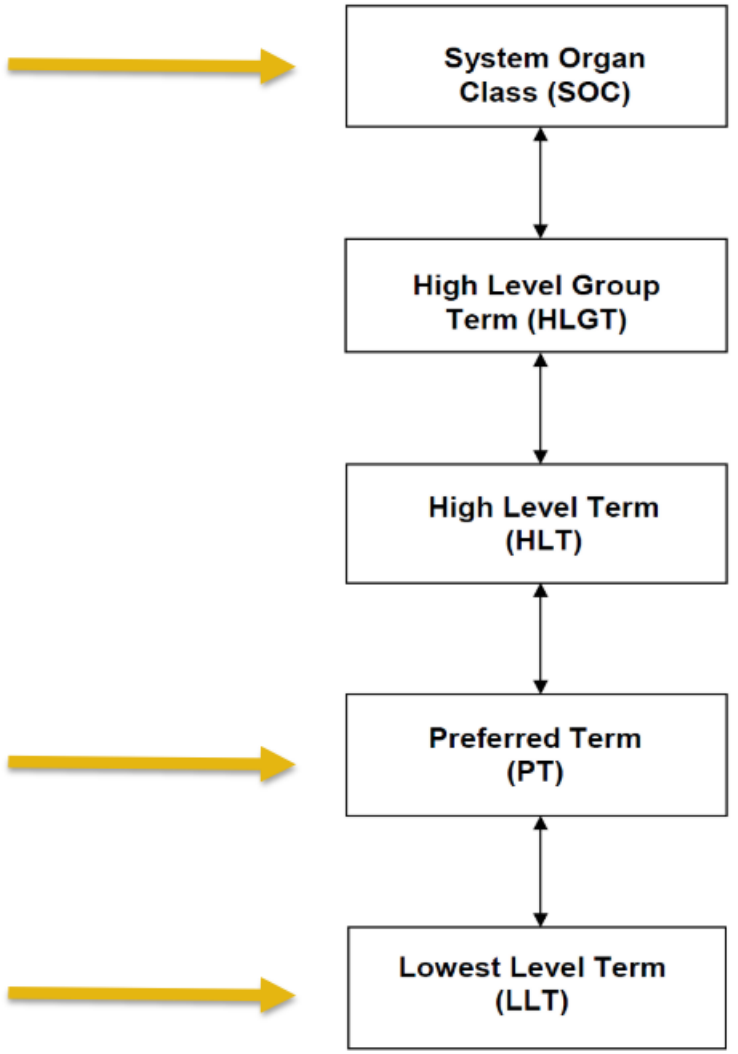
- Provide general guidance on parameters for monitoring safety in clinical trials (optional tool for sponsors and investigators)
- They are specific to:
  - Study population
  - Phase of product development (1-4)
  - Product evaluated (small molecule, therapeutic biologic, device, vaccine)
- Examples: NCI's CTCAE, DAIDS, FDA/CBER Toxicity Grading Scales
- In the classification of AEs, the term "severe" is not the same as "serious"

# 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)

# Structural Hierarchy of MedDRA

**Highest level of terminology, least specific**




**Represents a single specific medical concept**

**AE as reported on CRF "verbatim term"**



https://admin.meddra.org/sites/default/files/guidance/file/intguide_21_0_english.pdf

# 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

# Serious Adverse Event (SAE)
(21 CFR 312.32(a))

Any AE that results in the opinion of the Investigator or Sponsor in:

- Death or is life-threatening
- Hospitalization or prolongation of hospitalization
- Disability
- Congenital anomaly / birth defect
- Important medical events

# Examples of Uncommon SAEs

- Anaphylaxis
- Aplastic anemia
- Blindness
- Deafness
- Bone marrow suppression
- Disseminated Intravascular Coagulation
- Hemolytic anemia
- Liver failure
- Liver necrosis
- Liver transplant
- Renal failure
- Seizure
- Stevens-Johnson Syndrome
- Sudden death
- Torsades de pointes
- Thrombotic Thrombocytopenic Purpura
- Ventricular fibrillation

# Points to Consider for Investigators in Evaluation of SAEs

- Is it a 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?
  - For example, was death also a study endpoint?

# AE Reporting Requirements: Investigator to Sponsor (21 CFR 312.64(b))

- An investigator must immediately report all SAEs, whether or not considered drug related
  - Must include an assessment of whether there is a reasonable possibility that the drug caused the event
- Study endpoints that are SAEs must be reported in accordance with the protocol
  - **Exception:** If the study endpoint is an SAE and there is evidence suggesting a causal relationship between the drug and the event, the investigator must immediately report the event to the sponsor

# Hypothetical Case 1

You are the **investigator** for a clinical trial evaluating whether antihypertensive Drug A is associated with a reduced risk of death, MI, or stroke.  Death is a study endpoint.

An 80-year-old white male died in the trial. The cause of death was anaphylaxis.

Do you have to immediately report this case to the sponsor?

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

**An AE is considered unexpected if it is:**

- Not listed in the Investigator Brochure (IB) or if IB not available or required
- Not consistent with the risk information described in the general investigational plan or elsewhere in the current application
- Not listed at the specificity or severity observed
- Mentioned in IB as anticipated due to pharmacological properties of the drug or occurred with other drugs in this class, but not with the particular drug under investigation

# Hypothetical Case 2

You are the **investigator** for a clinical trial evaluating a new antimalarial Drug B for the treatment of acute uncomplicated malaria.

The Investigator Brochure lists elevated hepatic enzymes.

Would an event of hepatic necrosis in this trial for Drug B be considered an unexpected AE?

# Suspected Adverse Reaction (SAR) (21 CFR 312.32(a))

Any AE for which there is a **reasonable possibility** that the drug caused the AE

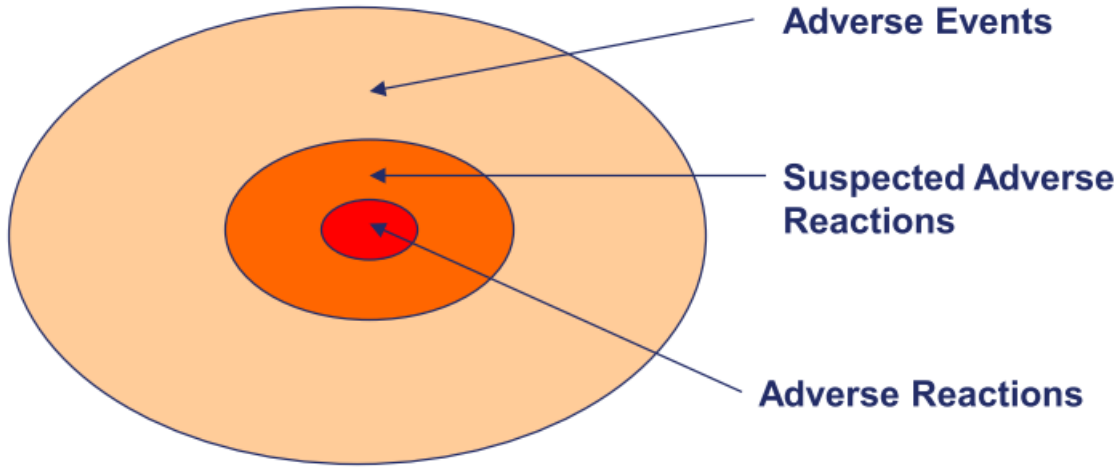
- Reasonable possibility' - evidence to suggest a causal relationship between the drug and the AE
- Examples:
  - A single occurrence of an uncommon event that is known to be strongly associated with drug exposure
  - ≥1 occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the exposed population
  - An aggregate analysis of specific events observed in a trial indicates that those events occur more frequently in the drug treatment group than in a control group

# Suspected Adverse Reaction (SAR)
(21 CFR 312.32(a))

- Determination of an AE as an SAR is difficult, but critical to avoid submission of uninformative IND safety reports
- The **sponsor** should evaluate all available information and decide whether there is a reasonable possibility that the drug caused the AE

# Suspected Adverse Reaction
## (21 CFR 312.32; 21 CFR 314.80)

Suspected Adverse Reaction: an AE with a reasonable possibility of drug related causality (i.e., there is evidence to suggest a causal relationship between the drug and the AE)



# IND Safety Reporting by Sponsor (§ 312.32(c)(1)(i))

- Before submitting an IND safety report, sponsor needs to ensure that the event generally meets 3 criteria [this standard is referred to as a SUSAR]
  - ❑ serious; and
  - ❑ unexpected; and
  - ❑ suspected adverse reaction
- Sponsor is also expected to submit an IND annual report
  - Includes a summary of most frequent adverse events in addition to a summary of SAEs (21 CFR 312.33)

# 15- and 7-Day IND Safety Reporting by Sponsor

- Reporting required for:
  - SUSAR (21 CFR 312.32(c)(1)(i))
  - Findings from other studies (21 CFR 312.32(c)(1)(ii))
  - Findings from animal and in-vitro testing (21 CFR 312.32(c)(1)(iii))
  - Increased rate of occurrence of serious suspected adverse reactions (21 CFR 312.32(c)(1)(iv))
  - SAEs from bioavailability and bioequivalence studies not under IND (21 CFR 320.31)
- Reporting required within 15 days UNLESS:
  - Unexpected fatal or life-threatening suspected adverse reactions THEN reporting required within 7 days of submission (21 CFR 312.32(d)(3))

# Summary

- Overview of safety in Phase 1 trials
  - Important considerations prior to dosing humans
- Relevance of toxicities in non-clinical studies to adverse events in humans
  - Examples of predictable and unpredictable toxicities
- Safe starting dose in humans
  - Examples of MRSD calculation; safety factor
- Ascertainment of safety in clinical trials and monitoring
- Investigators play an integral part in assuring quality safety assessments by reporting to the sponsor
- Sponsor evaluate all available safety information and report to FDA and all participating investigators

# Challenge Question 2

## True or False?

If the adverse event meets all three of the definitions (suspected adverse reaction, serious, and unexpected), it should be submitted as an IND safety report.

# References


- **ICH E8: General considerations for clinical trials.**
  - http://www.ich.org/LOB/media/MEDIA484.pdf
- **Guidance for industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers.**
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078932.pdf
- **Guidance for industry: S7A Safety pharmacology studies for human pharmaceuticals.**
  - http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074959.pdf
- **Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products.**
  - http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002988.pdf
- **M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization
- **21 CFR 312.32, 21 CFR 314.80**

# References (continued)

- **2010 IND Safety Reporting Final Rule**
  - *http://www.gpo.gov/fdsys/pkg/FR-2010-09-29/pdf/2010-24296.pdf*
- **2012 Safety Reporting Requirements for INDs and BA/BE Studies FINAL Guidance**
  - *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.pdf*
- **2021 Sponsor Responsibilities DRAFT guidance**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sponsor-responsibilities-safety-reporting-requirements-and-safety-assessment-ind-and
- **2021 Investigator Responsibilities DRAFT guidance**
  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/investigator-responsibilities-safety-reporting-investigational-drugs-and-devices
- **Toxicity grading (FDA /CBER guidance)**
  - *http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf*
- **IND Annual Reporting:**
  - *https://www.fda.gov/drugs/investigational-new-drug-ind-application/ind-application-reporting-annual-reports*