Pharmacokinetic Considerations in Advancing Animal Models for Antibacterial Drug Development

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Disclaimer

The opinions contained in this presentation are my own and do not necessarily represent the views of the FDA

Objective and Scope

Discuss pharmacokinetic (PK) considerations for animal infection model experiments (AIME) that would be conducted during the late stages* (LS) of antibacterial drug development ("LS-AIME")

**Late stages: At or after the point in a drug development program when a clinical dosage regimen for clinical efficacy studies has been determined*

PK Considerations: Dosing Selection

Two potential approaches to select dosing regimen for LS-AIME:

Approach A: Based on bacterial killing

- Dosing regimen that is likely to achieve human PK-PD target (i.e., achieve thresholds values for applicable PK-PD index) OR likely to achieve free drug concentration-time profile known to produce desirable bacterial killing (e.g., mechanistic model informed dosing regimen selection)

Approach B: Based on drug exposure

- Dosing regimen that is likely to provide free drug exposure similar to that anticipated in humans who receive a clinical dosage regimen ("humanized dosing")

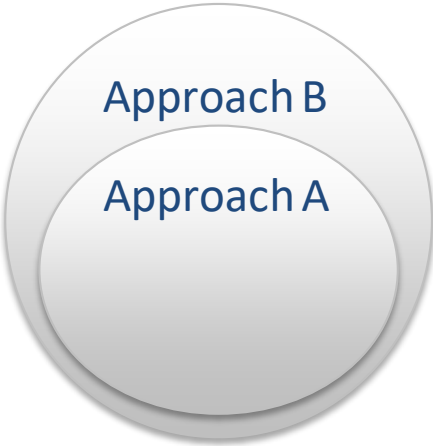
PK Considerations: Dosing Selection$_{cntd.}$

Preferred for LS-AIME:

Approach B. Humanized Dosing

Rationale: Approach B encompasses Approach A

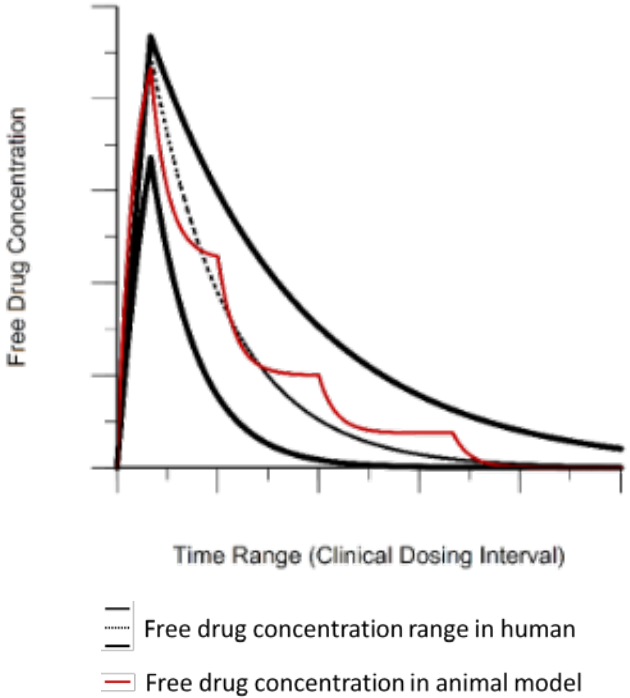
- Avoids uncertainties associated with the use of PK-PD target estimates
- Mimics overall drug exposure cycles (rate and extent) anticipated in humans



Potential Dosing strategies:

Staggered continuous infusion or **Intermittent dosing**

Humanized Dosing: Staggered Continuous Infusion



Advantage

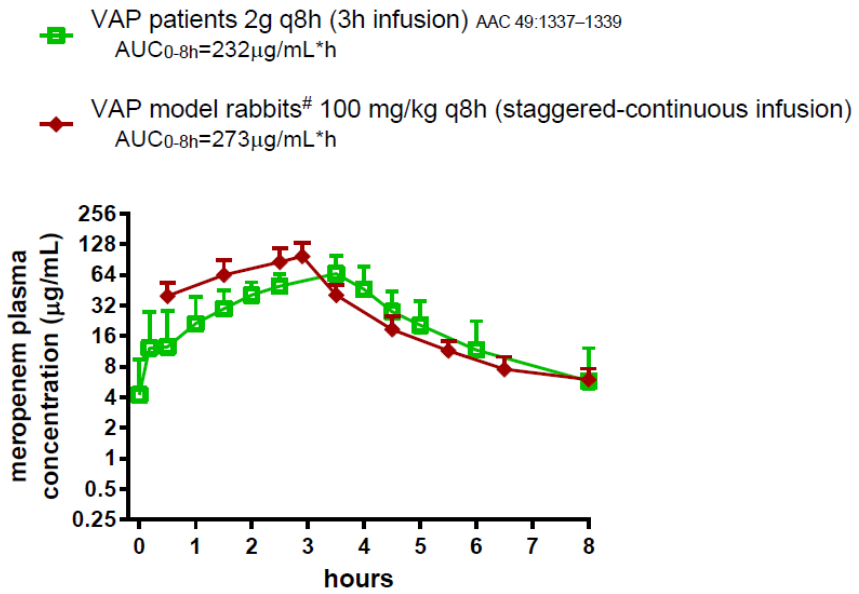
- Provides flexible dosing options and comparable free drug concentration (C_{free})-time profile to human

Disadvantages

- Infusion may not be a feasible route of administration for all animal infection models
- Requires relatively complex dosing calculations and experiment setup

Staggered Continuous Infusion: Meropenem Example

VAP Rabbit Model (preliminary data)‡

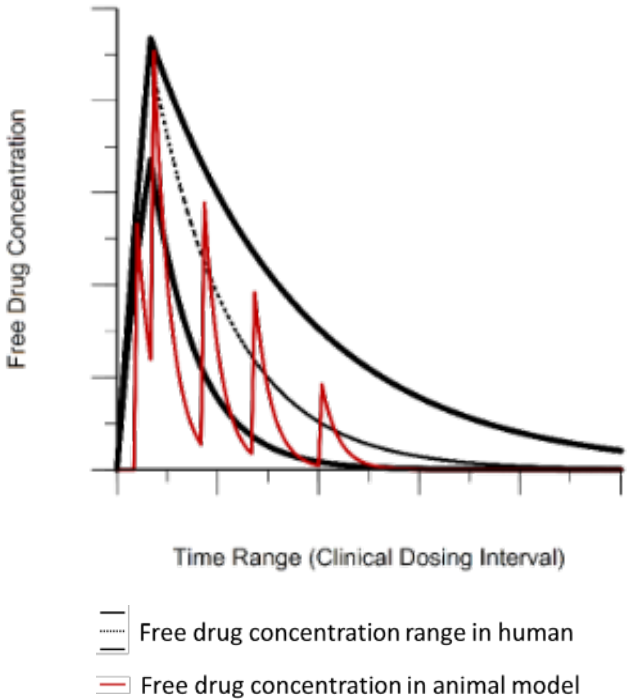


Notes:

- Multiple prior PK experiments informed humanized dosing
- Complex experiment setup used dosing with programmable infusion pumps to deliver five different doses over the intervals of 0-1 h, 1-2 h, 2-3 h, 3-4 h, 4-6 h, and 6-8 h

‡ Unpublished data reproduced with permission from Drs. Binh Diep and William J Weiss; VAP Model: Ventilator-associated pneumonia; #uninfected VAP model.

Humanized Dosing: Intermittent dosing



Advantages

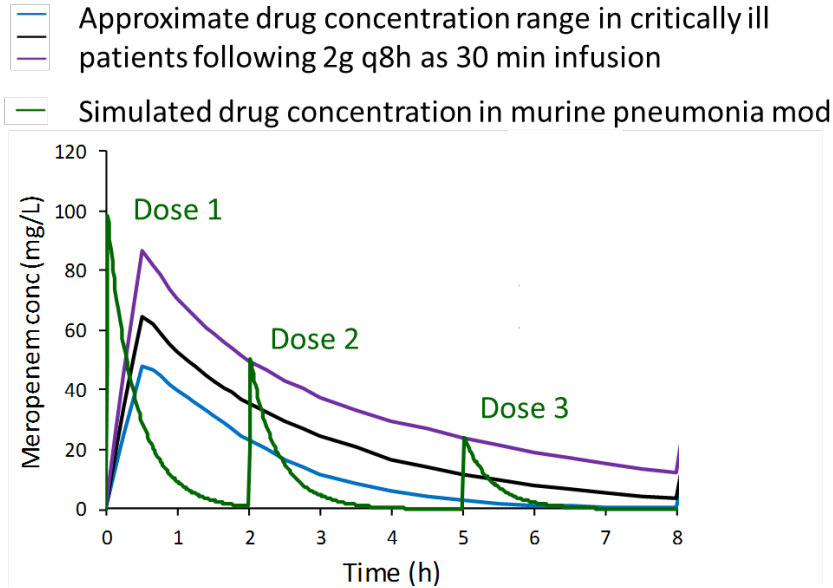
- Requires relatively simple experiment setup
- Feasible for most animal infection models

Disadvantages

- May not be always feasible to provide C_{free}-time profile comparable to human
- Relatively coarse C_{free} -time profile compared to human
- Relatively higher number of doses may increase PK variability

Intermittent Dosing: Meropenem Example

Murine Pneumonia Model (preliminary data‡)



Notes:

- Humanized dosing refinement dependent upon the maximum number of doses that can be administered in a day
- Strategy of slowing meropenem clearance using cilastatin and probenecid is being considered to further refine humanized dosing

‡ Unpublished data reproduced with permission from Drs. Brian Luna and Jürgen Bulitta; conc= concentration.

PK Considerations: Supportive Assessments

- Bioanalytical method validation for all the relevant matrices (i.e., plasma, ELF)
  - Including assessment of sensitivity, selectivity, accuracy, precision, stability
- Protein binding assessments
- Dose ranging PK experiments (healthy or infected animals)
- Confirmatory PK assessments in the selected animal infection model to demonstrate humanized dosing provides free drug exposure comparable to exposure in humans

Summary

Current thoughts for LS-AIME:

- The use of **humanized dosing** may be advantageous
- It is important to perform thorough **supportive PK assessments** (e.g., bioanalytical method validation, protein binding assessments)

Remaining Questions:

- Is there a need for incorporating drug exposure at site of action (i.e., relevant tissue compartment for the intended clinical indication)?
- Are there disadvantages of using humanized dosing in addition to logistics/feasibility issues in certain situations?

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