FDA Approaches to Facilitate Antibacterial Drug Development for Patients with Unmet Medical Need

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Stopping the Superbug Threat: A Growing Imperative
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Outline

- Challenges in developing drugs to address antimicrobial resistance
- FDA approaches to facilitate antibacterial drug development
  - Regulatory
  - Scientific

Challenges in Drug Development to Address Antimicrobial Resistance

- Difficulties with trial enrollment
  - Patients are often critically ill and delays in treatment related to enrollment procedures may not be acceptable
  - Diagnostic uncertainty with regard to the index infectious disease and/or its bacterial etiology
  - Multiple study sites need to be recruited as the cases of resistant infections may be spread geographically and occur infrequently
- Challenges in interpretation of trial results
  - Small sample size
  - Mortality and morbidity related to underlying comorbidities
  - Prior and concomitant antibacterial therapy

Challenges in Developing Drugs to Address Antimicrobial Resistance

- Financial disincentives
  - Population in need may be relatively small
  - Antibacterial drugs are prescribed for a short duration
  - Development of resistance may limit the use of the drug
- The use of the drug, if approved, may be limited by non-availability of antimicrobial susceptibility testing at the time of approval because testing devices are developed by companies independent from the drug developer.

Regulatory Approaches to Facilitate Antibacterial Drug Development

- Expedited development programs
- Qualified Infectious Disease Product designation
- Streamlined unmet need development programs
- Limited Population Antibacterial and Antifungal Drugs (LPAD) approval pathway

Expedited Programs for Serious Conditions

	Fast-Track Designation*	Priority-Review Designation*	Breakthrough-Therapy Designation	Accelerated-Approval Pathway
Criteria	• Nonclinical or clinical data demonstrate potential to address unmet medical need	• Provides significant improvement in safety or effectiveness over existing therapies	• Preliminary clinical data demonstrates substantial improvement over existing therapies	• Provides meaningful advantage over existing therapies • Demonstrates effect on a surrogate endpoint or intermediate clinical endpoint
Features	• Frequent FDA feedback • Rolling review	• 6 month review period (instead of 10 months)	• All benefits of Fast-Track Designation • Intensive guidance beginning Phase 1 • Organizational commitment involving senior FDA managers	• Approval based on an effect on a surrogate or intermediate clinical endpoint that is reasonably likely to predict an effect on IMM or other clinical benefit

*Products with QIDP designation are eligible for fast track designation and priority review
IMM: Irreversible morbidity or mortality; Guidance on Expedited Programs for Serious Conditions, May 2014
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf

QIDP Designation

- Antibacterial or antifungal human drug that is intended to treat serious or life-threatening infections
- Provides for the following incentives
  - Additional 5 years marketing exclusivity
  - Priority review for the first application for a QIDP
  - Eligible for fast track designation
- Designation can be requested at any time before submission of the marketing application
  - Designation cannot be withdrawn by FDA, unless the request contained an untrue statement of material fact

GAIN Provision (Title VIII of FDASIA under section 505E of the FD&C Act)
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM594213.pdf

Standard and Unmet Need Antibacterial Drug Development

- **Standard Development Programs**
  - Provides foundation for evaluating safety and efficacy of a drug
  - Degree of uncertainty regarding efficacy and safety is limited
- **Unmet Need Development Programs**
  - Address an existing or future unmet need
  - Reserved for use in patients with limited or no treatment options
  - Smaller trials / programs with greater uncertainties in safety and efficacy
  - Single well-controlled trial may be adequate with supportive evidence from in vitro and animal models
  - Risks and benefits will be communicated in labeling

Unmet Need Programs

- Recent development programs have followed the approaches outlined in the draft unmet need guidance; final guidance issued in August 2017
- Most common approach has been a single NI trial at a body site of infection with supportive evidence from in vitro and animal models to support an indication
- Beta-lactamase (BL)/B-inhibitor combinations have used either
  - A single NI trial approach (meropenem/vaborbactam)
  - Phase 2 trial(s) in indication(s) for which the BL is approved (ceftazidime-avibactam)

https://www.fda.gov/downloads/Drugs/Guidances/UCM359184.pdf

Unmet Need Programs
Lessons Learned

- Need to consider attributes of the drug and suitability for streamlined development programs
- We have seen requests for streamlined programs for small incremental benefits and not really addressing an unmet need
- Pharmacokinetics of drugs in the unmet need population may differ from that in less sick patients
- Trials in patients with infections due to organisms of a specific resistance phenotype, e.g., carbapenemase resistant Enterobacteriaceae (CRE), are challenging to enroll
- Some programs included a small descriptive study in patients with CRE; having no pre-specified analysis makes interpretation of study results difficult
- With expedited clinical development programs, chemistry manufacturing and controls aspects of the program often lag behind

21st Century Cures Act

- Signed into law on December 13, 2016
- Title III, Subtitle E – Antimicrobial Innovation and Stewardship
  - Section 3044. Susceptibility test interpretive criteria for microorganisms; antimicrobial susceptibility testing devices
  - Section 3041. Antimicrobial Resistance Monitoring
  - **Section 3042. Limited Population Pathway for antibacterial and antifungal drugs (LPAD)**

https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf

LPAD

- The drug is intended to treat a serious or life-threatening infection in a limited population of patients with unmet needs
- Standards for approval under 505(c) and (d) or standards for licensure under 351 of Public Health Service Act are met
- Labeling will indicate that safety and effectiveness has only been demonstrated in a limited population

FDA Scientific Approaches to Facilitate Antibacterial Drug Development

- Establishing antimicrobial susceptibility test (AST) interpretive criteria and creation of AST criteria website
- Coordinated development of antimicrobial drugs and AST devices
- Guidances on drug development for specific indications
- Office of Antimicrobial Products research activities
- FDA public meetings on antibacterial drug development
- Collaboration with other regulatory authorities

Susceptibility Test Interpretive Criteria Website

www.fda.gov/STIC

Coordinated Development of Antimicrobial Drugs and AST Devices

- Many challenges in making AST available in a timely manner following approval of a new antibacterial drug
- Discussions at a public workshop held on September 29, 2016
  - Key bottlenecks and potential solutions to facilitate timely development of AST devices
  - Guidance on Coordinated Development of Antimicrobial Drugs and AST Devices
- CDER and CDRH have participated in joint meetings with drug/device manufacturers to discuss potential developmental approaches

https://www.fda.gov/Drugs/NewsEvents/ucm512519.htm
https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm521421.pdf

Guidances

- **Issued, 2016-2018**
  - QIDP Designation Questions and Answers, Draft
  - Systemic Antibacterial and Antifungal Drugs: Susceptibility Test Interpretive Criteria Labeling for NDAs and ANDAs Guidance for Industry, Final
  - Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases, Final
  - Microbiology Data for Systemic Antibacterial Drugs — Development, Analysis, and Presentation, Final
  - Bacterial Vaginosis: Developing Drugs for Treatment, Draft
  - Vulvovaginal candidiasis: Developing Drugs for Treatment, Draft
  - Anthrax: Developing Drugs for Prophylaxis of Inhalational Anthrax, Draft
- **Planned**
  - Uncomplicated urinary tract infections
  - Antibacterial drugs that treat a single species

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064980.htm

Research Projects

- **Ongoing projects in the antibacterial space through Broad Agency Announcements**
  - Development of an automated and sustainable electronic approach for data mining to evaluate clinical outcomes of patients with bacterial Infections
  - Evaluation of measurement properties of patient-reported outcomes (PRO) instruments in patients with CABP, HABP, and ABSSSI
  - Bridging novel laboratory animal and hollow fiber infection models to evaluate central nervous system penetration of drugs in infants
- **Research contracts for animal model of infections are awarded**
- **Research proposals to address antibacterial drug resistance are evaluated on an ongoing basis throughout the fiscal year**

www.fda.gov/OAPresearch

Research Activities

Office of Antimicrobial Products Research Activities

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Antimicrobial Regulatory Science Research

Antibacterial drug resistance is a major threat to public health. In March 2015, The National Action Plan for Combating Antibiotic-resistant Bacteria was developed in response to Executive Order 13676: *Combating Antibiotic-Resistant Bacteria*, which was issued on September 18, 2014. The National Action Plan outlines steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria to address urgent and serious drug-resistant threats that affect people in the U.S. and around the world. Implementation of the National Action Plan will also support World Health Assembly resolution 67.25 (Antimicrobial Resistance), which urges countries to take urgent action at the national, regional, and local levels to combat resistance.
The FDA's roles in combatting antibacterial drug resistance include:

- Facilitating the development of new antibacterial drugs to treat patients; and
- Advancing the science of clinical trial design. The design and conduct of clinical trials to evaluate new antibacterial drugs in patients with serious bacterial infections is challenging and therefore of particular interest for FDA's regulatory science program.

What's New

- ORISE Fellowship Announcements
- Fiscal Year 2017 and 2018 Office of Antimicrobial Products Research Priorities (PDF - 105 KB)
- FY 2017 Office of Antimicrobial Products Research Contracts (PDF - 112KB)

www.fda.gov/OAPresearch

FDA Public Meetings

- July 18 and 19, 2016: Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs that Target a Single Species
  http://www.fda.gov/Drugs/NewsEvents/ucm497650.htm
- September 15, 2016: Anti-Infective Drug Development in Neonates:
  https://www.fda.gov/Drugs/NewsEvents/ucm507958.htm
- September 29, 2016: Coordinated Development of Antimicrobial Drugs and Antimicrobial Susceptibility Test Devices: https://www.fda.gov/Drugs/NewsEvents/ucm512519.htm
- March 1, 2017: Current state and further development of animal models of serious infections caused by *A. baumannii* and *P. aeruginosa:*
  https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm
- April 13, 2017: Meeting of the Antimicrobial Drugs Advisory Committee
  https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/ucm551361.htm
- July 19, 2017: Development of New Tuberculosis Drug Regimens-Scientific and Clinical Design Considerations https://www.fda.gov/Drugs/NewsEvents/ucm548365.htm
- September 13, 2017: Antimicrobial Susceptibility and Resistance: Addressing Challenges of Diagnostic Devices
  https://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm564756.htm

Additional FDA Efforts to Facilitate Development of Antibacterial Drugs

- Collaboration with the Clinical Trials Transformation Initiative (CTTI), focused on improving trial efficiencies
- Collaboration with the Biomarkers Consortium of the Foundation for the National Institutes of Health (FNIH) to develop new endpoints for studying antibacterial drugs
- Collaboration with the Duke-Margolis Center for Health Policy on issues related to challenges in antibacterial drug development

Recently Approved Antibacterial Drugs

- Bedaquiline for multidrug-resistant pulmonary tuberculosis, December 2012
- Raxibacumab for anthrax, December 2012
- Telavancin for HABP/VABP, June 2013
- 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; for HABP/VABP, February 2018
- Obiltoxaximab for anthrax, March 2016
- Bezlotoxumab for reducing recurrence of *C. difficile* infection, October 2016
- Delafloxacin for ABSSSI, June 2017
- Meropenem-vaborbactam for cUTI, August 2017
- Secnidazole for bacterial vaginosis, September 2017

CABP: Community acquired bacterial pneumonia
ABSSSI: Acute bacterial skin and skin structure infections
cUTI: Complicated urinary tract infections
cIAI: Complicated intra-abdominal infection
HABP/VABP: Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia

Thank You