Approaches for Dose Translation Under the Animal Rule Paradigm: Regulatory Experience

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• This presentation reflects the views of the presenter and not the position or policies of the Food and Drug Administration.
Outline

• Animal Rule requirements
• Role of clinical pharmacology in development of drugs under the Animal Rule
• Examples of human dose selection under the Animal Rule
• Challenges
• Conclusions
The FDA Animal Rule Requirements

- There is a reasonably well-understood pathophysiological mechanism of the toxicity of the (chemical, biological, radiological, or nuclear) substance and its prevention or substantial reduction by the product;
- The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
- The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
- **The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.**
The Animal Rule: Role of Clinical Pharmacology

- Determining Fully Effective Animal Dose
- Translation to Effective Human Dose
- Specific Populations Intrinsic and Extrinsic Factors
Fully Effective Dose in Animals

FDA Animal Rule Guidance
Selection of an Effective Human Dose

**Data Elements**
- PK in healthy animals and humans
  - Address differences in ADME between species
- PK in affected animals (and humans, if available)
  - Healthy vs. diseased comparison
- PD/efficacy in diseased animals (and humans, if available)
  - Dose ranging
  - E/R analyses

**Human Dose Selection**
- Identify the fully effective dose in animals
- Identify human dose that achieves exposures that exceed those with the fully effective dose in animals
  - Specific populations
Factors that can Affect Selection of an Effective Human Dose

• Target of the investigational drug or biologic
  • Effect of the drug/biologic is mediated through its action on the etiologic or challenge agent (e.g., antimicrobials, detoxifiers) rather than the host
    – Target concentrations and exposures from in vitro studies
    – PK/PD parameters from animal models (e.g., for anti-infectives)

• Prior human experience in related indications
  • New molecular entity or not?
  • Existing E/R data from similar indications
Factors that can Affect Selection of an Effective Human Dose

• Use of a biomarker shown to correlate with the desired clinical outcome, either **reduction in mortality or major morbidity**
  
  • Determine drug doses for humans that would result in biomarker levels in the desired range based on the biomarker levels associated with efficacy in the adequate and well-controlled animal studies
Factors that can Affect Selection of an Effective Human Dose

• Assume that the E/R relationship in humans will be similar to the E/R relationship in animals
  • Derive the human dose by comparing relevant exposure parameters (e.g., AUC, Cmax, Cmin, Css) between humans and animals
  • This situation carries the highest level of uncertainty and should be used only when there is no better alternative.
Assumption that the E/R relationship in humans will be similar to animals

- Given the uncertainty, the goal is to minimize the possibility of sub-therapeutic exposures (ideally, low outliers in humans exposure should be greater than those associated with efficacy in animals)
Pharmacokinetic/Pharmacodynamic Approach

Fully Effective Animal Dose

Dose/Exposure

Survival

Desired PD effect

Desired Human dose

Dose/Exposure

Survival
Effective Human Dose: Specific Population

Range of AUC Values in Surviving Animals

Body Weight (kg)

Dose 1

Dose 2

Dose 3
Selection of an Effective Human Dose Summary

1. Identify fully effective dose (FED) in animals
2. Animal PK
3. Human PK
4. Identify dose/regimen for humans yielding exposures exceeding those with the FED in animals
5. Specific Populations Intrinsic/Extrinsic Factors
Dose Selection Examples

1 Pyridostigmine Br
2 Hydroxocobalamin
3, 4 Levofoxacin
5 Raxibacumab
3 Ciprofoxacin
4 Anthrax human globulin
6 Filgrastim
3 Moxifloxacin
6 Pegfilgrastim
4 Biothrax
4 Obiltoxaximab


1 Nerve agent poisoning
2 Cyanide poisoning
3 Plague
4 Anthrax
5 Botulism
6 HS-ARS

http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMRegulatoryScience/ucm391604.htm
<table>
<thead>
<tr>
<th><strong>Filgrastim</strong></th>
<th><strong>Pegfilgrastim</strong></th>
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<tr>
<td>• Initial approval 1999</td>
<td>• Initial approval 2002</td>
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<td>• One dose 10 µg/kg QD was evaluated in pivotal efficacy study.</td>
<td>• One dose 300 µg/kg (given a week apart) was evaluated in pivotal efficacy study.</td>
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<td>• SR = 79% [TRT] vs. 41% [PL]</td>
<td>• SR = 91.3% [TRT] vs. 47.8% [PL]</td>
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<td>• Dose translation: PK approach</td>
<td>• Dose translation: PK/PD approach</td>
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<td>• Human Dose: 10 µg/kg SC 2-weeks apart</td>
<td>• Human dose: 6 mg SC one week apart (&gt; 45 kg)</td>
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<td>• Pediatric Dose: same as adult dose</td>
<td>• Pediatric Dose: PK matching to adult exposure using allometric scaling down to birth</td>
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• Monoclonal antibody
  – Binds free protective antigen (PA) of *B. anthracis*
  – Inhibits the binding of PA to its cellular receptors, preventing the intracellular entry of the anthrax factors

• Indications:
  – Treatment of inhalational anthrax due to *B. anthracis* in combination with appropriate antibacterial drugs
  – Prophylaxis of inhalational anthrax due to *B. anthracis* when alternative therapies are not available or appropriate

• Dose for Adult Patients:
  – A single dose of 16 mg/kg administered intravenously over 90 minutes
Oblitoxaximab - Efficacy Data

Monkeys

Oblitoxaximab Clinical Pharmacology Review
Obl toxaximab: Dose-Response

Obl toxaximab Clinical Pharmacology Review
Obiltoxaximab: Exposure Comparison

Healthy Human 16 mg/kg vs Monkeys 14.5 mg/kg

Red: Healthy Humans 16 mg/kg
Blue: Infected Monkeys 14.5 mg/kg

Time, day
Obiltoxaximab: Exposure Comparison

Obiltoximab Clinical Pharmacology Review
Raxibacumab - Pediatric Dosing

AUC (ug·day/mL) vs. WT

- 26971 ug·day/mL (Max in adults)
- 22478 ug·day/mL (95 Percentile in adults)
- 12068 ug·day/mL (5 Percentile in adults)
- 8720 ug·day/mL (Min in adults)
- 2499 ug·day/mL (Min in surviving monkey)
Challenges

• Limited data
  – Recommending human dosing regimens with limited animal and human experience
  – Challenges surrounding capture of PK and PD assessments
  – Estimating variability in diseased humans

• Managing uncertainty
  – Balancing medical need with uncertainty
  – How do we weigh uncertainty?
Conclusions

• Clinical pharmacology plays a vital role in development of drugs under the Animal Rule.

• Human dose selection under the Animal Rule involves unique approaches and leveraging of multiple data elements and sources of information to:
  – Identify the fully effective dose in animals
  – Evaluate potential dose regimens in humans, including specific populations
  – Extrapolate animal efficacy to humans

• Human dose selection under the Animal Rule is a complex process; early and frequent interactions with the FDA are encouraged.
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