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

Islam R. Younis, PhD
Team Leader
Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
03/23/2018

Disclaimer

- 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*.**

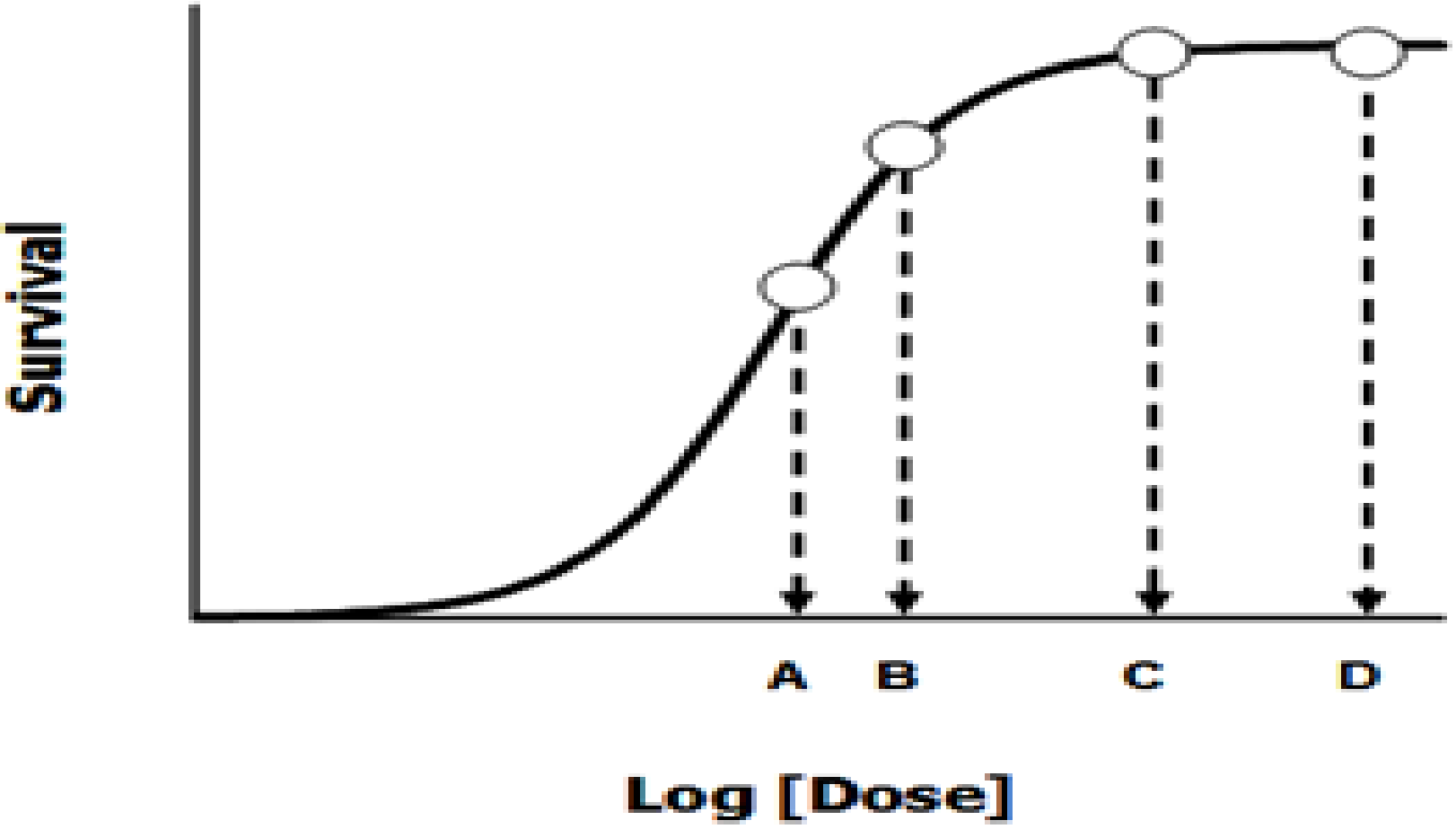
The Animal Rule: Role of Clinical Pharmacology

Determining Fully Effective Animal Dose

Translation to Effective Human Dose

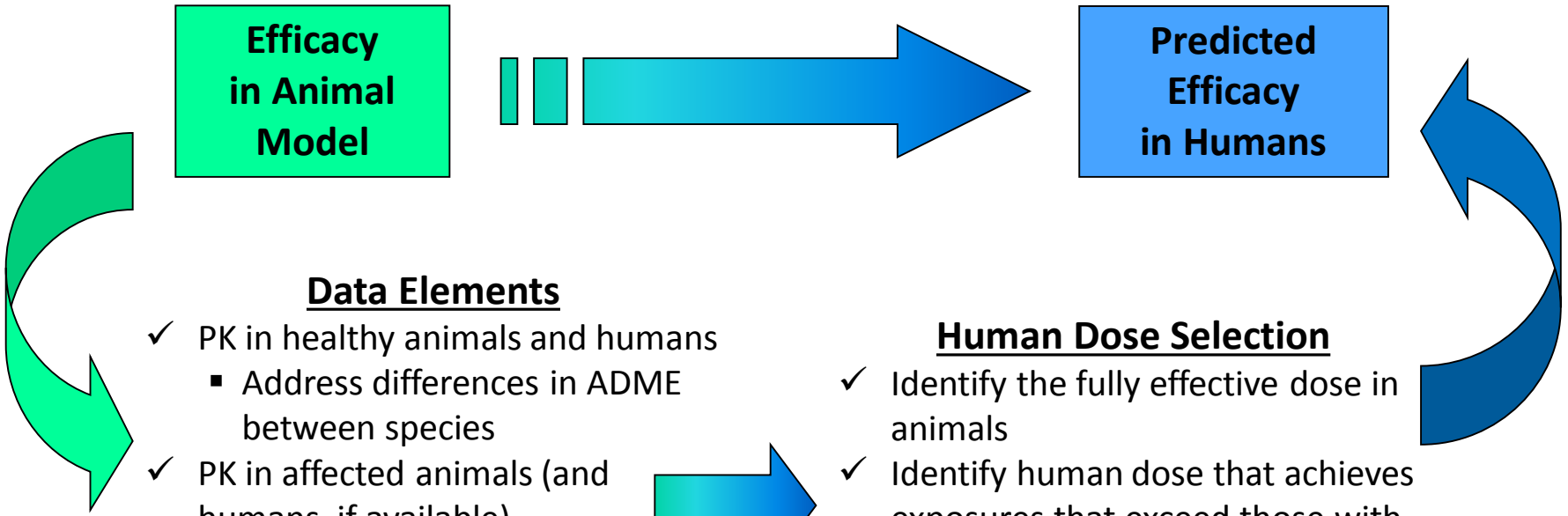
Specific Populations Intrinsic and Extrinsic Factors

Fully Effective Dose in Animals



FDA Animal Rule Guidance

Selection of an Effective Human Dose



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 (eg 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

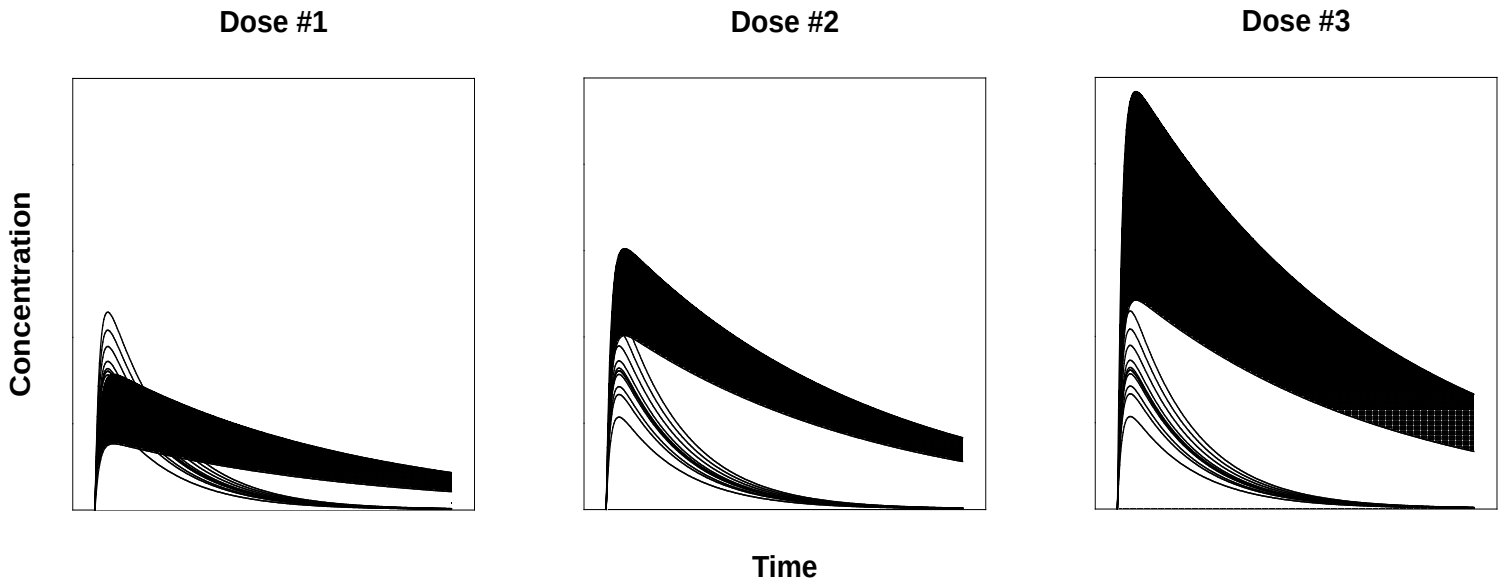
- Use of a biomarker shown to correlate with the desired clinical outcome, either **reduction in mortality or major morbidity**
    - Determine drug doses for humans that would result in biomarker levels in the desired range based on the biomarker levels associated with efficacy in the adequate and well-controlled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

Factors that can Affect Selection of an Effective Human Dose

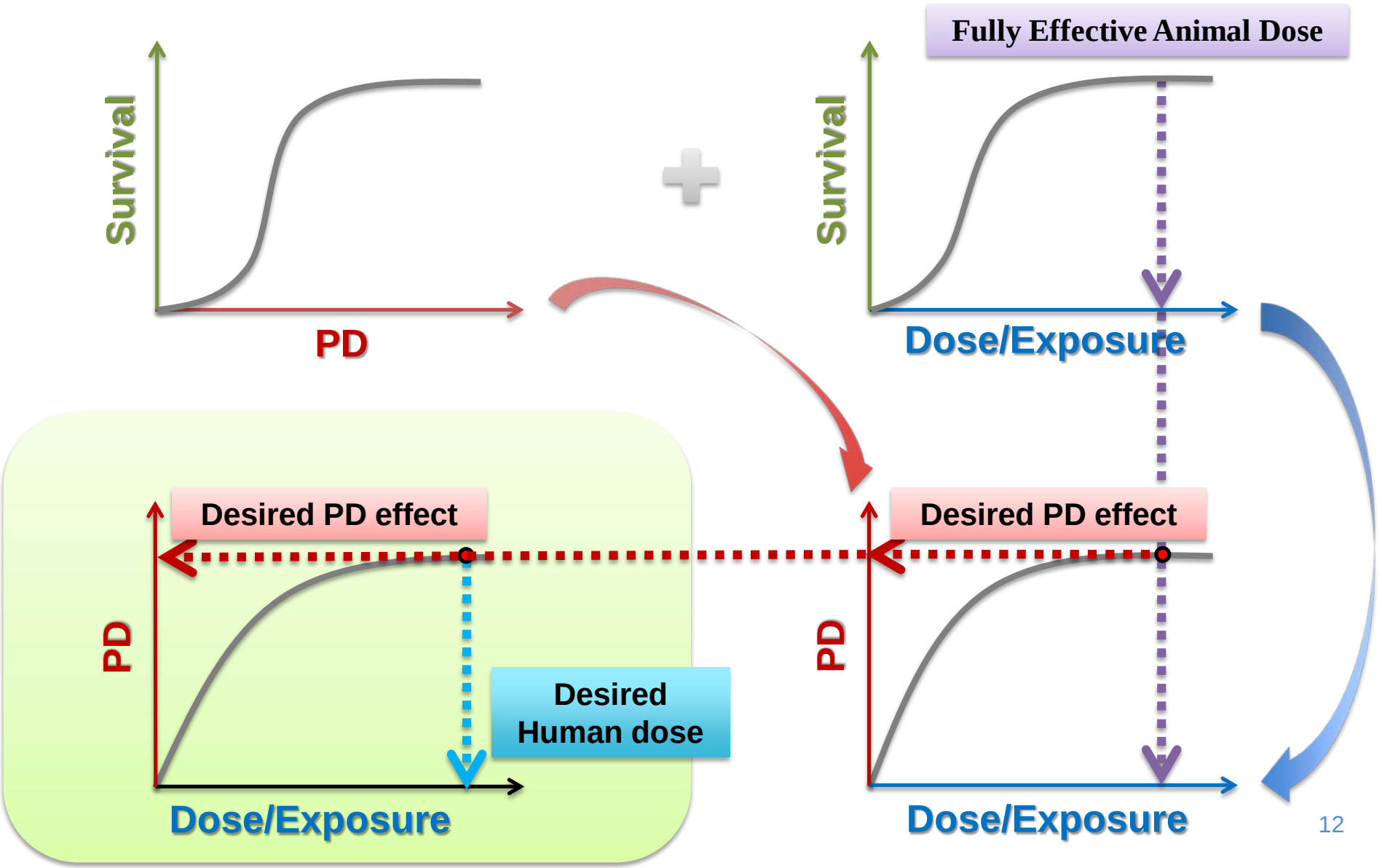
- Assume that the E/R relationship in humans will be similar to the E/R relationship in animals
  - Derive the human dose by comparing relevant exposure parameters (e.g., AUC, Cmax, Cmin, Css) between humans and animals
  - ***This situation carries the highest level of uncertainty and should be used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

Pharmacokinetic Approach

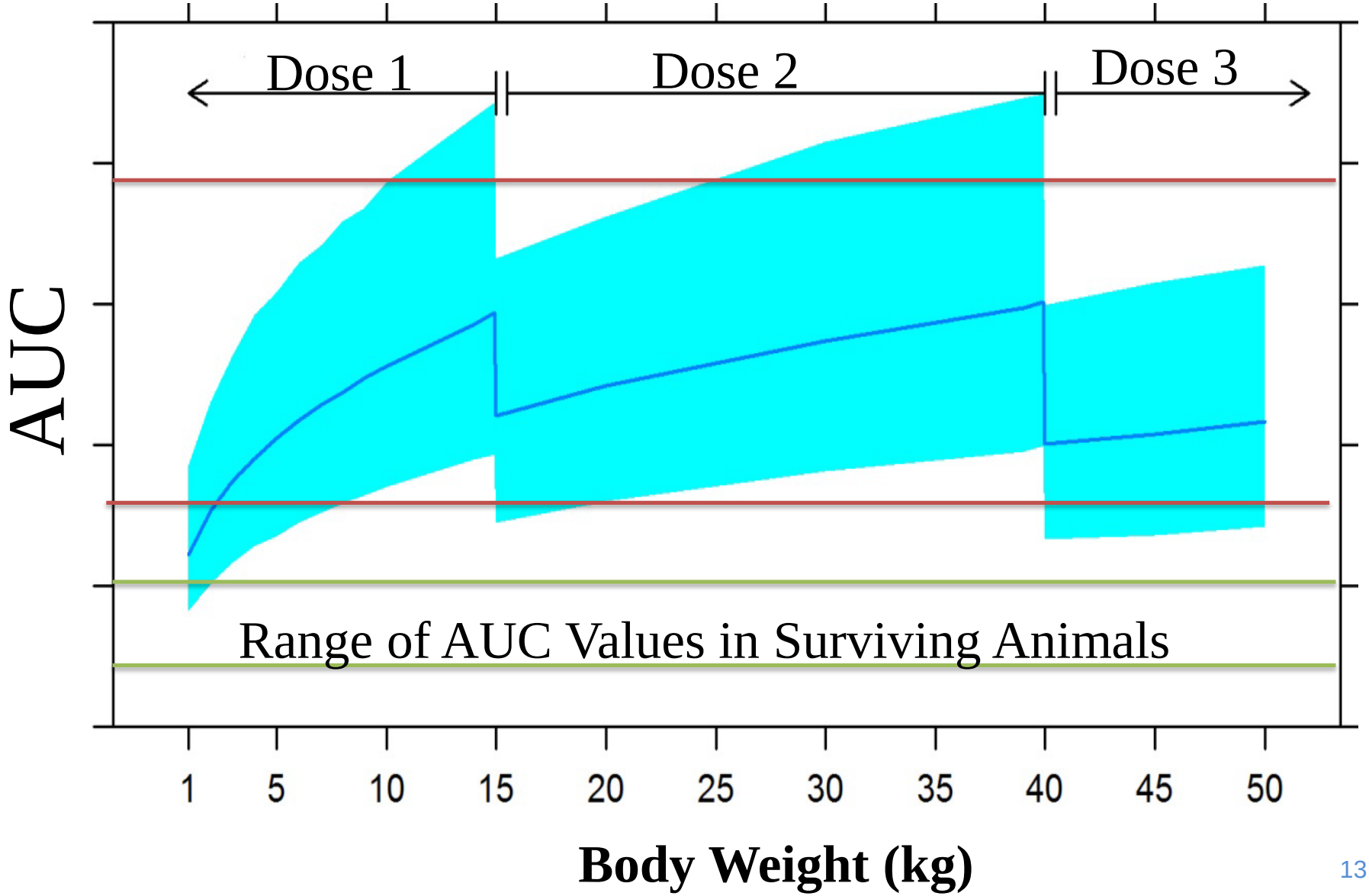
- Assumption that the E/R relationship in humans will be similar to animals
  - Given the uncertainty, the goal is to minimize the possibility of sub-therapeutic exposures (ideally, low outliers in humans exposure should be greater than those associated with efficacy in animals)



Pharmacokinetic/Pharmacodynamic Approach



Effective Human Dose: Specific Population



Selection of an Effective Human Dose Summary

Identify fully effective dose (FED) in animals

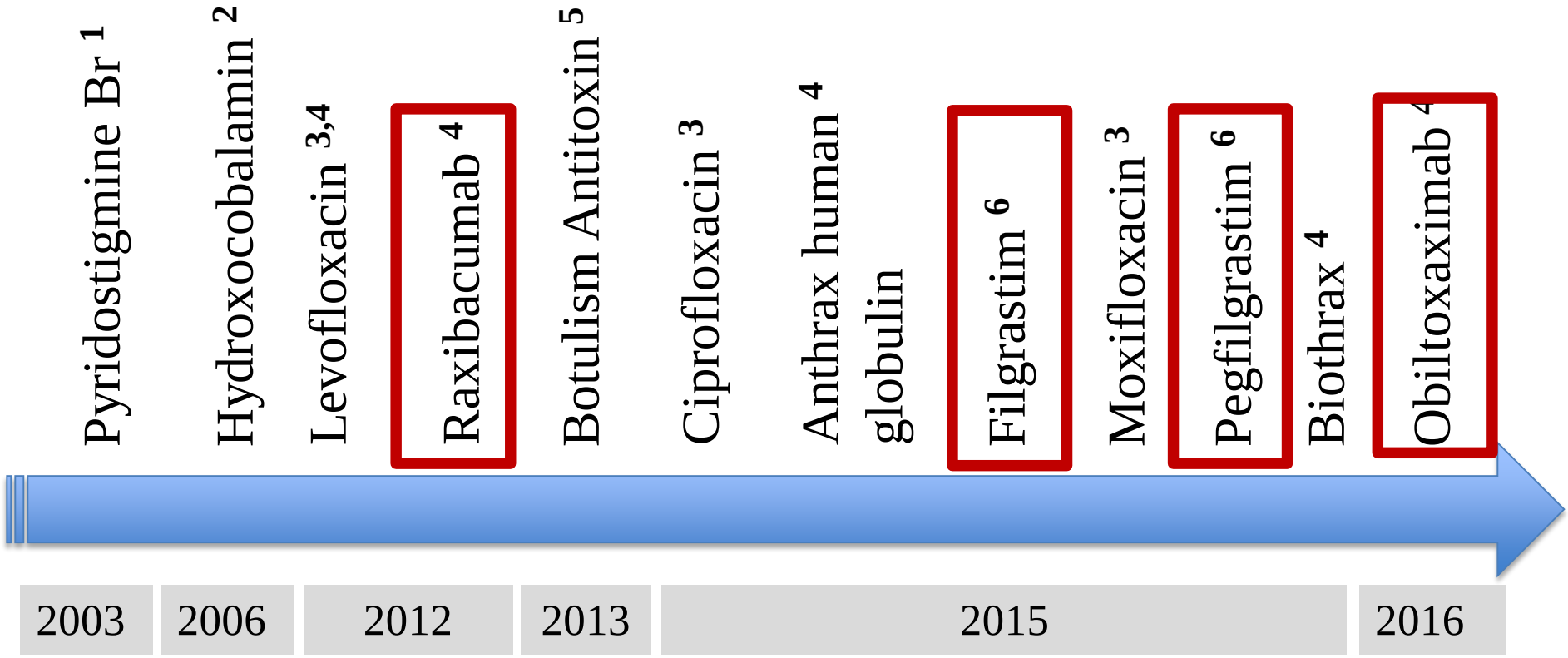
Animal PK

Human PK

Identify dose/regimen for humans yielding exposures exceeding those with the FED in animals

Specific Populations Intrinsic/Extrinsic Factors

Dose Selection Examples



[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

HS-ARS

Filgrastim

- Initial approval 1999
- One dose 10 µg/kg QD was evaluated in pivotal efficacy study.
- SR = 79% [TRT] vs. 41% [PL]
- Dose translation: PK approach
- Human Dose: 10 µg/kg SC 2-weeks apart
- Pediatric Dose: same as adult dose

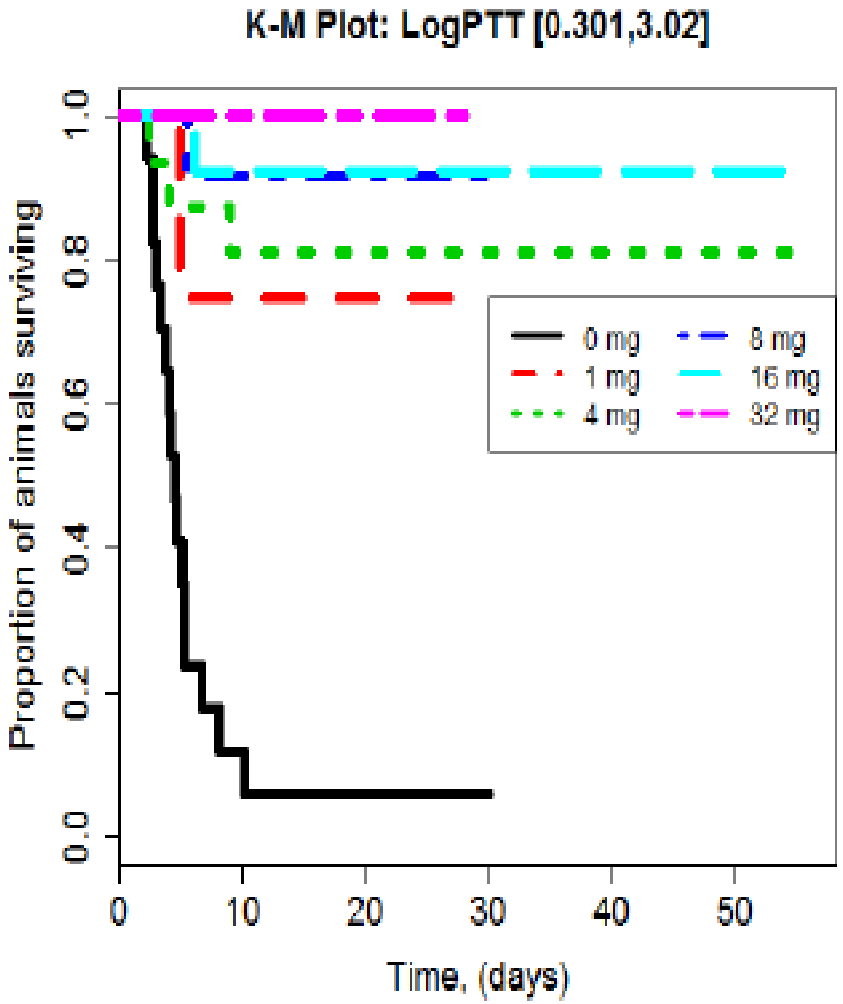
Pegfilgrastim

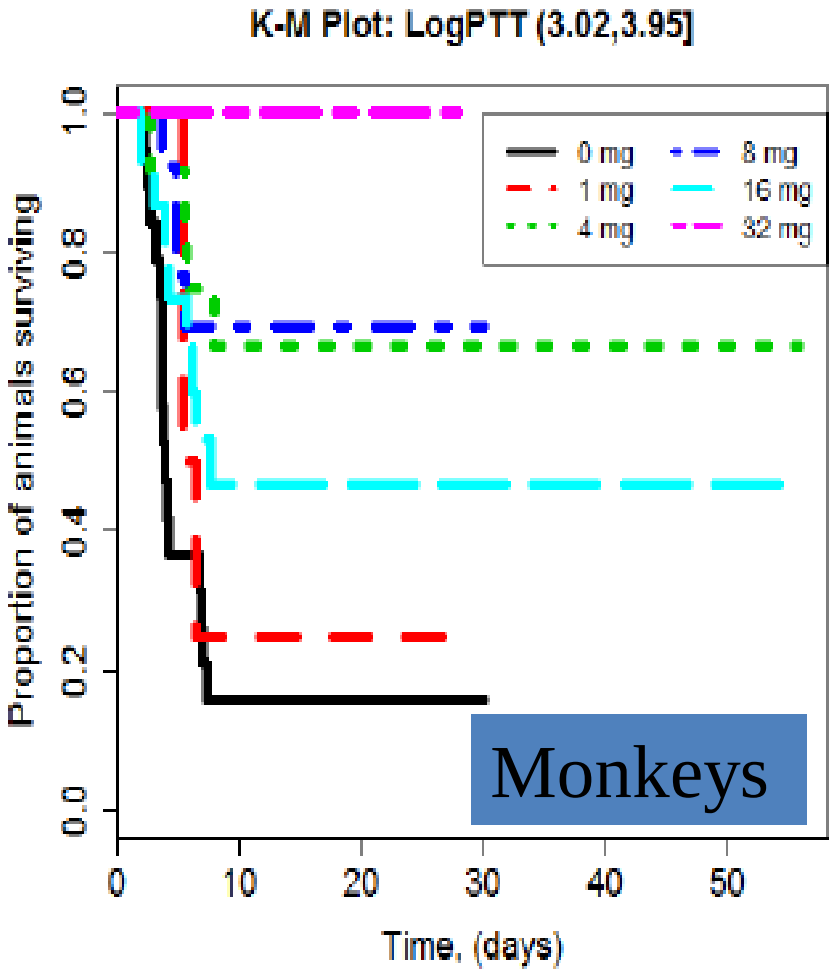
- Initial approval 2002
- One dose 300 µg/kg (given a week apart) was evaluated in pivotal efficacy study.
- SR = 91.3% [TRT] vs. 47.8% [PL]
- Dose translation: PK/PD approach
- Human dose: 6 mg SC one week apart (> 45 kg)
- Pediatric Dose: PK matching to adult exposure using allometric scaling down to birth

Inhalation Anthrax- **Obiltoxaximab**

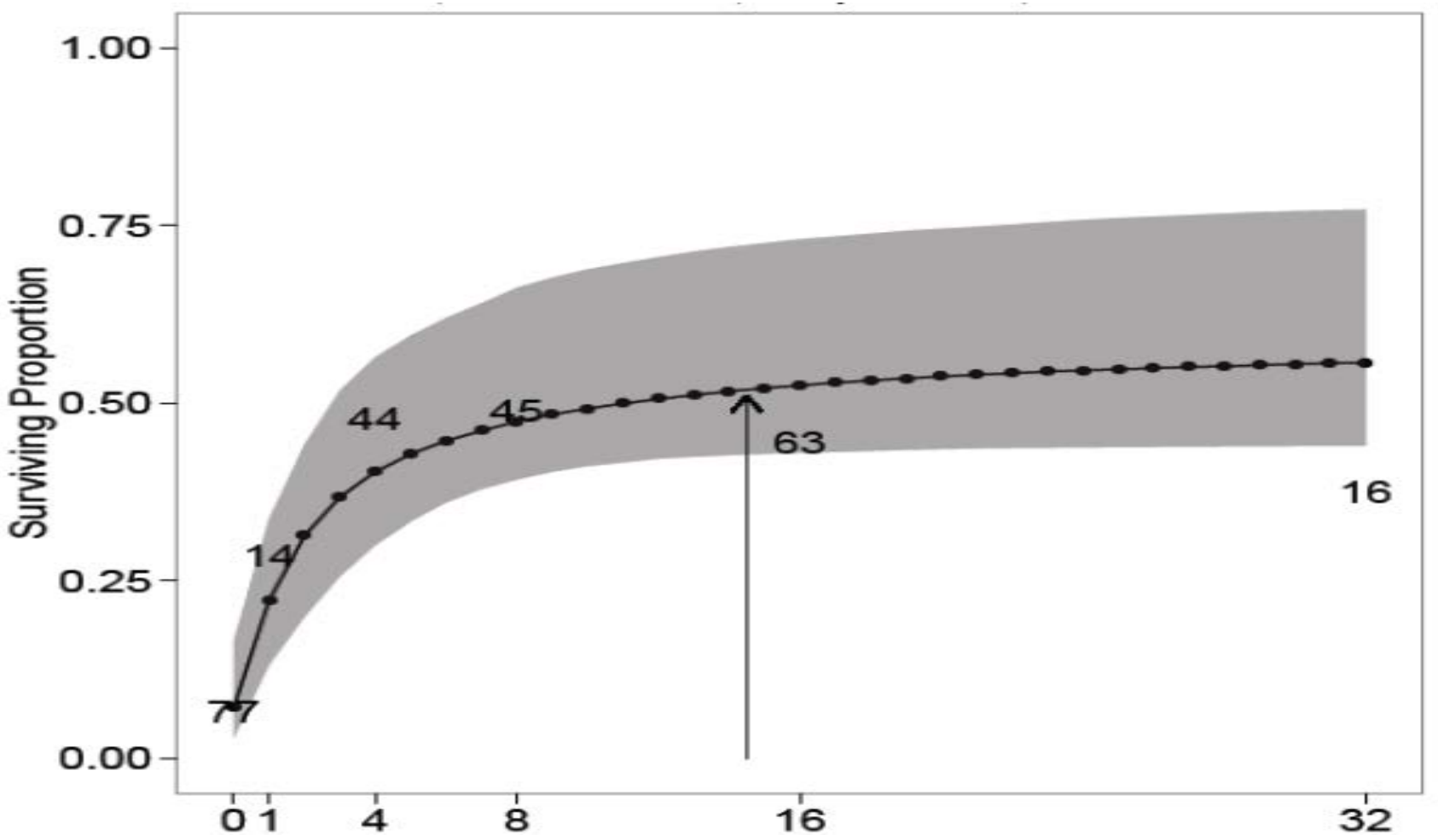
- Monoclonal antibody
  - Binds free protective antigen (PA) of *B. anthracis*
  - Inhibits the binding of PA to its cellular receptors, preventing the intracellular entry of the anthrax factors
- Indications:
  - Treatment of inhalational anthrax due to *B. anthracis* in combination with appropriate 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

Obiltoxaximab- Efficacy Data

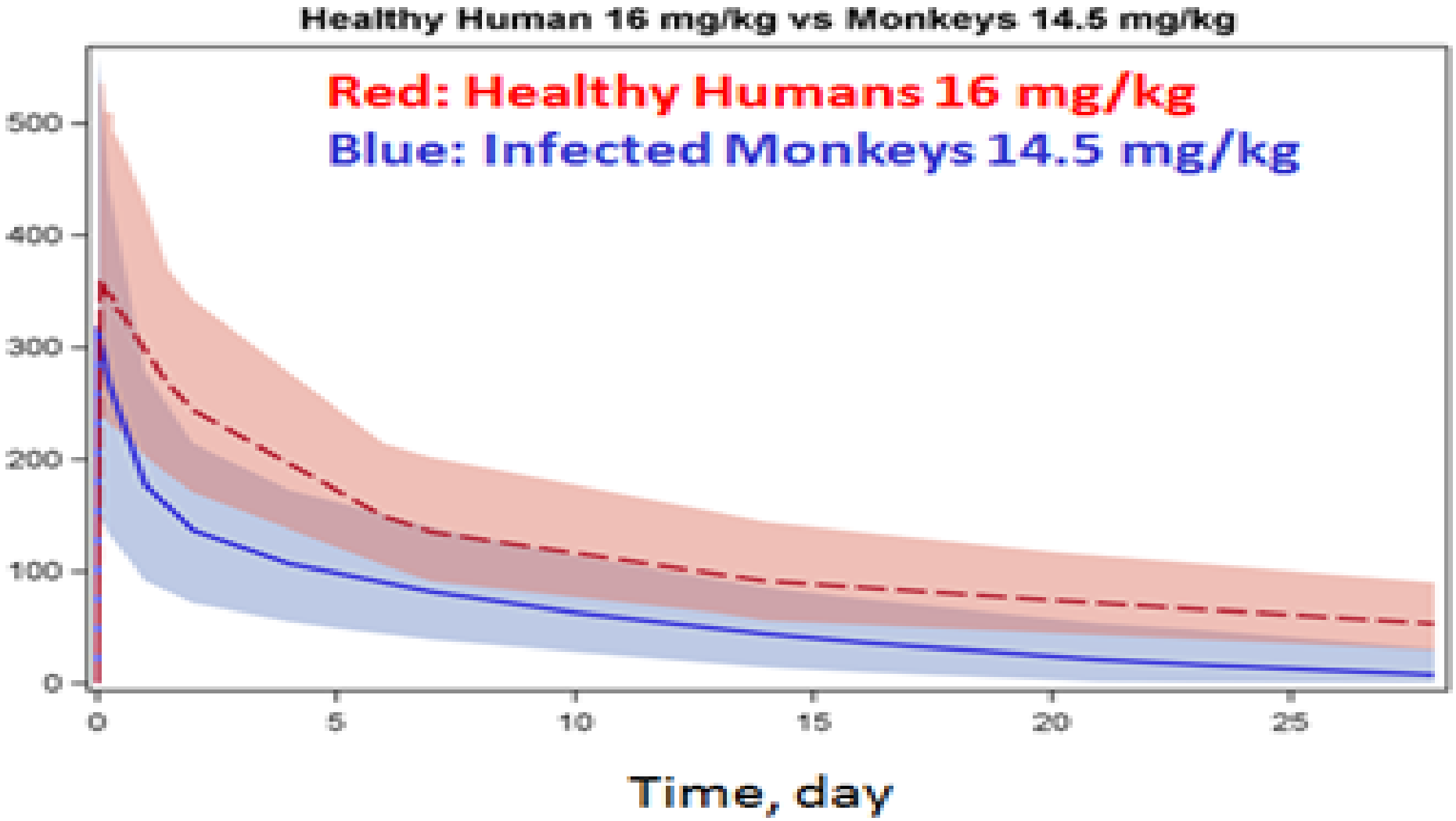




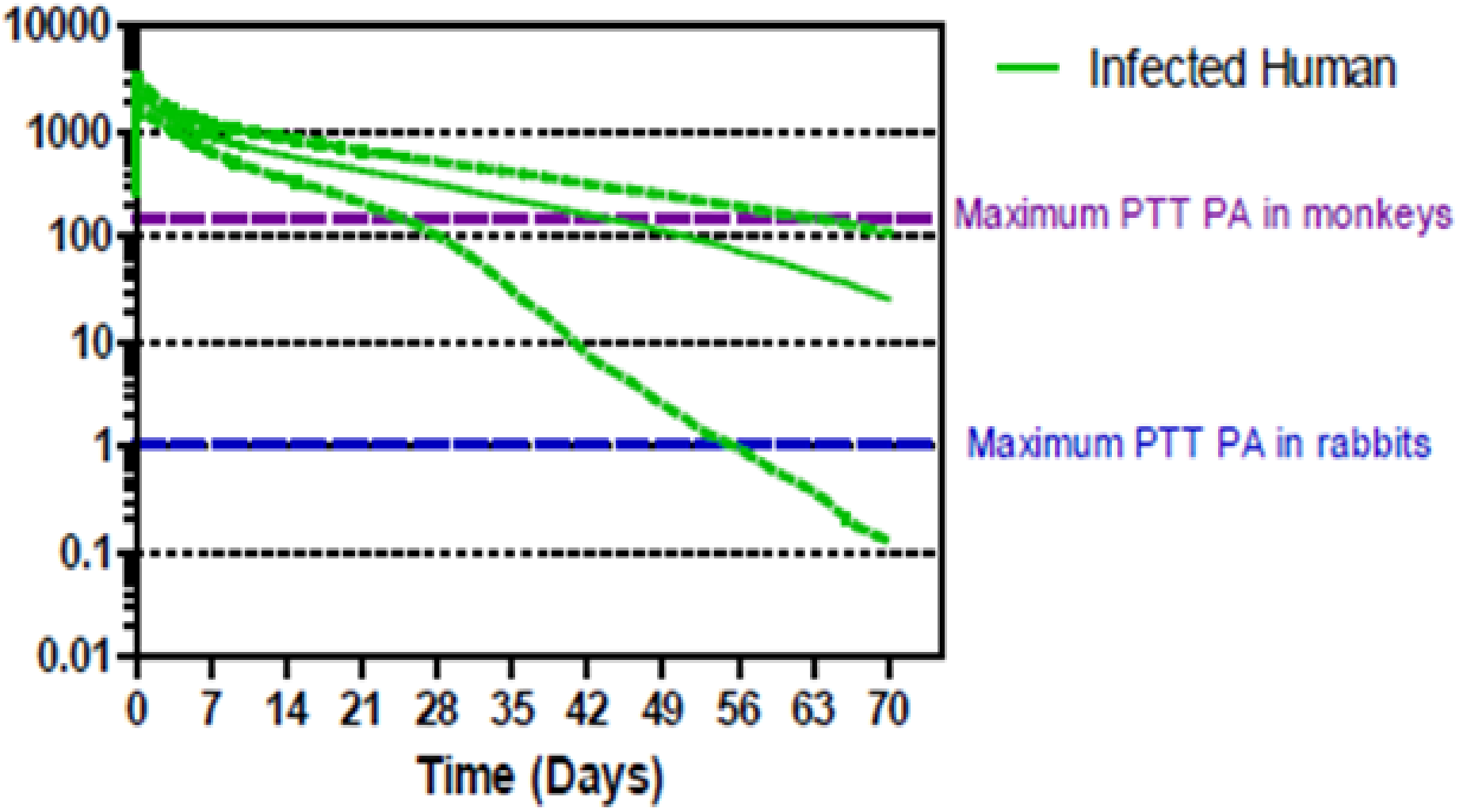
Obiltoxaximab: Dose-Response



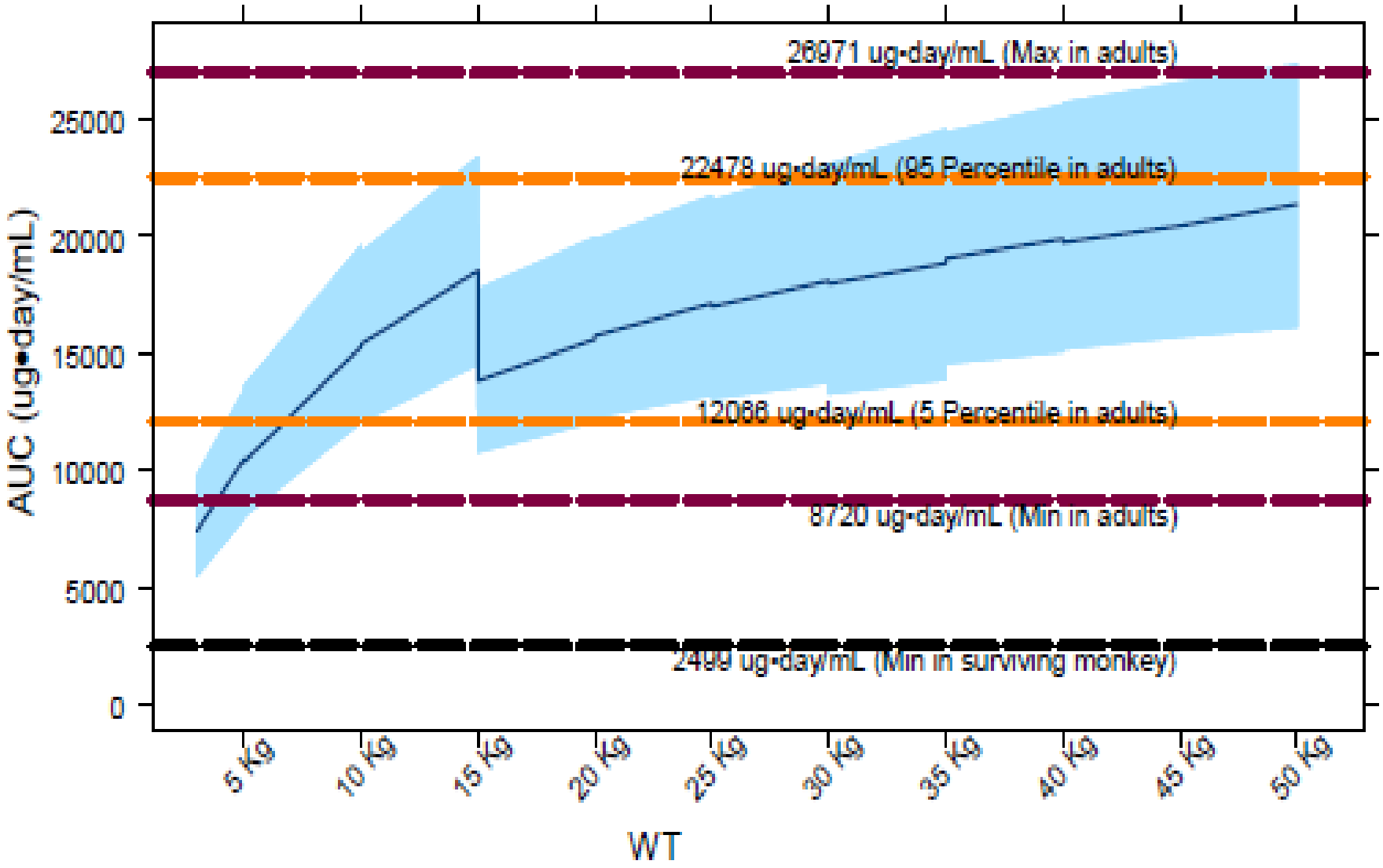
Obiltoxaximab: Exposure Comparison



Obiltoxaximab: Exposure Comparison



Raxibacumab - Pediatric Dosing



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.

Acknowledgment

- Kimberly Bergman
- Kunyi Wu
- Lian Ma
- Nitin Mehrorta