Key Themes/Questions to be Addressed in each Session:

Session #1:
Each speaker will address topics indicated by titles in agenda

Session #2:
- Overview of technical methodology for various in vitro assays
- Merits and limitations of different in vitro models
- Key Questions:
  - Consideration for bacterial strain selection
  - How (not) to conduct mutation frequency study?
  - Impact of heterogeneous drug biodistribution
  - Interpretation of PK index magnitudes – duration of experiment
  - Impact of atypical and very high protein binding
  - Approach to combination therapy
  - Correlation to clinical targets - bactericidal vs. bacteriostatic

Session #3:
- Infection models in neutropenic mice (primarily thigh infection) are the workhouse animal models used in PKPD packages for most antibacterial programs.
  - What precedent data exists to validate use of these models for different indications?
  - How do technical methodology details potentially impact results or interpretation, and what are best practices for conducting these studies?
- Quality pharmacokinetic data and analysis are critical to facilitate interpretation of PKPD results from animal models and translation to clinical efficacy targets.
  - What are appropriate methods for determining relevant drug exposures in plasma and at infection sites in animal models?
  - What are the best approaches to account for variability and effectively translate the animal data to clinical efficacy targets?
- Data from animal models (combined with in vitro studies) are used to estimate efficacious exposures, assess toxicology risk, select doses for clinic, establish breakpoints, and inform many key decisions throughout development.
  - What are some of the challenges with integrating diverse data from multiple models for appropriate decision-making?
  - Are specific end-points in the models more predictive than others for target clinical indications?
  - Are all clinical indications equally and adequately supported by existing animal models?
Session #4:
- **Overview**
  - What are the important considerations to ensure that the preclinical PK/PD data package will most likely translate to success in the clinic and any additional considerations that will support smaller programs?

- **Ensuring Robust and Informative PK/PD data and Using PK/PD to Support Smaller Clinical Trial Size**
  - What is required from preclinical PK/PD packages to forecast doses for clinical trials? Can we define the most informative models (and numbers of models) and extent of data required (eg number of bacterial isolates to evaluate)?
  - How much preclinical data is enough?
  - Can robust PK/PD data allow skipping phase II trials and going directly to pivotal trials? What are the requirements for such data?
  - How to use PK/PD to reduce the size of clinical trial programs?

- **Confirming Forecasts**
  - What data should be collected in clinical trials to support target attainment predications (and when are such data required)?

- **Developing New Classes**
  - Do new classes of drugs or targets require more comprehensive supportive PK/PD data or more clinical data to validate PK/PD targets?

- **Biomarkers and Clinical Trials**
  - Can biomarkers be helpful in PK/PD assessments (and how?)? What biomarkers?
  - Can we use PK/PD-centric trials to validate predictive biomarkers?

- **Special Populations**
  - What special populations should be routinely considered for PK/PD evaluation? Can special population recommendations be based on PK/PD considerations without confirmatory clinical data?
  - Are PK/PD targets in children the same as in adults? If different, in what way?

- **How Do We Qualify a Quantitative Approach?**
  - Is there a way to quantify the certainty of PK/PD predictions, allowing smaller clinical trials?

- **Antibody and other Non-Traditional Therapeutics**
  - How to do PK/PD?
Session #5:

- Transition from Pre-Clinical to Clinical PK/PD
  - Thesis for the session: Future programs will have substantial pre-clinical packages but more limited clinical trial packages
  - Q1: What is the most useful sampling strategy for clinical programs?
  - Q2: Can we (How can we) use clinical PK data and outcomes to validate different pre-clinical modeling approaches to estimating PD targets? Are there any quality or data integrity issues here that would not be addressed by the usual approach to pivotal trials and Good Clinical Practice (GCP)?
  - Q3: Can we investigate infection-specific exposure/MIC breakpoints for outcome (e.g. survivorship for VABP)?
  - Q4: Are targets different for Enterobacteriaceae vs. non-fermenters?
  - Q5: Can we (How can we) investigate factors that drive emergence of resistance? What is the role of investigating dosing strategies to suppress resistance? Beyond the simple strategy of dosing to toxicology limits, how should trade-offs between safety, efficacy, and resistance suppression be weighed?
  - Q6: How much is enough? How do you decide when the package is adequate? How do you know when you can select a dosing regimen?

- Leveraging clinical trial databases
  - Thesis for the session: It may be possible to leverage clinical trial networks to permit accrual of databases examining outcomes for patients with specific less common infection types/organisms (e.g. Acinetobacter in VABP). Is this useful?
  - Q1: Can such a database be of adequate quality (clear documentation of disease, clinical course, etc.) with adequate data integrity to be useful? Is this something that should be targeted for funding programs?
  - Q2: Can we look at such outcome databases and look at PK/PD estimates of no-treatment outcomes (e.g. through logistic regression functions) to improve our ability to develop new agents?

- How will best practices evolve in this space?
  - Thesis for the session: Preclinical models and procedures are not standardized.
  - Q1: Would standardization be useful? Possible?
  - Q2: If pursued, where would you start?
  - Q3: If pursued, what is the best home for a forum on this?

- Training
  - Thesis: There is limited bench strength in this space
  - Q1: How can future PK-PD experts be trained?
  - Q2: Is there a role for specific funding to ensure such training?

- This meeting
  - Thesis: After spending 1.5d surveying this area...
  - Q1: Where are the gaps?
- Q2: What topics would be appropriate for a future workshop?