Notice: Archived Document

The content in this document is provided on the FDA’s website for reference purposes only. It was current when produced, but is no longer maintained and may be outdated.
FDA’s Clinical Investigator Course

Cosponsored by

FDA’s Office of Critical Path Programs (OCPP)
and
The Clinical Trials Transformation Initiative (CTTI)
Safety Considerations in Phase 1 Trials

Sumathi Nambiar MD MPH
Deputy Director for Safety
Division of Anti-Infective Products

November 8, 2011
Outline

• General considerations
  – Objectives, types of trials, subjects
• Predictable and unpredictable adverse events
• First in Human studies
  – Key considerations
  – Starting dose
  – Safety factor
• Safety monitoring
  – Stopping rules, safety reporting
General Considerations

• Objectives
  – Assess safety
  – Evaluate pharmacokinetics and pharmacodynamics
  – Explore drug metabolism and drug interactions

• Types of trials
  – Single and multiple dose pharmacokinetic trials
  – Exposure-response studies
  – Drug interactions
  – Bioavailability/Bioequivalence studies
General Considerations

- Subjects
  - Healthy volunteers
  - Patients: Used when drug is known or expected to be toxic
    - cytotoxic agents, biological agents
  - Special populations (elderly, pediatrics, renal or hepatic impairment)
General Considerations

- Before proceeding with First in Human trials, consider evidence from non-clinical 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)
Initial Human Studies

• Do animal studies provide sufficient safety support for the proposed clinical trials?
  – Choice or relevance of 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)
Adverse Events

- Both predictable and unpredictable toxicities can appear in any phase of development or sometimes only post-marketing
- Some toxicities noted in nonclinical studies translate into adverse events noted in humans, while some do not
- Certain subjective adverse events or hypersensitivity reactions cannot be assessed in nonclinical testing
Examples of predictable and unpredictable adverse events in humans based on toxicities in non-clinical studies
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

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
- Non-clinical 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
First in Human Studies: Questions to Consider

- Are the clinical trial protocols designed appropriately to ensure safety and meet objectives?
- Is the proposed starting dose appropriate?
  - Maximum recommended starting dose
- Is the dose escalation scheme appropriate?
- Is the dose increment for escalation appropriate?
First in Human Studies: Questions to Consider

• Is the amount of information and follow up before each escalation appropriate?
• Are the number of subjects at each dose appropriate?
• Is there information regarding quality of investigational products?
  – Formulations should be well characterized with respect to purity, potency, stability, and sterility (if applicable)
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
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
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)
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 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

- **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
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
Dose Escalation

- For first in human studies, the time course of potential adverse event(s) is unknown
- Cautious rate of dose escalation if small therapeutic window seen in preclinical data, poor animal models, or concerns about toxicity
- When the adverse event is delayed, repeated administration can lead to accumulated toxicity
- Once initial pharmacokinetics and safety profile has been determined, duration of multiple dose studies should be based on duration of preclinical studies
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](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.


- Drug approval package for Vibativ: [http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022110s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/022110s000TOC.cfm)