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 thrombo-cytopenia
- 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

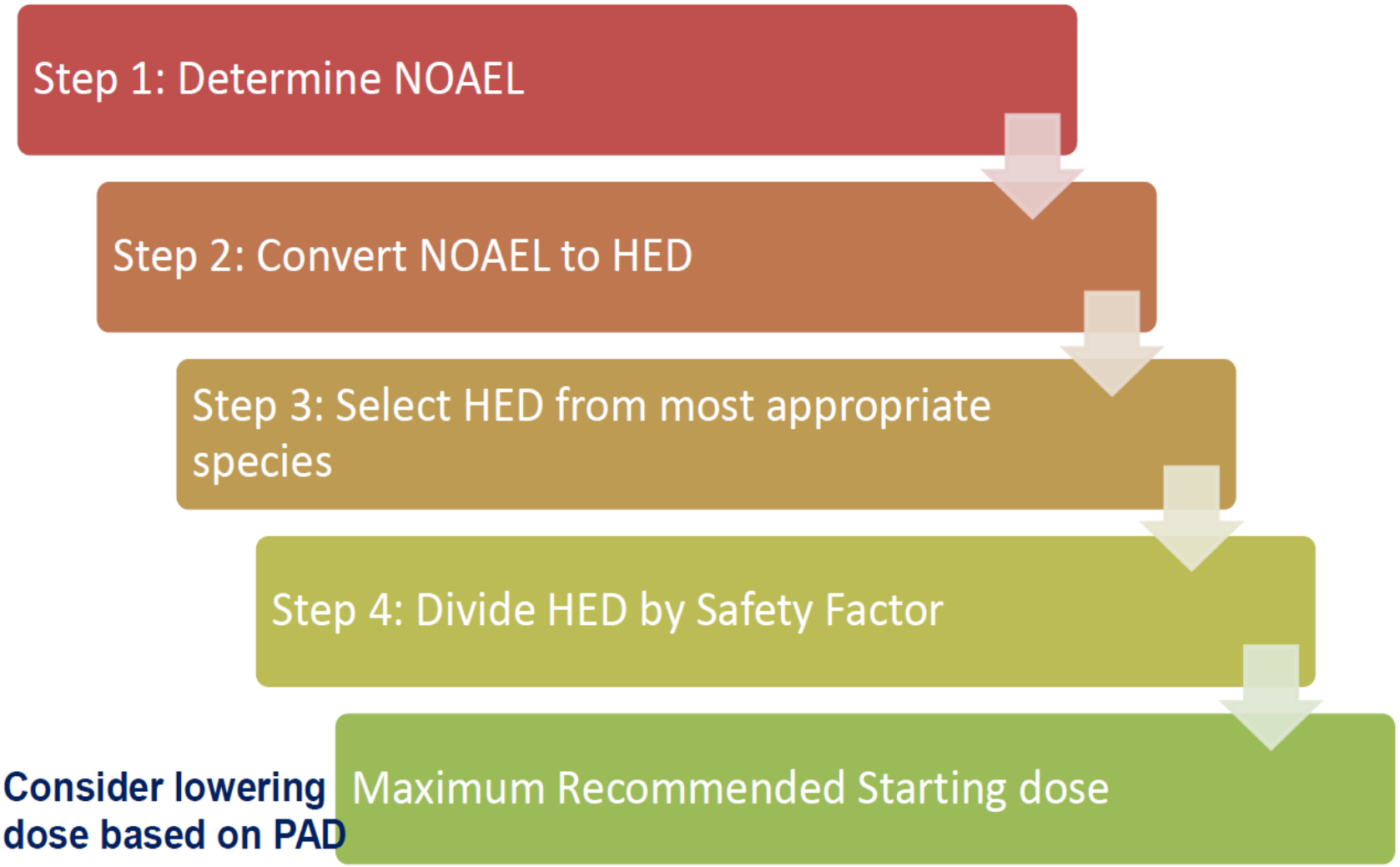
- Two products; both members of beta-lactam class; structure modified to enhance spectrum of activity
  - No unexpected toxicities seen in animals – NOAEL established
  - Proceeded to Phase 1 trials
    - Single-dose well tolerated
    - In multiple-dose trials, subjects developed moderate-severe skin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

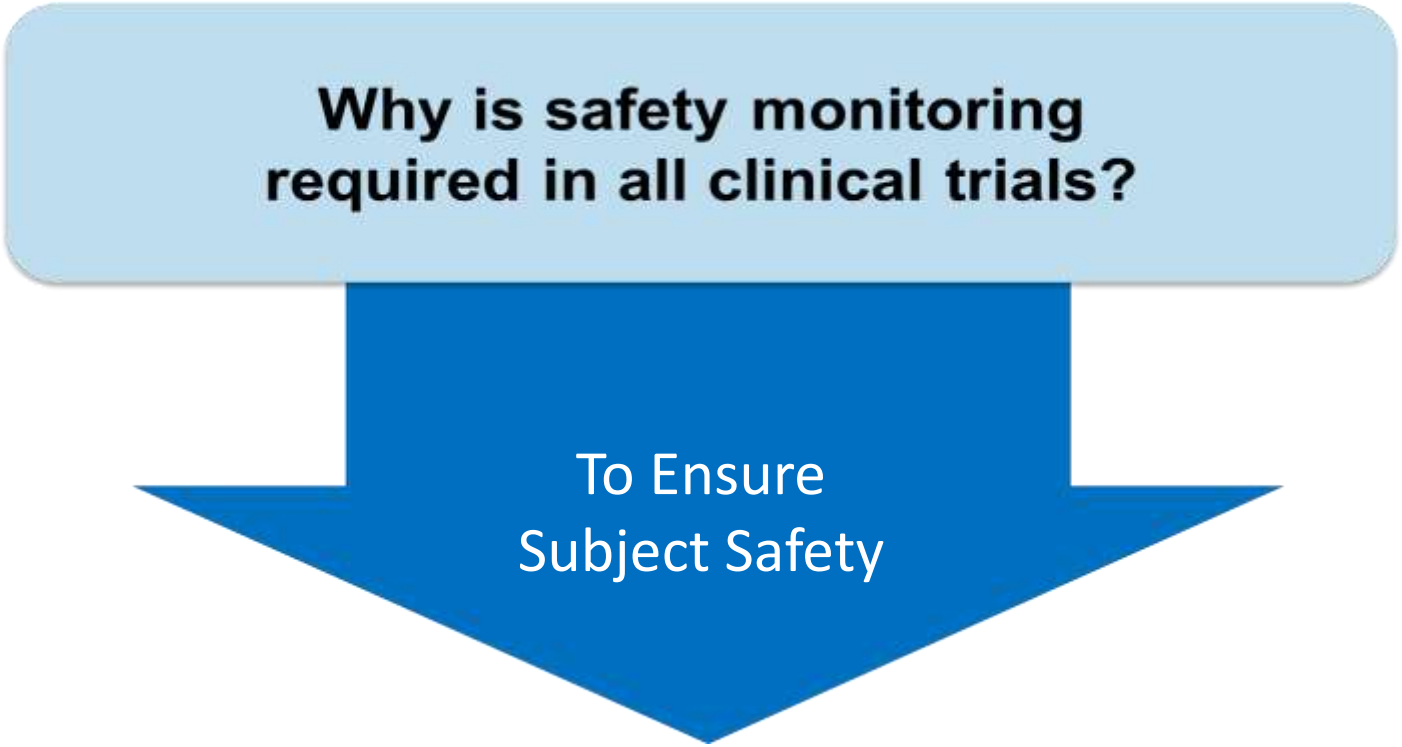
Evaluation of Safety

- 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



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"

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

Discussion: 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. A 75 years old white male patient died in the trial.

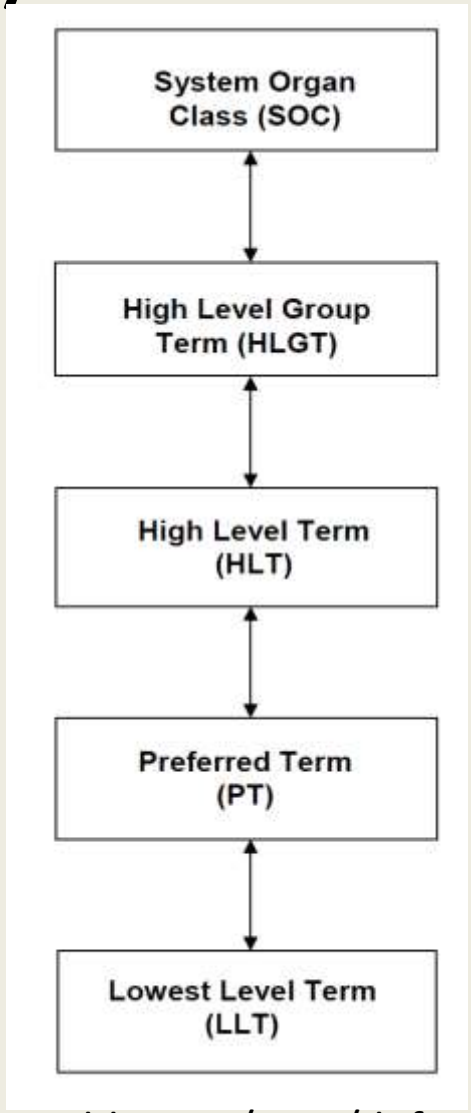
Do you have to immediately report this case to the sponsor?

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)

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

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 listed at the specificity or severity observed
  - Not consistent with the risk information described in the general investigational plan or elsewhere in the current application
  - 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

Discussion: Hypothetical 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 SAEs associated with use of quinolone drugs, including neurotoxicity.

Is a seizure in this trial considered an expected AE?

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

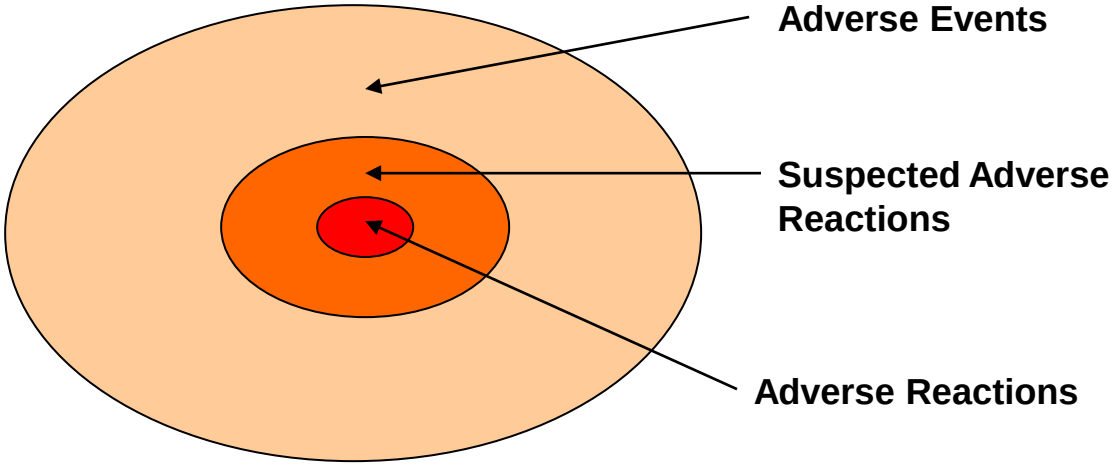
- Any AE for which there is a **reasonable possibility** that the drug caused the AE
  - Reasonable possibility' - evidence to suggest a causal relationship between the drug and the AE
  - Examples:
    - A single occurrence of an uncommon event that is known to be strongly associated with drug exposure
    - ≥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))

Discussion: Hypothetical Case 3

In a trial of a marketed HIV Drug C, an 8 months 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 by the investigator immediately?

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

An investigator would not have to report a case of hepatic failure if the investigator brochure listed elevated hepatic enzymes or hepatitis.

True or False ?

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

References

- 21 CFR 312.32, 21 CFR 314.80
- 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*

- EXTRA/backup slides

Table 1: Conversion of Animal Doses to Human Equivalent Doses Based on Body Surface Area			
Species	To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by k_m	To Convert Animal Dose in mg/kg to HED[a] in mg/kg, Either:	
		Divide Animal Dose By	Multiply Animal Dose By
Human	37	---	---
Child (20 kg)[b]	25	---	---
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates:			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

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

Table 1 Recommended Duration of Repeated-Dose Toxicity Studies to Support the Conduct of Clinical Trials:

Maximum Duration of Clinical Trial	**Recommended Minimum Duration of Repeated-Dose Toxicity Studies to Support Clinical Trials**	
	Rodents	Non-rodents
Up to 2 weeks	2 weeks[a]	2 weeks[a]
Between 2 weeks and 6 months	Same as clinical trial[b]	Same as clinical trial[b]
> 6 months	6 months[b, c]	9 months [b, c, d]