CTTI Antibacterial Drug Development:
Statistical Issues Think Tank Meeting
Bethesda Hyatt Regency
August 20, 2012
Teleconference: 1-888-450-5996 passcode: 382825

8:30 – 9:00 a.m. **Continental Breakfast**

9:00 – 9:30 a.m. **Welcome, Introductions, and Meeting Objectives** *(10 minutes)*
Rob Califf, Duke Translational Medicine Institute, Duke University Medical Center

Background *(20 minutes)*
Lisa LaVange, Office of Biostatistics, OTS/CDER/FDA

- Provide a brief history of the evolution of statistical thinking in anti-bacterial clinical trials and review the current statistical challenges
- Briefly introduce questions for the group to consider (*see below*)
- Describe what constitutes a successful outcome of this meeting

9:30 – 10:45 a.m. **Session 1: One- versus two-study paradigm for approval**

- **Question 1**: What requirements should be imposed on the Phase 3 study in a single-study submission in terms of level of evidence, sample size, subgroup representation, data quality, etc.?
- **Question 2**: What type of supporting evidence should be required to accompany a single Phase 3 submission (e.g., Phase 2 study, non-clinical data)?
- **Question 3**: Can Bayesian or other methods be used to formally take into account the supporting evidence when analyzing the single Phase 3 study?

10:45 – 11:00 a.m. **BREAK**

11:00 – 12:30 p.m. **Session 2a & 2b: Non-inferiority (NI) trial designs, choice of margins, and analysis strategy**

- Brief history of NI margin determination in nosocomial infection/hospital acquired pneumonia (HAP) *(5 minutes; Scott Komo)*
- **Question 1**: What methods or what types of data are needed to be able to translate or bridge margins from one endpoint (e.g., mortality) to another (e.g., clinical response)? Would case-control studies, for example, provide the additional information needed? Can the estimation of correlation between endpoints from other studies be helpful in this regard?
- **Question 2**: What are the advantages/disadvantages of other approaches to margin determination in regulatory studies, e.g., a Bayesian approach?
- **Question 3**: Are there efficiencies to be gained through the use of other analysis methods, such as Bayesian analysis (e.g., Gamalo, Wu, and Tiwari), and if so, at what cost? Example analyses provided for illustration *(10 minutes; Ram Tiwari and M. Gamalo)*

12:30 – 1:00 p.m. **Lunch** *(continue discussion of NI trials during a working lunch)*

1:00 – 2:00 p.m. **Session 3: Development plans that span multiple infection (body) sites**

- Brief background on challenges posed by trials for multiple drug resistant gram negative pathogens and pooling of body sites *(5 minutes; Dan Rubin)*
- **Question 1**: What types of study designs, including multiple testing strategies, should be considered for a single submission that includes clinical trials conducted in multiple infection sites, taking into account different background rates at different sites, etc.?
- **Question 2**: How should data from those trials be synthesized during analysis?

2:00 – 2:45 p.m. **Session 4: Other design and analysis considerations** *(time permitting)*

- Brief presentation of motivating examples from community acquired pneumonia (CAP) *(5 minutes; Dan Rubin)*
- **Question 1**: Please discuss design and analysis considerations that may impact the ability of a non-inferiority trial to differentiate effective and ineffective therapies, such as enrollment stratification (e.g., use of prior therapy); use of a sub-ITT population (e.g., assay positive for organism) for primary efficacy analysis, handling missing data and protocol violations, etc.

2:45 – 3:00 p.m. **Next Steps**

3:00 p.m. **Adjourn**