Fiscal Years 2016 – 2019 Office of Antimicrobial Products Research Priorities

Department of Health and Human Services

Food and Drug Administration, Silver Spring, MD

February 2019

Public Health Impact:

As bacteria continue to develop resistance, standard treatment can become ineffective and bacterial infections threaten global health. Therefore, there is an urgent need to develop new antibacterial drugs that are active against pathogens associated with antibacterial drug resistance and poor clinical outcomes to improve patient health and well-being worldwide.

FDA's roles in combatting antibacterial drug resistance are to: (1) facilitate the development of new antibacterial drugs to treat patients and (2) advance the science of clinical trial design.

Background:

In March 2015, The National Action Plan for Combating Antibiotic-Resistant Bacteria (CARB) 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. FDA/CDER receives funding from Congress on a yearly basis to support CARB related regulatory science research.

To facilitate the development of new antibacterial drugs active against multi-drug resistant bacteria and identify regulatory science research needs, FDA convened the following meetings:

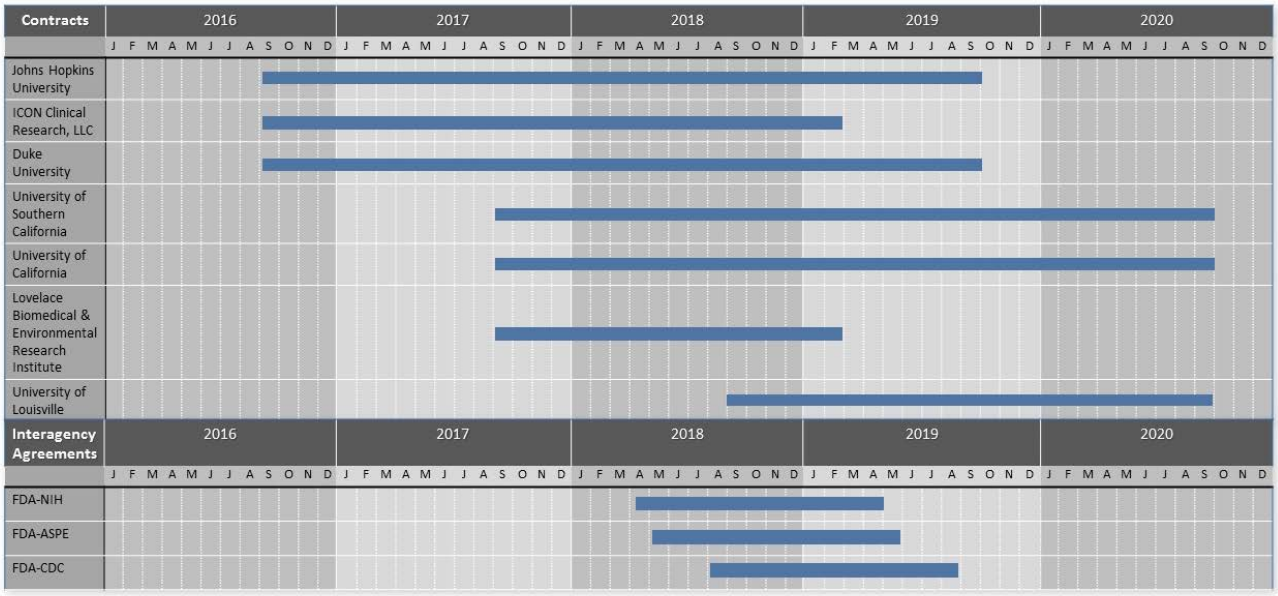
- July 18 - 19, 2016 FDA Public Workshop "Facilitating Antibacterial Drug Development for Patients with Unmet Need and Developing Antibacterial Drugs that Target a Single Species." Meeting materials can be reviewed at: http://www.fda.gov/Drugs/NewsEvents/ucm497650.htm
    - FDA Request for Information "Develop Animal Models of Infection." The December 13, 2016 announcement can be found at: https://www.fbo.gov/index?s=opportunity&mode=form&id=d9928804bf9bde9c313a7eb5697a1945&tab=core&_cview=1
- March 1, 2017 FDA Public Workshop "Current State and Further Development of Animal Models of Serious Infections Caused by *Acinetobacter baumannii* and *Pseudomonas aeruginosa.*" Meeting materials can be reviewed at: https://www.fda.gov/Drugs/NewsEvents/ucm534031.htm.
- April 13, 2017 Advisory Committee Meeting "Developing Antibacterial Therapies Targeting a Single Bacterial Species." Meeting materials can be reviewed at: https://www.fda.gov/AdvisoryCommittees/Calendar/ucm551347.htm.

- June 27, 2018 FDA Public Workshop "Development of Inhaled Antibacterial Drugs for Cystic Fibrosis and Non-Cystic Fibrosis Bronchiectasis." Meeting materials can be viewed at: https://www.fda.gov/Drugs/NewsEvents/ucm602331.htm
- August 21, 2018 FDA Public Workshop "Development of Non-Traditional Therapies for Bacterial Infections." Meeting materials can be viewed at: https://www.fda.gov/Drugs/NewsEvents/ucm606052.htm

FDA/Office of Antimicrobial Products Research (OAP):

To help stimulate development programs for antibacterial drugs where limited resources or a lack of incentives is preventing the development of new antibacterial drugs, FDA is identifying research areas where regulatory science can support new antibacterial drug development in general, by creating new drug development tools or standards for use by industry or other stakeholders, to meet patient needs.

Consistent with the CARB goals in the area of unmet medical need, fiscal years 2017 - 2019 research focused on: (1) development of databases, (2) developing Patient Reported Outcome (PRO)s, (3) evaluating CNS penetration of antibacterial drugs in human neonates, (4) animal model development or animal model refinement for serious infections caused by *Acinetobacter baumannii* or *Pseudomonas aeruginosa*, (5) understanding the market size for antibacterial drugs, (6) understanding the human microbiome, and (7) and developing and qualifying a Patient Reported Outcome (PRO) for Non-Cystic Fibrosis Bronchiectasis (NCFB) under FDA's Drug Development Tools Qualification Program.



Project Descriptions

Development of an Automated and Sustainable Electronic Approach for Data Mining to Evaluate Clinical Outcomes of Patients with Bacterial Infections

- Awarded to Johns Hopkins University School of Medicine (HHSF223201610070C)

- The objective of this project is to develop the coding needed for the electronic transfer of selected clinical data for patients with gram-negative bacteremia (bloodstream infection) in a commonly used electronic health records (EHR) system. The transferred data will populate a database for the evaluation of clinical outcomes considering patient characteristics and antibacterial drug breakpoints (the standards used by laboratories to report susceptibility of bacteria isolated from a patient to different antibacterial drugs).
- This study addresses an important regulatory science priority. The paucity of clinical outcomes data results in increasing reliance upon pharmacokinetic modeling for breakpoint updating with a trend toward lowering breakpoints primarily based on this modeling. The lowering of breakpoints may have stewardship implications as the use of second and third line agents may increase. The availability of this clinical outcome information is expected to be useful in discussions concerning revising breakpoints.

Evaluation of the Measurement Properties of Patient-Reported Outcome (PRO) Instruments in Patients with Community-Acquired Bacterial Pneumonia (CABP) and Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

- Awarded to ICON Clinical Research LLC (HHSF223201610100C)
- The objectives of this contract are to carry out psychometric evaluations of new Patient Reported Outcome (PRO) instruments for Community-Acquired Bacterial Pneumonia (CABP), Hospital-Acquired Bacterial Pneumonia (HABP), and Acute Bacterial Skin and Skin Structure Infection (ABSSSI). These CABP-specific, HABP-specific, and ABSSSI-specific PRO instruments will be submitted for qualification in accordance with both the FDA PRO guidance and the FDA drug development tool (DDT) qualification draft guidance.
- These objectives address the improvement of clinical endpoints for antibacterial drug trials listed in the Broad Agency Announcement (FDABAA-17-00123; section 2.4). The overall goals of this project are to develop qualified instruments for each disease that can be used by drug developers for the qualified context of use in IND and NDA/BLA submissions.

Bridging Novel Laboratory Animal and Hollow Fiber Infection Models to Evaluate Central Nervous System Penetration of Drugs in Infants

- Awarded to Duke University (HHSF223201610082C)
- The overall goal of this project is to develop and evaluate a new paradigm for evaluating CNS penetration of antibacterial drugs in human neonates. The objectives of this project are: (1) develop and validate a rabbit model of CNS infection and define the pharmacodynamics of the antibacterial drugs meropenem and tobramycin for the treatment of meningitis, (2) develop and validate a hollow fiber infection model (HFIM) of neonatal meningitis to characterize the pharmacodynamics of meropenem and tobramycin by evaluating bacterial killing and emergence of antimicrobial resistance, (3) bridge the preclinical results to infants using population PK-PD modeling to guide dosing regimens of meropenem and tobramycin for treatment of meningitis in infants.
- The study may help identify new approaches to study antibacterial drugs in infants, with the goal of obtaining the information needed to label an antibacterial drug for pediatric use more efficiently.

Rabbit Models of *Pseudomonas aeruginosa* Acute Pneumonia, Severe Sepsis, and Ventilator-Associated Pneumonia for Novel Antibacterial Development

- Awarded to University of California, San Francisco (HHSF223201710112C)
- The objectives of this contract are to advance the development of rabbit infection models as a translational approach for testing new drug candidates for the treatment of serious infections caused by *Pseudomonas aeruginosa* in humans.
- This study aligns with section 2.4.2 of the Broad Agency Announcement (FDABAA-17-00123) to advance the science of animal model development to facilitate antibacterial drug development.

Development of a Porcine Model of Ventilator-Associated Pneumonia Caused by *Acinetobacter baumannii*

- Awarded to Lovelace Biomedical & Environmental Research Institute (HHSF223201710130C)
- The objective of this contract is to advance the development of porcine infection models as a translational approach for testing new drug candidates for the treatment of serious infections caused by *Acinetobacter baumannii* in humans.
- This study aligns with section 2.4.2 of the Broad Agency Announcement (FDABAA-17-00123) to advance the science of animal model development to facilitate antibacterial drug development.

A Preclinical Mouse Model of *Acinetobacter baumannii* Infection for Antibacterial Development

- Awarded to University of Southern California (HHSF223201710199C)
- The project is aimed at refinement of an established mouse model of *Acinetobacter baumannii* pneumonia and bacteremia infection.
- This study aligns with section 2.4.2 of the Broad Agency Announcement (FDABAA-17-00123) to advance the science of animal model development to facilitate antibacterial drug development.

Development of a Mouse Model for Preclinical Screening of Investigational Drugs Against Pseudomonas aeruginosa

- Awarded to University of Louisville School of Medicine (HHSF22320180171C)
- The project aim is: (1) to validate this model against multiple *P. aeruginosa* isolates with different drug resistance profiles by establishing the LD50 and natural history for each isolate and (2) to establish dosing parameters for two control antibiotics using PK/PD analysis/models so that these antibiotics can be used as controls/comparators to better gauge the efficacy of novel investigational drugs against *P. aeruginosa*.
- This study aligns with section 2.4.2 of the Broad Agency Announcement (FDABAA-17-00123) to advance the science of animal model development to facilitate antibacterial drug development.

Estimating the National Market size for Novel Gram-negative Active Agents

- Interagency Agreement between FDA and National Institutes of Health (224183008S)
- Project aim: (1) Investigators at NIH will quantify the opportunities for empiric and targeted antibacterial therapy for patients within the Cerner Healthfacts dataset with infections secondary to Gram-negative isolates displaying resistance to: (a) all first-line treatment options including

carbapenems where novel agents with superior efficacy and toxicity profiles would be optimal and (b) extended-spectrum cephalosporins for which new carbapenem-sparing agents could be utilized and (2) work collaboratively with HHS economists to generate national market projections for novel agents that either spare carbapenems or retain activity when existing first-line gram-negative active agents remain inactive.

Understanding Markets for Antibacterial Drug Development

- Interagency Agreement between FDA and HHS Office of the Assistant Secretary for Planning and Evaluation (224183013S)
- The goals of the project are to understand the: (1) market for antibacterial drugs, (2) incentives for developing new antibacterial drugs, and (3) social value of developing new bacterial drugs.
- The project aims are to: (1) undertake a comparison of the development and production costs, clinical value, and market performance of a cohort of recent antibacterial approvals with an appropriate control group, (2) analyze potential market failures in the antibacterial drug market, and (3) predict future market failure and how to address them.

A Human Microbiome Disruption Model

- Interagency Agreement between FDA and Centers for Disease Control and Prevention (224183015S)
- The goals of this project are to to address the need for a tool that drug developers can use early in drug development to help select agents that are less disruptive, more protective, or better restore the microbiome toward a state less likely to promote colonization or infection with multidrug-resistant organisms.
- The project will advance the science of measuring antibiotic-specific human microbiome disruption and adverse events associated with this disruption

Additional Research Areas of Interest

FDA is also interested in the following research topic areas as part of CARB efforts:

- Evaluate potential innovations in clinical trial design for new antibacterial drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches
- Advance the science of in-vitro, animal model, and/or pharmacokinetic studies to facilitate antibacterial drug development, including studies focused on drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction
- Evaluate strategies to enrich enrollment in clinical trials for new antibacterial drugs such as the use of rapid diagnostic tests
- Advance the science of antibacterial drug susceptibility testing

Detailed information on the research activities can be found on FDA's Office of Antimicrobial Products Research webpage: https://www.fda.gov/OAPResearch