U.S. FOOD & DRUG ADMINISTRATION

Safety Considerations in Phase 1 Trials

Joseph Toerner, MD, MPH

Deputy Director for Safety

Division of Anti-Infective Products

Center for Drug Evaluation and Research

FDA Clinical Investigator Course

November 14, 2018

Outline

- General considerations for Phase 1 trials
  - Objectives, types of trials, subjects
- First in Human studies
  - Key considerations
  - Starting dose
  - Safety factor
- Safety monitoring
  - Stopping rules, safety reporting
- Predictable and unpredictable adverse events

General Considerations

- Objectives
  - Assess safety
  - Evaluate pharmacokinetics and pharmacodynamics
  - Explore drug metabolism and drug interactions

- Types of Phase 1 trials
  - Single ascending dose pharmacokinetic trials
  - Multiple ascending dose pharmacokinetic trials
  - Exposure-response studies
  - Drug interactions
  - Bioavailability/Bioequivalence studies

General Considerations

- Phase 1 Subjects
  - Usually healthy volunteers
  - Patients are enrolled when drug is known or expected to have toxicities
    - cytotoxic agents, biological agents
  - Specific populations (elderly, renal or hepatic impairment)

First in Human Trials

Before proceeding with First in Human trials, consider evidence from **non-clinical studies** with respect to:

- Characteristics of the test drug (biologic, long half-life)
- Duration and total exposure proposed in humans
- Disease targeted for treatment
- Populations in which drug will be used
- Route of administration (systemic, topical)

First in Human Trials

Non-clinical animal studies should provide sufficient safety support for the proposed clinical trials

- Choice or relevance of the animal species
- Identifying potential target organs of toxicity
- Duration, dose, route of exposure
- Pharmacokinetic and pharmacodynamic assessments
- Identifying dose response
- Safety in special populations (pediatrics, pregnant women)

First in Human Trials

Questions to Consider:

- Is the proposed starting dose appropriate?
- Is the dose escalation scheme, dose increment, and amount of information before escalation appropriate?
- Are the sample sizes appropriate for each dose escalation?
- What is the quality of the investigational product (Chemistry, Manufacturing, and Controls)
- Are the clinical trial protocols designed appropriately to ensure safety and meet objectives?

First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

- Steps in selecting MRSD:
  - Determination of no observed adverse effect level (NOAEL) in the tested animal species
  - Conversion of NOAELs to human equivalent dose (HED)
  - Selection of the most appropriate animal species
    - In the absence of data on species relevance, the most sensitive species is chosen (i.e. the species in which the lowest HED can be identified)
  - Application of a safety factor

First in Human Trials

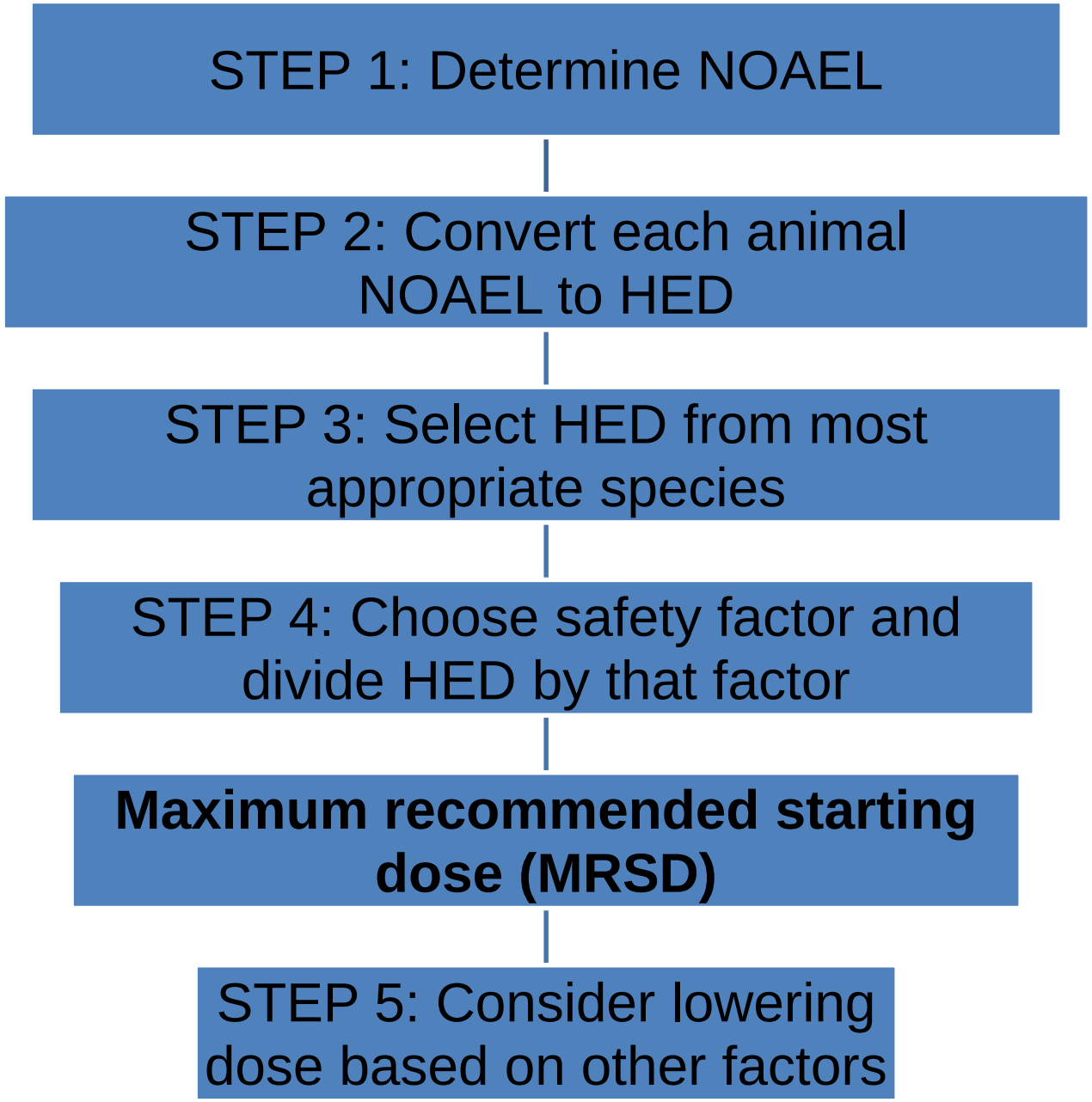
Starting Dose (MRSD)

- Application of the safety factor
  - The default safety factor is usually 10-fold lower NOAEL HED
  - Allows for variability in extrapolating from animal toxicity studies to studies in humans
    - Differences in receptor densities or affinities
    - Interspecies difference in absorption, distribution, metabolism, excretion (ADME)
  - Uncertainties due to enhanced sensitivity in humans vs. animals
  - Difficulty in detecting certain toxicities in animals (headache)
  - Unexpected toxicities

First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

- Increasing the safety factor to greater than 10-fold
  - Novel therapeutic class
  - Severe, irreversible, or toxicities that are not easily monitored
  - Non-linear pharmacokinetics: limits the ability to predict dose-related toxicity
  - Variable bioavailability in animals might underestimate toxicity
  - Sequential enrollment of study subjects
- Decreasing the safety factor to less than 10-fold
  - Members of a well-characterized class
  - Easily monitored, reversible, predictable toxicities
  - NOAEL based on toxicity studies of longer duration


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

First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

- Example 1 of safety factor greater than 10-fold
  - HEDs derived from NOAEL in rats was ~ 400 mg
  - Starting dose of 20 mg was proposed
    - Safety factor of 20
  - Rationale provided
    - More toxicity was observed in animals (doses higher than 400 mg) in comparison to members of the drug class from which it was derived
    - Neurological toxicity: potentially irreversible and difficult to monitor
    - Bioavailability was low in animals – human exposure could be higher

First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

- Example 2 of safety factor less than 10-fold
  - HEDs derived from NOAEL in 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 able to be monitored and reversible

First in Human Trials

Starting Dose (Maximum Recommended Starting Dose MRSD)

- Example 3 of poor study design: lack of sequential enrollment
  - Novel biologic drug intended to treat a serious disease
  - There were animal toxicology findings of concern, starting dose safety factor greater than 10-fold
  - Drug administered simultaneously to healthy volunteers at a clinical trials unit
  - All 6 healthy volunteers became acutely ill and within hours were hospitalized with multi-organ failure, ICU admissions

First in Human Trials

Dose Escalation

- The time course of potential adverse event(s) is unknown
- Cautious incremental rate of dose escalation
  - small therapeutic window seen in preclinical data
  - animal models don't predict human experience
  - toxicity concerns
  - when the adverse event is delayed
- Advancing to multiple ascending dose, duration of multiple dose studies should be based on duration of nonclinical animal toxicology studies

Safety Monitoring in Phase 1 Trials

General Approaches

- 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 in Phase 1 Trials

- 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
  - Follow up should be long enough to preclude the possibility of undetected serious toxicity
  - Sometimes need for prolonged observation of the subject in a hospital setting following initial dosing

Safety Monitoring in Phase 1 Trials

- 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 Monitoring in Phase 1 Trials

Stopping Rules

- Protocol-defined rules to halt study drug administration and/or halt enrollment of additional subjects
  - Based on observed adverse event of greater severity
    - Can be self-evident but toxicity grading scales are helpful!
  - Observe study subject until adverse event has resolved
  - Review safety data in all prior subjects
  - Careful evaluation of all safety data
  - Then resume the study with or without protocol changes
  - FDA informed of every step – may impose “clinical hold”

Example of Predictable Toxicities

- Linezolid:
  - Antibacterial drug
  - New member of the oxazolidinone class
  - Activity against Gram positive organisms including some resistant organisms
- Myelosuppression noted in non-clinical toxicology studies
  - bone marrow hypocellularity
  - decreased extramedullary hematopoeisis
  - decreased levels of circulating erythrocytes, leukocytes, and platelets
- Clinical development pursued because of its potential for therapeutic benefit

Example of Predictable Toxicities

Linezolid:

- Phase 1: careful monitoring of CBC – no concerns
- Phase 3 trials: thrombocytopenia observed in a few patients
- At the time of initial approval the package insert included:
  - PRECAUTIONS section had information about development of thrombocytopenia
  - Pharmacology section: hematopoietic effects noted in animals
- Post-marketing: Myelosuppression including leukopenia, anemia, pancytopenia, as well as thrombocytopenia
  - Package insert updated WARNING regarding myelosuppression

Linezolid label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021130s037,021131s030,021132s035lbl.pdf

Example of Predictable Toxicities

Telavancin: Lipoglycopeptide antibacterial; effective against MRSA

- Non-clinical studies: Renal tubular vacuolization, renal tubular degeneration, elevations of BUN/serum creatinine
- Phase 3 trials: decreased efficacy/mortality in patients with renal impairment; nephrotoxicity more common in telavancin-treated patients
- Package Insert:
  - Boxed Warning, Warnings and Precautions
  - Animal Toxicology and/or Pharmacology

Telavancin label: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022110s012lbl.pdf

Example of Predictable Toxicities

Hypothetical example of Drug A

- Member of a known class of drugs that has been associated with hepatotoxicity
- Studies initiated at smaller dose (MSRD greater than 10-fold NOAEL HED) with evaluation of safety data in each cohort prior to dose escalation
- Hepatotoxicity was noted during dose escalation in the second dose cohort prior to reaching the targeted dose
- Further development not pursued

Example of Unpredictable Toxicities

Hypothetical example of Drug B

- Member of a drug class with the FDA-approved drugs considered to be well-characterized: safe and effective
- New drug B: structure modified to enhance spectrum of activity
  - No unusual toxicities seen in animal studies: NOAEL established
  - Proceeded to Phase 1 trials
    - Single-dose well tolerated
    - In multiple-dose Phase 1 trials, subjects developed moderate-severe skin reactions: stopping rule met! Hypersensitivity reactions
    - Product development halted

Safety Reporting

- Reporting requirements
  - 21 CFR 312.32: “IND Safety Reporting”
- Definitions: 21 CFR 312.32(a)
  - Adverse event: any untoward medical occurrence
  - 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 of Phase 1 Trials

- Overview of safety in phase 1 trials
  - Important considerations prior to dosing in humans
- Safe starting dose in humans
  - Examples of MRSD calculation; safety factor
- Safety monitoring, stopping rules, safety reporting
- Relevance of toxicities in non-clinical studies to adverse events in humans
  - Examples of predictable and unpredictable toxicities

References

- ICH E8: General considerations for clinical trials.
  - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073132.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
- Guidance for industry: Toxicity grading scale for healthy volunteers
  - https://www.fda.gov/downloads/BiologicsBloodVaccines/ucm091977


FDA
U.S. FOOD & DRUG
ADMINISTRATION