



FDA's Clinical Investigator Course

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Safety Considerations in Phase 1 Trials

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Outline

- General considerations with clinical trials early in development
- Predictable and unpredictable adverse reactions
- Maximum Recommended Starting Dose (MRSD)
- Safety considerations
 - Safety monitoring
 - Stopping rules
 - Safety reporting

■ ■ ■ 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: Used 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 (elderly, pediatrics, 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

■■■ Predictable Toxicity: Example 1

- Linezolid:
 - Antibacterial drug
 - New member of the oxazolidinone class
 - Activity against Gram positive organisms including some resistant organisms
- Myelosuppression was identified as a possible toxicity in non-clinical studies
- Due to potential therapeutic benefit, further clinical development pursued

■■■ Predictable Toxicity: Example 1

- In non-clinical studies, dose-and time-dependent myelosuppression noted
 - bone marrow hypocellularity
 - decreased extramedullary hematopoiesis
 - decreased levels of circulating erythrocytes, leukocytes, and platelets
 - findings similar in juvenile and adult animals

■■■ Predictable Toxicity: Example 1

- Phase 3 trials: Increased frequency of thrombocytopenia noted
- At the time of initial approval the package insert included:
 - Precautions section had information about development of thrombocytopenia
 - Animal Pharmacology section described the hematopoietic effects noted in animals
- Post-marketing: Myelosuppression including leukopenia, anemia, pancytopenia, and thrombocytopenia
 - Package insert was updated to reflect a warning regarding myelosuppression

■ ■ ■ Predictable Toxicity: Example 2

- Member of a known class of drugs that has been associated with hepatotoxicity
- Proposed starting dose was not found to be acceptable
- Studies initiated at smaller dose with evaluation of safety data in each cohort prior to dose escalation
- Hepatotoxicity was noted during dose escalation prior to reaching the targeted dose
- Further development not pursued

■ ■ ■ Predictable Toxicity: Example 3

- Telavancin: Lipoglycopeptide antibacterial; effective against MRSA
- Nonclinical studies: Renal tubular vacuolization, renal tubular degeneration, elevations of BUN/serum creatinine
- Phase 3 trials: Elevation of serum creatinine and renal adverse events more common in telavancin-treated patients
- Package Insert:
 - Warnings and Precautions
 - Animal Toxicology and/or Pharmacology

Unpredictable Toxicity: Example 1

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

■ ■ ■ Unpredictable Toxicity: Example 2

- Subjective adverse events:
 - New class; novel mechanism of action
 - Animal studies
 - Tremors and decreased activity were noted in animals; no other significant findings of nervous system involvement
 - Phase 1 trials conducted outside US
 - Patients had reported sensory symptoms such as hypo/paresthesias, pain, burning; vital sign fluctuations

■ ■ ■ 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



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/m ² , 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



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graph TD; A[STEP 1: Determine NOAEL] --> B[STEP 2: Convert each animal NOAEL to HED]; B --> C[STEP 3: Select HED from most appropriate species]; C --> D[STEP 4: Choose safety factor and divide HED by that factor]; D --> E[Maximum recommended starting dose (MRSD)]; E --> F[STEP 5: Consider lowering dose based on other factors e.g. physiologically active dose (PAD)];
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STEP 1: Determine NOAEL

STEP 2: Convert each animal
NOAEL to HED

STEP 3: Select HED from most appropriate species

STEP 4: Choose safety factor and divide HED by that factor

Maximum recommended starting dose (MRSD)

STEP 5: Consider lowering dose based on other factors
e.g. physiologically active dose (PAD)





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- 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
- 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

■■■ MRSD calculation (1)

- 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

■■■ MRSD calculation (1)

- 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)

■ ■ ■ MRSD calculation (2)

- HED of 1.3 and 1.7 mg/kg (2 animal species)
- 1 mg/kg used for the initial single dose study
- No additional safety factor to determine a safe clinical starting dose
 - PK and toxicities well known with class
 - Toxicity profile consistent with other members of the class
- For higher and multiple-dose studies
 - Close monitoring for toxicity
 - Safety Review Committee to assess safety prior to dose escalation
 - Review of PK and safety data prior to dose escalation



Safety Considerations

- Are the clinical trial protocols designed appropriately to ensure safety and meet stated objectives?
- Is there information regarding quality of investigational products?
 - Formulations should be well characterized with respect to purity, potency, stability, and sterility (if applicable)
- Are the route and rate of administration appropriate?
 - Slow infusion vs. bolus dose

■ ■ ■ Safety Considerations

- 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 Considerations: Duration

- Once initial pharmacokinetics and safety profile has been determined, duration of multiple dose studies should be based on duration of preclinical studies
- Generally, repeat-dose toxicity studies in two species (one non-rodent) for a minimum of two weeks would support a clinical trial up to 2 weeks in duration

Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals M3(R2)

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Multidisciplinary/M3_R2/Step4/M3_R2_Guideline.pdf

■ ■ ■ Safety Monitoring

- Appropriate monitoring scheme to monitor for clinical signs or symptoms of adverse events likely to be associated with the drug
- Stopping rules for administering the drug, stopping enrollment, and stopping dose escalation
- Duration of clinical observation should be adequate with respect to
 - stated objectives and endpoints
 - the anticipated response to product
 - health-related conditions being studied



Safety Monitoring

- Duration of monitoring
 - 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
- 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

■ ■ ■ Safety Monitoring

- 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

- Protocol changes that are to be implemented when toxicity is observed
- To generate stopping rules, one should 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)

■ ■ ■ Safety Stopping Rules

- Options:
 - Halt subject dosing or study enrollment until the toxicity data can be further studied
 - Evaluate additional subjects in a particular dose cohort or in each dose cohort to make the study more sensitive to characterizing adverse events
 - Implementation of smaller dose increases between dose cohorts
 - Exclusion of certain subjects thought to be more at-risk for a particular adverse event

■ ■ ■ Safety Reporting

- Reporting requirements: 21 CFR 312.32(a)
 - Adverse event
 - Life-threatening adverse event or life-threatening suspected adverse reaction
 - Serious adverse event or serious suspected adverse reaction
 - Suspected adverse reaction
 - Unexpected adverse event or unexpected suspected adverse reaction



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
- Safety monitoring, stopping rules, safety reporting



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>
- Guidance for industry and investigators safety reporting requirements for INDs and BA/BE studies
 - <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM227351.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