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 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 hematopoiesis
  - 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

http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022407s000,022110s003lbl.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

<table>
<thead>
<tr>
<th>Species</th>
<th>To Convert Animal Dose in mg/kg to Dose in mg/m², Multiply by $k_m$</th>
<th>To Convert Animal Dose in mg/kg to HED(a) in mg/kg, Either:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Divide Animal Dose By</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Multiply Animal Dose By</td>
</tr>
<tr>
<td>Human</td>
<td>37</td>
<td>---</td>
</tr>
<tr>
<td>Child (20 kg)(^b)</td>
<td>25</td>
<td>---</td>
</tr>
<tr>
<td>Mouse</td>
<td>3</td>
<td>12.3</td>
</tr>
<tr>
<td>Hamster</td>
<td>5</td>
<td>7.4</td>
</tr>
<tr>
<td>Rat</td>
<td>6</td>
<td>6.2</td>
</tr>
<tr>
<td>Ferret</td>
<td>7</td>
<td>5.3</td>
</tr>
<tr>
<td>Guinea pig</td>
<td>8</td>
<td>4.6</td>
</tr>
<tr>
<td>Rabbit</td>
<td>12</td>
<td>3.1</td>
</tr>
<tr>
<td>Dog</td>
<td>20</td>
<td>1.8</td>
</tr>
<tr>
<td>Primates:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monkeys(^c)</td>
<td>12</td>
<td>3.1</td>
</tr>
<tr>
<td>Marmoset</td>
<td>6</td>
<td>6.2</td>
</tr>
<tr>
<td>Squirrel monkey</td>
<td>7</td>
<td>5.3</td>
</tr>
<tr>
<td>Baboon</td>
<td>20</td>
<td>1.8</td>
</tr>
<tr>
<td>Micro-pig</td>
<td>27</td>
<td>1.4</td>
</tr>
<tr>
<td>Mini-pig</td>
<td>35</td>
<td>1.1</td>
</tr>
</tbody>
</table>

\(^a\) HED: Human Equivalent Dose

\(^b\) Assuming a body surface area of 1.7 m²

\(^c\) Includes rhesus, cynomolgus, and squirrel

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**Guidance for Industry: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers**
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
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)

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.

- Guidance for industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers.


- Guidance for industry and investigators safety reporting requirements for INDs and BA/BE studies

- Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products;