FDA's Clinical Investigator Course

Cosponsored by

CDER Office of Medical Policy
and
Duke University School of Medicine

U.S. Department of Health and Human Services
Food and Drug Administration

Safety Considerations in Phase 1 Trials

Sumathi Nambiar MD MPH

Deputy Director for Safety
Division of Anti-Infective Products

November 13, 2012

U.S. Department of Health and Human Services
Food and Drug Administration

Outline

- General considerations with clinical trials early in development
- Predictable and unpredictable adverse events
- 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)

Considerations in early human trials

- 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)

Considerations in early human trials

- 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)

Considerations in early human trials

- 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/nda/2000/21130_Zyvox.cfm

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/2010/021130s022lbl.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

http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022110s000lbl.pdf

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)

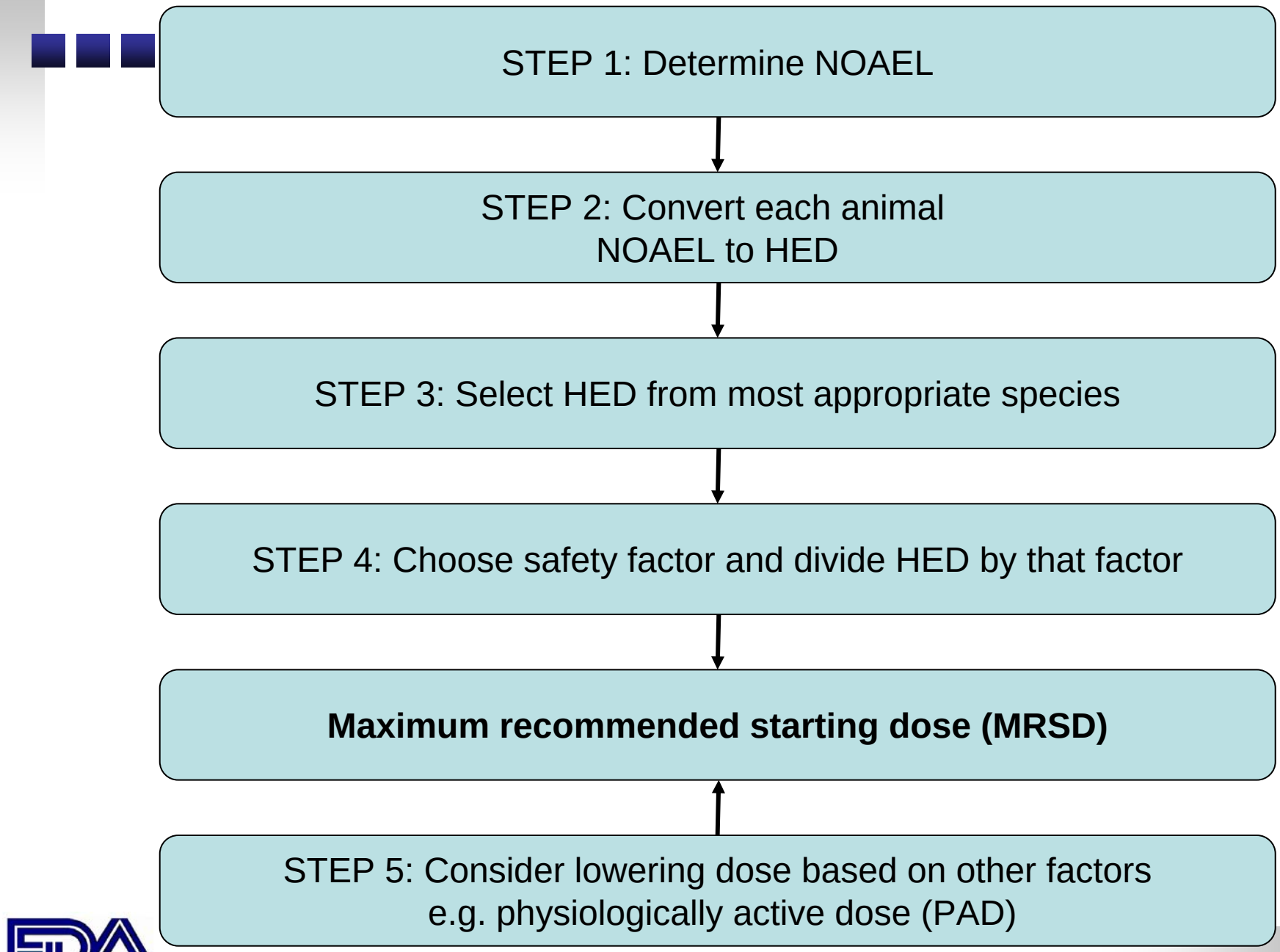
- Principles in selecting an MRSD
  - avoid toxicity at the initial clinical dose
  - allow reasonably rapid attainment of the trial objectives (tolerability and PK)
- Algorithmic approach based on administered doses and observed toxicities
- Alternate approaches based on animal pharmacokinetics and 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
- Drug approval package for Vibativ: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022110s000TOC.cfm
- Drug approval package for Zyvox: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21130_Zyvox.cfm
- 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