Trial Considerations for Unmet Need

Sumati Nambiar, MD MPH
Director, Division of Anti-Infective Products, FDA

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Unmet Need Antibacterial Drugs

- Examples of types of antibacterial drugs suitable for an unmet need development pathway
  - Act via new mechanisms of action
  - Have an added inhibitor that neutralizes a mechanism of resistance
  - Activity preserved in setting of resistance to other antibacterial drugs

Antibacterial Therapies for Patients With Unmet Medical Need for the Treatment of Serious Bacterial Diseases: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm359184.pdf

General Considerations

- Smaller data package; greater uncertainty about risks and benefits
  - Single adequate and well-controlled trial may be adequate with supportive evidence
  - Thorough evaluation of activity in vitro and in animal models of infection would be needed to support the smaller clinical data package
- Healthcare community should be aware of greater uncertainty about risks and benefits
- Risks and benefits will be communicated appropriately in labeling
  - Labeling from such programs will include a limited use statement

Expected Data

- Adequate *in vitro* data and activity in relevant animal models of infection
- Evaluation of PK/PD relationships from animal models of infection
- Understanding the PK in patients with renal or hepatic impairment early in development
  - Generating these data early would facilitate enrollment of such patients as they often have important comorbidities
- Collection of PK data in clinical trials (e.g., informative sparse sampling in all patients enrolled)

Statutory Standards

- Drugs being developed to address unmet need must meet the statutory standard for effectiveness
  - Substantial evidence as "evidence consisting of adequate and well-controlled investigations, including clinical investigations,…" (FD&C Act)
    - 21 CFR 314.126(b): Adequate and well-controlled studies
  - Section 115(a) of the Modernization Act clarified that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence

Unmet Need: Noninferiority Trials (1)

- Well-conducted noninferiority (NI) trials of antibacterial drugs are critical to maintaining a robust pipeline of antibacterial drugs to meet patient needs
- Treatment options should be available before new mechanism(s) of resistance emerge
- If clinical trials in patients with unmet need are easy to conduct due to the high levels of resistance, then antibacterial drug development has not kept pace with emergence of resistance

Unmet Need: Noninferiority Trials (2)

- A well-conducted NI trial will provide evidence of a drug's efficacy in a given body site of infection
- Generally, will be limited to situations where the baseline microorganism(s) are susceptible to both test and comparator drug
  - Trial often enrolls relatively few (or no) patients infected with MDR phenotype microorganism(s)
- Supported by evidence for the drug's activity from *in vitro* data and animal models of infection

Unmet Need: Noninferiority Trials (3)

1. A single noninferiority trial at one body site
   - Important to enroll patients with severity of illness/comorbidities similar to those seen in patients with unmet need
   - Wider NI margin acceptable

- May be supplemented with data from a study in patients with infection due to the resistance phenotype of interest
  - Provides PK data in a sicker population/more comorbidities
  - Provides some clinical experience in patients with infections due to organisms with the resistance phenotype of interest

Unmet Need: Noninferiority Trials (4)

2. NI trial pooling across body sites; poses additional challenges
   - The magnitude of treatment effect varies across infection types
   - Endpoints vary between infection types
   - Trial may not demonstrate a potential deficit in treatment effect across the different infection types that are pooled

Pertel PE, et al. CID 2008;46(8):1142-51;
Doripenem Drug Safety Communication; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm;
Tigecycline Drug Safety Communication::http://www.fda.gov/drugs/drugsafety/ucm369580.htm;

Superiority Trials (1)

- Provides a clear finding of efficacy
- Ability to rely on superiority is likely time-limited
  - Once a new therapy becomes available, ongoing trial designed to show superiority over standard of care (SOC) will likely become unethical and would probably need to be stopped
  - Subsequent trials will be NI trials
- Superiority can be demonstrated at a single body site or by pooling across certain body sites with a representative sample from each type of infection

Superiority Trials (2)

1. Superiority over active comparator
   - Usually dependent upon the comparator arm of the trial representing suboptimal treatment
   - Very infrequently an antibacterial drug provides additional benefit over active SOC
   - Recent example of a trial in cUTI with ceftolozane-tazobactam where superiority of ceftolozane-tazobactam over levofloxacin was demonstrated
     - ~26% of baseline isolates in the comparator arm were levofloxacin non-susceptible

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/206829s001lbl.pdf

Superiority Trials (3)

2. Superiority over external controls
   - Challenges in obtaining comparable external control group are described in ICH E10
   - Comparability of the treatment and control groups is a challenge as the groups can differ not only in known risk factors but also in unrecognized or inadequately measured risk factors leading to potential bias
   - Untreated historical control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study, possibly reflecting a selection bias
3. Add on design: Test drug plus standard of care (SOC) vs. SOC plus placebo

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf

Superiority Trials (4)

- Pooling across body sites (cIAI, cUTI, HABP/VABP) is acceptable; ~ 50% HABP/VABP where deficits in performance of antibacterial drugs have been seen
- Patients with documented infections due to a certain resistance phenotype, e.g. carbapenemase production
- Best available therapy is used as comparator
- All-cause mortality or disease specific definition of clinical success are acceptable endpoints
- We have considered allowing the use of one sided alpha of 0.05, given that the comparator regimen might have some treatment effect

Doripenem Drug Safety Communication; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm;
Tigecycline Drug Safety Communication::http://www.fda.gov/drugs/drugsafety/ucm369580.htm;

Nested NI/Superiority Trial Design

- An NI trial where baseline pathogens may or may not have resistance phenotype of interest
  - Demonstrate NI in the population susceptible to comparator
  - Demonstrate superiority in the subset of patients with baseline microorganism(s) resistant to comparator
  - Non-inferiority should be demonstrated before superiority can be tested. However, if superiority not demonstrated, does not impact on the conclusion of noninferiority

IDSA, White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens. Clin Infect Dis, 55(8):1031-1046
Huque et al. Hierarchical nested trial design (HNTD) for demonstrating treatment efficacy of new antibacterial drugs in patient populations with emerging bacterial resistance. Stat Med. 2014 Jun 23.

Development Program: Example 1

Spectrum of activity includes Enterobacteriaceae and *P. aeruginosa*; activity against several ESBLs including serine carbapenemases

1. A single NI trial at one body site:
   - Can be tested as monotherapy in cUTI/cIAI
   - For HABP/VABP, will need to address issue of concomitant therapy used to treat *P. aeruginosa*
2. Superiority Trials
   - Superiority at a body site
   - Pooled across body sites
3. Nested NI/superiority

Development Program: Example 2

- Antibacterial drug has activity only against a single species, e.g. *Pseudomonas aeruginosa*, *Acinetobacter baumanii*
- Topic for Day 2 of the workshop

Development Program: Example 3

- New beta-lactamase inhibitor (BLI) being combined with an approved beta-lactam (BL) antibacterial drug
- Under 505(b)(2) of the FDCA, can rely in part on the Agency's finding of safety and effectiveness for the corresponding approved indications for the beta-lactam
  - This information can provide part of the evidence needed for the new BL-BLI combination

Development Program: Example 3

- Justification that the addition of the BLI addresses an unmet need should be provided
- Need robust evidence of the contribution of the BLI in restoring the activity of the beta-lactam from *in vitro* studies and animal models of infection
- Adequate dose rationale should be provided including the appropriate ratio of the BL and BLI
- Adequate safety data needed for the beta-lactamase inhibitor and the combination product

Development Program: Example 3

Clinical data package could vary; depends on the approved indications for the BL in the combination and the indications in which the BL-BLI have been studied

1. A single adequate and well-controlled NI trial in a body site of infection would suffice; does not need to be enriched for organisms that are non-susceptible to the chosen BL
2. Smaller trials in indications for which the BL is approved might be acceptable; would ideally include some patients with infections due to beta-lactamase producing microorganisms

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/206494Orig1s000TOC.cfm

Development Program: Example 4

- Product being developed as adjunctive therapy to standard of care (SOC)
  - Inhaled antibacterial drugs being developed for VABP
  - Immune modulators
  - Monoclonal antibody targeting a specific microorganism
- Trial design:
  - Superiority trial
  - Test drug plus standard of care versus standard of care

Summary

- Noninferiority trial at a single body site
  - Wider NI margin
  - Could include a nested superiority option
- Superiority trial
  - At one body site or pooling across body sites; compared to best available therapy
  - Test drug plus SOC vs. SOC
- For a new beta-lactamase inhibitor being combined with an approved beta-lactam antibacterial drug, could rely in part on Agency's finding of safety and effectiveness of the approved beta-lactam