M23 PK/PD Working Group
Draft Documents for Consideration

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"Cut-Offs" to Use in Determining Clinically Relevant Breakpoints

Epidemiologic cut-offs	"Wild Type" distribution
Non-clinical PK-PD cut-offs	1. Identify PK/PD target in non-clinical model (e.g. animal models such as neutropenic mouse thigh) 2. Using a population PK/PD model apply Monte Carlo Simulation to assess the probability of target attainment at potential PK-PD cut-off MICs
Clinical cut-offs **(MIC vs Outcome Cutoff)**	This is a simple observational correlation of response to MIC. In addition, it is helpful to review the overall efficacy of the study.
Clinical PK/PD cut-off **(Integrated Patient Exposure Response cut-offs)**	Identify **exposure-response relationship from patient clinical trial data** Integrated to incle assessment of Clinical Response modifiers

DRAFT Non-Clinical PK/PD Cut-offs

5.2.2.1 Static *In Vitro Studies*

5.2.2.2 Nonclinical PK/PD Studies

- "…data from these studies are used to ultimately derive the Non-Clinical PK-PD cutoff. "
- "Examples of acceptable models are the neutropenic mouse thigh and lung infection models[4,5] and *in vitro pharmacodynamic models[6] (e.g., chemostat or hollow-fiber systems).*
- Ideally, nonclinical models should mimic the human indication as closely as possible.
- The magnitude of the PK-PD index
  - For serious, life-threatening infections of high bacterial burden such as nosocomial pneumonia, a minimum of 1-log10 reduction using the neutropenic mouse thigh or lung model is generally appropriate.
  - For low-density infections that are treated in part by surgical interventions, like complicated skin and skin structure infections or complicated intra-abdominal infections, a minimum of net stasis using the neutropenic mouse thigh model is generally appropriate.

5.2.2.3 Human Pharmacokinetic Data

- Epithelial lining fluid (ELF) free drug concentration data should be provided for those drugs used to treat pneumonia

DRAFT Non-Clinical PK/PD Cut-offs

5.2.2.4 Monte Carlo Simulation

- Probability of Target Attainment: For the purpose of identifying Non-Clinical PK-PD cutoffs, 90% PTA at a given MIC is considered acceptable by CLSI. However, there are circumstances in which higher or lower percentages may be acceptable. For instance, if the consequence of not attaining the target PK-PD threshold is a high probability of a patient's death (e.g., suboptimal drug exposure in the context of a patient with pulmonary anthrax), higher PTA thresholds may be judged appropriate. Conversely, a lower PTA may be acceptable if the infection is less severe.

- It is preferred that the PK inputs …based on a target patient population PK model.

- If a target patient population PK model is not available, the sponsor may utilize a relevant volunteer-derived PK model. (with relevant inflated variance)

DRAFT Clinical PK/PD Cut-offs
(Integrated Patient Exposure Response cut-offs)

1. Using **patient clinical trial data**, clinical PK/PD (aka exposure-response) relationship(s) for efficacy and targets based on such relationship(s) can be identified

2. Using a population PK model and the results of the clinical PK/PD analyses, apply Monte Carlo Simulation to assess the following:
   a) **Model-predicted probability of clinical response by MIC** using the clinical PK/PD relationship
   b) **Probability of target attainment by MIC** using the clinically derived PK/PD target