Public Workshop—Facilitating Antibacterial Drug Development for Patients With Unmet Need

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OND/CDER/OMPT/FDA

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Welcome

Public Workshop—Facilitating Antibacterial Drug Development for Patients With Unmet Need

• An opportunity for discussion
• Not an Advisory Committee
• Conflict of Interest disclosures available
• Open time for comments
Panel Introductions
## Agenda

### Day 1: Monday July 18th, 2016

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 -10:30 AM</td>
<td><strong>Session 1: General Considerations for Unmet Need Programs</strong></td>
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<tr>
<td>8:30-8:50</td>
<td>Effectiveness standards including orphan products</td>
<td>Ed Cox</td>
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<td>8:50-9:10</td>
<td><strong>Trial Considerations for Unmet need</strong></td>
<td>Sumathi Nambiar</td>
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<td>9:10-9:30</td>
<td>Regulatory pathways and approaches to unmet need</td>
<td>Marco Cavaleri</td>
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<td>9:30-9:50</td>
<td>Developing antibacterial drugs for unmet need and so that we stay ahead of the epidemic: Points to consider for developers</td>
<td>John Rex</td>
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<td>9:50-10:10</td>
<td>Pharmacokinetic considerations in unmet need programs</td>
<td>Paul Ambrose</td>
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<td>10:10-10:30</td>
<td><strong>BARDA’s market research for a clinical trial network for antibiotics</strong></td>
<td>Joe Larsen</td>
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<td>10:30-11:00</td>
<td>Break 1</td>
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<td>11:00-11:30</td>
<td>Clarifying Questions (Panelists and Audience)</td>
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<td>Time</td>
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<tr>
<td>11:30-12:10</td>
<td>Session 2: Real World Experiences in Conducting such Trials</td>
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<tr>
<td>11:30-11:45</td>
<td>Developing antibacterial drugs for patients with unmet need: experience and recommendations</td>
<td>Ian Friedland</td>
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<td>11:45-12:00</td>
<td>Planning and Executing a Carbapenem/Beta-lactamase Inhibitor Program Focused on Treatment of KPC-Producing CRE</td>
<td>Mike Dudley</td>
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<td>12:00-12:15</td>
<td>Clarifying Questions (Panelists and Audience)</td>
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<td>12:15-1:00</td>
<td>Lunch</td>
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<td>1:00-2:00</td>
<td>Panel Discussion 1</td>
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<td>2:00-3:00</td>
<td>Session 3: Statistical Considerations</td>
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<td>2:00-2:20</td>
<td>Evaluating antibacterial drugs in unmet need settings</td>
<td>Dan Rubin</td>
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<td>2:20-2:40</td>
<td>Innovative Trial Designs</td>
<td>Kert Viele</td>
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<td>2:40-3:10</td>
<td>Clarifying Questions (Panelists and Audience)</td>
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<td>3:10-3:30</td>
<td>Break 2</td>
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<td>3:30-4:00</td>
<td>Public Comments</td>
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<td>4:00-5:00</td>
<td>Panel Discussion 2 (covering all topics)</td>
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Background

- Antibacterial drug development is challenging from both a scientific and economic standpoint

  - **Scientific**
    - urgent need to initiate therapy in seriously ill patients
    - diagnostic uncertainty
    - pre-study or overlapping antibacterial drug therapy can obscure evaluation of efficacy of an investigational drug
    - mature field with many targets already identified
    - alternatives to small molecule antibacterial drugs generally a less mature field – greater risk/uncertainty

  - **Economic**
    - short course of treatment used episodically
    - prudent use essential -- has economic implications
Antibacterial Drug Development

• Standard Development Programs
  – Other effective therapies are available
  – Provides foundation for evaluating safety and efficacy of a drug
  – Feasible to study the clinical conditions
  – Degree of uncertainty regarding efficacy and safety is limited

• Unmet Need Development Programs
  – Address an existing or future unmet need
  – Molecule has characteristics to address an unmet need
  – Smaller programs, with greater uncertainties in safety and efficacy
  – Reserved for use in patients with limited or no treatment options
Current State

• Fragile antibacterial drug pipeline
• GAIN – Qualifying Infectious Disease Product (QIDP) fast track designation upon request, priority review, 5y of additional exclusivity, for qualifying drugs
• 107 QIDP designations for 63 different unique molecules
• In general, most drugs that enter phase 1 are not ultimately shown to be safe and effective
• A high level of innovation is challenging to achieve in this mature field
• Response involves therapy, immune system, tissue repair
Recent Approvals

- Ceftaroline for CABP and ABSSSI, October 2010
- Fidaxomicin for *C. difficile*-associated diarrhea, May 2011
- Bedaquiline for multidrug-resistant pulmonary tuberculosis (MDRTB), December 2012
- Dalbavancin for ABSSSI, May 2014
- Tedizolid for ABSSSI, June 2014
- Oritavancin for ABSSSI, August 2014
- Ceftolozane-tazobactam for cUTI and cIAI, December 2014
- Ceftazidime-avibactam for cUTI* and cIAI, February 2015

CABP: Community acquired bacterial pneumonia; ABSSSI: Acute Bacterial Skin and Skin Structure Infections

* Reserve for use in patients who have limited or no alternative treatment options.

http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Unmet Need

- Emerging resistance and a less than robust antibacterial drug development pipeline have led to unmet need
  - Multidrug-resistant Gram-negative rods
- Ideally, ongoing development provides for new options to address current needs and needs that we anticipate will arise in the years ahead
- Difficult to react in a timely fashion once an unmet need situation has arisen
Unmet Need: Trial Design Options

- Non-inferiority trial in a body site of infection
- Superiority trial in one body site of infection or pooled across body sites
- Nested NI-superiority trial
- For an approved β-lactam being developed with a new β-lactamase inhibitor can rely in part on previous findings of safety and effectiveness
- Superiority of adjunctive therapy plus SOC versus SOC
Non-inferiority Trials – Important Design for Antibacterial Drugs - 1

- Opportunity to show superiority is likely time limited – dependent on standard of care that is less than adequate
- Enrolling patients with infrequently occurring highly resistant phenotypes in a clinical trial is difficult
  - testing the drug -- vs. -- testing the test and testing the drug
  - Drug may “fail” because the test can’t be performed
- Do not want to wait for incidence of highly resistant organisms to be high enough to make superiority trials easy to perform
- “Best available therapy” likely has a treatment effect – “resistance” often not binary a likelihood of response – so can be difficult to show superiority
Non-inferiority Trials – Important Design for Antibacterial Drugs - 2

- Once new standard of care (SOC) demonstrated, ongoing trials will need to incorporate new SOC to remain ethical – superiority hypothesis may become unrealistic
- Drugs that have different mechanisms of action, chemical modifications that are stable to resistance mechanism, or paired w/ resistance inhibitor may have value beyond what is shown in clinical trials
- The existing drugs we rely on were studied against prevailing resistance phenotypes at time of development – some retain activity and are useful for treating resistant organisms that were not prevalent when developed
Superiority Trials

• Provide clear evidence of efficacy
• Can be challenging to conduct
  – details to follow
• Some interested in such claims
• Avoids concerns some may have regarding generalizability
• May wish to balance with a more achievable approach if interested in pursuing superiority with
Disease Characteristics and Trial Designs

- Serious acute bacterial diseases
- Oncologic conditions
- HIV/HCV
- Rare metabolic disorders

- Identifying patients
- Disease course over time
- Diagnostic certainty
- Urgency to initiate therapy
- Variability in outcomes and time to clinical outcome
- Opportunities for rescue therapy for patients not responding
Clinical Trials - Lessons Learned

- Clinical trials continue to teach us important lessons that are often unexpected
  - Daptomycin: CABP didn’t meet NI margin; binding to surfactant
  - Doripenem: Higher mortality and lower cure rates in VABP
  - Tigecycline: Higher mortality and lower cure rates in VABP
  - Ceftobiprole: Lower cure rates in VABP
  - Delafloxacin: Monotherapy may not be sufficient to treat some patients with uncomplicated gonorrhea
  - Eravacycline: cUTI didn’t meet NI margin; successful trial in cIAI

http://www.fda.gov/drugs/drugsafety/ucm369580.htm
http://ir.tphase.com/releasedetail.cfm?ReleaseID=930613
HABP/VABP Studies – Clinical Trials.gov - 1

- Recruiting - Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia (MK-7625A-008)
  
  
  Condition: Nosocomial Pneumonia
  
  Interventions: Drug: ceftolozane/tazobactam; Drug: Meropenem

- Recruiting - A Study of Plazomicin Compared With Colistin in Patients With Infection Due to Carbapenem-Resistant Enterobacteriaceae (CRE)
  
  Conditions: Bloodstream Infections (BSI) Due to CRE; Hospital-Acquired Bacterial Pneumonia (HABP) Due to CRE; Ventilator-Associated Bacterial Pneumonia (VABP) Due to CRE; Complicated Urinary Tract Infection (cUTI) Due to CRE; Acute Pyelonephritis (AP) Due to CRE
  
  Interventions: Drug: plazomicin; Drug: colistin; Drug: meropenem; Drug: tigecycline; Drug: antibiotic of Investigator's choice

- Recruiting - Imipenem/Relebactam/Cilastatin Versus Piperacillin/Tazobactam for Treatment of Participants With Bacterial Pneumonia (MK-7655A-014)
  
  Condition: Bacterial Pneumonia
  
  Interventions: Drug: Imipenem; Drug: Relebactam; Drug: Cilastatin; Drug: Piperacillin; Drug: Tazobactam; Drug: Linezolid
HABP/VABP Studies – Clinical Trials.gov - 2

- Recruiting - Efficacy, Safety, Tolerability of Carbavance Compared to Best Available Therapy in Serious Infections Due to Carbapenem Resistant Enterobacteriaceae, in Adults
  
  Conditions: Urinary Tract Infection Complicated; Acute Pyelonephritis; Hospital Acquired Bacterial Pneumonia; Ventilator-associated Bacterial Pneumonia; Bacteremia

  Interventions: Drug: Carbavance; Drug: Best Available Therapy

- Recruiting - TR-701 FA vs Linezolid for the Treatment of Nosocomial Pneumonia
  
  Condition: Pneumonia

  Interventions: Drug: TR-701 FA IV; Drug: Linezolid

- Recruiting - Efficacy and Safety of Imipenem+Cilastatin/Relebactam (MK-7655A) Versus Colistimethate Sodium + Imipenem+Cilastatin in Imipenem-Resistant Bacterial Infection (MK-7655A-013)
  
  Condition: Bacterial Infections

  Interventions: Drug: Imipenem+Cilastatin/Relebactam; Drug: Colistimethate sodium (CMS); Drug: Imipenem+Cilastatin; Drug: Placebo to CMS
Advancing the Science of Clinical Trials

- FNIH – developing & evaluating endpoints
- CTTI – trial efficiency and design
  - HABP/VABP project to make trials more feasible
- Duke Margolis Center – over-arching issues in antibacterial drug development
- EMA and FDA frequent interactions – TATFAR and through our confidentiality agreements
- Curating the science supporting clinical trial design and endpoints is key both here in the U.S. and for harmonizing available approaches internationally
Value of a Multi-Faceted Multi-Stakeholder Approach

• Resistance Surveillance
• Prevention of Infection
• Stewardship
• Research and Development
• Role of
  – Academia
  – Industry
  – Government
  – Hospitals
  - Patients
  - Society
  - Prof. Societies
  - Others
  - Public Pvt Part
  - Payers
Overcoming the Challenges

• Solutions will need to address multiple factors

• Basic science R&D → early development → advanced development
  – Pharmaceutical companies
  – NIAID & BARDA

• ERG report – societal value >> private value
  – incentives / purchasing strategies
    • push and pull
Clinical Trial Network

• BARDA Request for Information*
• Clinical trial network for studying antibacterial drugs
  – Infrastructure – avoid starting from scratch each time
  – Expertise – improve quality and conduct
  – Lab support
  – Common protocol
    • Can study more than one drug – share control arm
  – Utility for diagnostic test development

Master Protocol – Antibacterial Drugs

An example Master Protocol schematic to study several drugs for the treatment of patients with a particular bacterial disease

- Enroll patients with HABP/VABP

Shared control arm

Drug A ctrl | A&B ctrl | A,B & C ctrl | Drug B ctrl

Drug A →

Drug B →

Drug C → stopped early - futility

Time →
Thank you