FDA's Clinical Investigator Course

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Safety Considerations in Phase 1 Trials

Sumathi Nambiar MD MPH

Acting Director
Division of Anti-Infective Products

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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 with respect to:
  - 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 hematopoeisis
  - decreased levels of circulating erythrocytes, leukocytes, and platelets
  - findings similar in juvenile and adult animals

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

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

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

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)

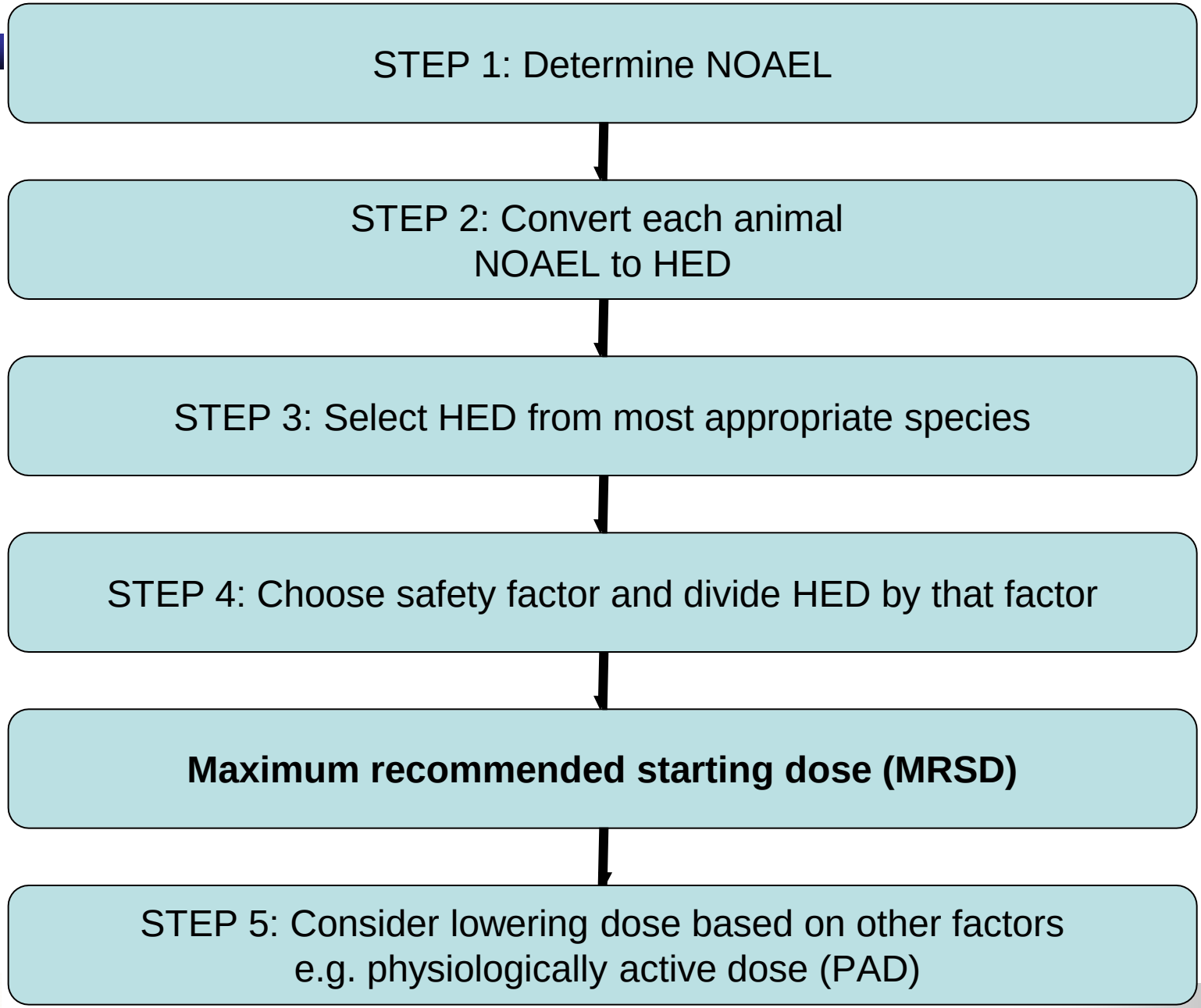
- Principles in selecting an MRSD
  - avoid toxicity at the initial clinical dose
  - allow reasonably rapid attainment of the trial objectives (tolerability and PK)
- Algorithmic approach based on administered doses and observed toxicities
- Alternate approaches based on animal pharmacokinetics and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


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 the 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 the 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

Example of 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

Example of 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)

Example of 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
  - Final Rule for IND Safety Reporting Requirements, 21 CFR 312 and 320; published September 29, 2010
- Definitions: 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 in 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