Fiscal Years 2016 – 2021

Office of Infectious Diseases

CARB Research Overview

Department of Health and Human Services

Food and Drug Administration, Silver Spring, MD

October 2021

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. The updated National Action Plan for 2020 - 2025 continues to outline steps for implementing the National Strategy for Combating Antibiotic-Resistant Bacteria to address urgent and serious drug-resistant threats (bacteria and fungi) 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
- 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 FDA 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
- April 18, 2019 "Development of Antibacterial Drugs for the Treatment of Nontuberculous Mycobacterial Disease." Meeting materials can be reviewed at: https://www.fda.gov/drugs/development-antibacterial-drugs-treatment-nontuberculous-mycobacterial-disease-04082019-04082019
- November 18 – 19, 2019 FDA Public Workshop "Enhancing the Clinical Trial Enterprise for Antibacterial Drug Development in the United States." Meeting materials can be viewed at: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/enhancing-clinical-trial-enterprise-antibacterial-drug-development-united-states-11182019-11192019
- March 5, 2020 FDA Public Workshop "Advancing Animal Models for Antibacterial Drug Development." Meeting materials can be viewed at: https://www.fda.gov/drugs/news-events-human-drugs/advancing-animal-models-antibacterial-drug-development-03052020-03052020.
- August 5, 2020 FDA Public Workshop "Coccidioidomycosis (Valley Fever): Considerations for Development of Antifungal Drugs" Meeting materials can be reviewed at: https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/coccidioidomycosis-valley-fever-considerations-development-antifungal-drugs-08052020-08052020
- September 25, 2020 FDA Public Workshop "Addressing Challenges in Inhaled Antifungal Drug Development" Meeting materials can be reviewed at: https://www.fda.gov/drugs/news-events-human-drugs/addressing-challenges-inhaled-antifungal-drug-development-09252020-09252020.

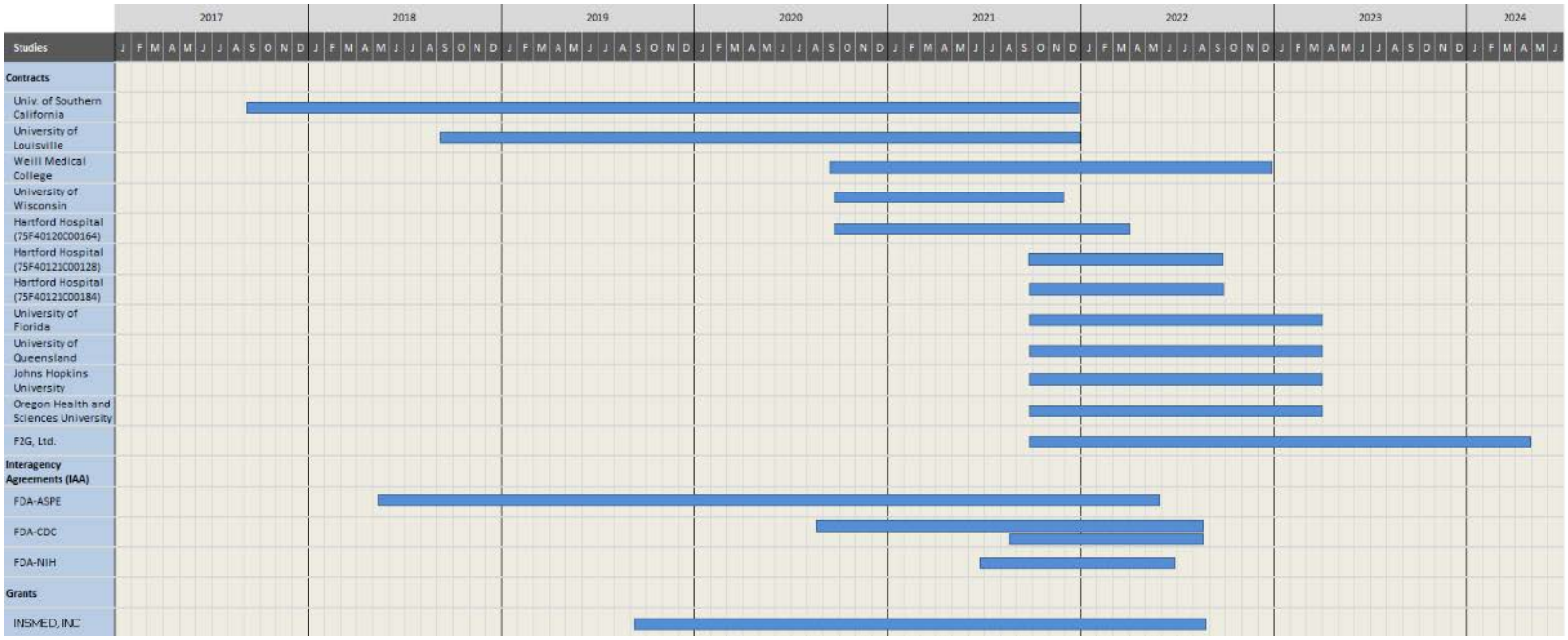
FDA CARB Research Priorities

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 has identified research areas where regulatory science can support new antibacterial drug development in general. These areas include:

- 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.

Consistent with the CARB goals in the area of unmet medical need, fiscal years 2017 - 2021 research focuses on: (1) animal model development or animal model refinement for serious infections caused by *Acinetobacter baumannii* or *Pseudomonas aeruginosa*, (2) understanding the market size for antibacterial drugs, (3) understanding the human gut and lung microbiome, (3) developing and qualifying a Patient Reported Outcome (PRO) for Non-Cystic Fibrosis Bronchiectasis (NCFB), (4)

understanding the development and use of clinical practice guidelines for infectious diseases, (5) advancing the science of drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care, (6) developing PROs for non-tuberculous mycobacterial (NTM) disease and coccidioidomycosis, and (7) evaluating the impact of extended-infusion of β-lactam antibiotics on patient outcomes and the development of resistance.



Timelines for Ongoing CARB Research Studies

Project Descriptions for Ongoing CARB Research Studies

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

- BAA contract awarded to University of Southern California (FY17: 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 to advance the science of animal model development to facilitate antibacterial drug development.
- Study Outcomes:
    - Publication: Nielsen TB, Yan J, Luna B, Spellberg B. Murine Oropharyngeal Aspiration Model of Ventilator-associated and Hospital-acquired Bacterial Pneumonia. J Vis Exp. 2018 Jun 28;(136):57672. doi: 10.3791/57672. PMID: 30010650; PMCID: PMC6102004. (Link)
    - Publication: Luna BM, Yan J, Reyna Z, Moon E, Nielsen TB, Reza H, et al. (2019) Natural history of *Acinetobacter baumannii* infection in mice. PLoS ONE 14(7): e0219824. https://doi.org/10.1371/journal.pone.0219824 (Link)

- Publication: Luna B, Trebosc V, Lee B, Bakowski M, Ulhaq A, Yan J, Lu P, Cheng J, Nielsen T, Lim J, Ketphan W, Eoh H, McNamara C, Skandalis N, She R, Kemmer C, Lociuro S, Dale GE, Spellberg B. A nutrient-limited screen unmasks rifabutin hyperactivity for extensively drug-resistant Acinetobacter baumannii. Nat Microbiol. 2020 Sep;5(9):1134-1143. doi: 10.1038/s41564-020-0737-6. Epub 2020 Jun 8. PMID: 32514072; PMCID: PMC7483275. (Link)

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

- BAA contract awarded to University of Louisville School of Medicine (FY18: HHSF22320180171C)
- The project aim is: (1) to validate this model against multiple *P. aeruginosa* isolates with different drug resistance profiles by establishing the LD_{50} 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 (to advance the science of animal model development to facilitate antibacterial drug development.

Understanding Markets for Antibacterial Drug Development

- Interagency Agreement between FDA and HHS Office of the Assistant Secretary for Planning and Evaluation (FY18: 224183013S; FY19: 75F40119S30008)
- 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.
- Study Outcomes:
    - Poster Presentation: Integrating Existing Metrics to Assess Comparative Real-World Clinical Effectiveness of Recently Approved Antimicrobial Drugs (Academy Health Annual Research Meeting, June 2021, Link)

Development of a Novel PRO Tool for Use in Clinical Trials to Measure Symptoms in Patients with Non-Cystic Fibrosis Bronchiectasis (NCFB) with and without Non-Tuberculous Mycobacterial (NTM) Lung Infection

- Awarded to INSMED, INC (FY19: 1U01FD006687-01)
- The specific aims of this project are to: (1) conduct concept elicitation research to identify the unique symptoms and experience of people diagnosed with NCFB with and without NTM, (2) conduct a non-interventional study in order to validate a novel draft Patient Reported Outcome (PRO) instrument for NCFB, and (3) evaluate the PRO developed in aim 1 to be fit-for-purpose in assessing symptoms among patients with NCFB and NTM and by contrasting the performance of the core PRO between patients diagnosed with NCFB with and without NTM.

- Currently, there are no validated endpoints to advance new therapies for populations with NCFB with or without NTM lung infection. The overall goal of this project is to develop a novel PRO instrument that is advanced to the stage of readiness to be included in a clinical trial to allow qualification for drug development and regulatory decision making in the NCFB field. The qualified PRO could then help design and conduct better clinical trials as well as lead to better interpretation of anti-infective drug trials for NCFB.

Understanding the Development and Use of Clinical Practice Guidelines for Infectious Diseases.

- Interagency Agreement between FDA and HHS Office of the Assistant Secretary for Planning and Evaluation (FY 20, FY 21: 75F40120S30020).
- In FY 20 the study aims include: 1) explore how to support evidence-based clinical practice in the treatment of antibiotic-resistant infectious disease, 2) address knowledge gaps around the effective development and updating of clinical practice guidelines.
- In FY 21 ASPE plans to finish analysis and disseminate results from the study at a public stakeholder meeting and also through peer-reviewed publication.
- This study will explore considerations that may make the treatment of resistant infections different than other areas of clinical practice. Furthermore, the study may lead to more effective development of antibacterial treatment guidelines by exploring best practices used during treatment guideline development. More effective treatment guidelines for infectious diseases would positively affect patient outcomes.

Leveraging the Microbiome to Improve Patient Management and Control of Antibiotic Resistance in Cystic Fibrosis Patients.

- Interagency Agreement between FDA and Centers for Disease Control and Prevention (FY 20: 75F40120S10020).
- The aims of this study are: 1) Determine the treatment drivers (e.g. drug selection, dosage, and treatment duration) of microbiome disruption and competitive release of resistant *P. aeruginosa* in defined polymicrobial contexts; 2) Determine the drivers of microbiome disruption and competitive release of resistant *P. aeruginosa* in *ex vivo* microbial communities of Cystic Fibrosis (CF) patient sputa; 3) Determine the drivers of competitive release of resistant pathogens in CF patients under antibiotic treatment
- Results from this study will guide understanding on how various antibiotic treatments impact the lung microbiome. Long term, this study will contribute to the development of microbiome indices for antibiotics and a standard approach that prevents adverse events resulting from antimicrobial use, such as the emergence of antibiotic resistant organisms.

Development of Rabbit Animal Models of Ventilator-Associated Bacterial Pneumonia Produced by Carbapenem-Resistant *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

- Awarded to Weill Medical College of Cornell University (FY20: 75F40120C00140)
- The objectives of this study are: 1) develop a rabbit model of carbapenem-resistant *P. aeruginosa* VAP, 2) develop a rabbit model of carbapenem-resistant *A. baumannii* VAP, 3) characterize the pulmonary pathophysiology, microbiology, and pharmacology of the rabbit VAP models, 4) investigate one or more new antibacterial agents in the VAP models.
- The study is expected to result in the development of two rabbit models of VAP. Currently, there are no well characterized VAP animal models which use carbapenem-resistant bacterial strains. These

rabbit models would provide the nonclinical foundation for future development of antimicrobials against resistant infections.

- This study aligns with section 2.4.2 of the Broad Agency Announcement to advance the science of animal model development to facilitate antibacterial drug development.

Development of Modernized *Acinetobacter baumannii* Susceptibility Guidance for Recommended Antimicrobial Agents using Pharmacometric Approaches.

- Awarded to the University of Wisconsin System (FY20: 75F40120C00111)
- The overall objective for this study is to characterize the contemporary *A. baumannii* minimum inhibitory concentration (MIC) for various antibiotics (e.g. minocycline, ciprofloxacin, etc.). The study will characterize PK-PD of each antibiotic using validated mouse-thigh and mouse-lung infection models and to identify candidate STIC for each antibiotic by integrating animal model-derived PK-PD relationships and PK model-derived human exposures through Monte Carlo simulation in the context of contemporary MIC distribution data.
- The results of this study will improve clinical guidance for the care of patients suffering with multi-drug resistant *A. baumannii* infections.
- This study aligns with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.

Pharmacodynamics of Minocycline, Levofloxacin, and Trimethoprim/Sulfamethoxazole Against *Stenotrophomonas maltophilia*: Implications for Susceptibility Breakpoint Revisions.

- Awarded to the Hartford Hospital (FY20: 75F40120C00171)
- The overall objective for this study is to determine the *in vivo* pharmacodynamics of minocycline and levofloxacin and *in vitro* pharmacodynamics of trimethoprim/sulfamethoxazole against clinically representative *S. maltophilia*. This study will support the assessment of susceptibility breakpoints for these antibiotics against *S. maltophilia*.
- The results of this study may assist in revising or updating the current susceptibility breakpoints for certain antibiotics against *S. maltophilia*.
- This study aligns with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - Poster Presentation: Levofloxacin pharmacodynamics against *Stenotrophomonas maltophilia* in a neutropenic murine thigh infection model: implications for susceptibility breakpoint revision (World Microbe Forum 2021).
    - Oral Abstract: *In Vivo* Efficacy of Human Simulated Minocycline against *Stenotrophomonas maltophilia* (IDWeek 2021).
    - Poster Presentation: Minocycline Pharmacodynamics against *Stenotrophomonas maltophilia* in a Neutropenic Murine Thigh Infection Model (IDWeek 2021).
    - Publication: Fratoni AJ, Nicolau DP, Kuti JL. Levofloxacin pharmacodynamics against Stenotrophomonas maltophilia in a neutropenic murine thigh infection model: implications for susceptibility breakpoint revision. J Antimicrob Chemother. 2021 Sep 20:dkab344. doi: 10.1093/jac/dkab344. Epub ahead of print. PMID: 34542637. (link)

Expanding Current and Future Susceptibility Testing Criteria with Genotypic Data: Comparative Efficacy of Human-Simulated Exposures of Ceftazidime/Avibactam, Imipenem/Relebactam, and Meropenem/Vaborbactam against Oxa-48-β-lactamase-Producing Enterobacterales in the Neutropenic Murine Thigh Infection Model.

- Awarded to the Hartford Hospital (FY20: 75F40120C00152)
- The study aims to advance the field of susceptibility breakpoint determination by assessing the contribution of bacterial genotype to antibiotic efficacy. Current breakpoint decisions are made based primarily on the MIC phenotype. This study will utilize genotypic profiles, phenotypic MIC testing, and a neutropenic murine (mouse) thigh infection model to determine whether genotypic information should be considered as part of the antibiotic breakpoint determination package.
- The results of this study may help guide utilization practices for relevant antibiotics such as meropenem-vaborbactam, ceftazidime-avibactam, or imipenem-relebactam when treating resistant infections.
- This study aligns with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.
- Study Outcomes:
    - *Poster Presentation*: Phenotypic assessment of carbapenem and carbapenem/β-lactamase inhibitor activity against OXA-48-producing Enterobacterales: The challenge of variable hydrolysis and definitive breakpoints (World Microbe Forum 2021).

Metallo-β-Lactamase (MBL) Resistance in Enterobacterales: Is It Time to Rethink our In Vitro Assessment Tools?

- Awarded to the Hartford Hospital (FY20: 75F40120C00164)
- The study aims to assess whether carbapenem therapy can be utilized to effectively manage serious infections due to MBL-producing *Enterobacterales*. This will be achieved by evaluating the effect that zinc concentrations may have on the MIC interpretation of the activity of carbapenems. It has been observed that conventional susceptibility testing, using conventional culture media, may impair the interpretation of the activity of carbapenems against MBL-producing *Enterobacterales*. This has been attributed to the higher zinc concentration in conventional culture media as compared to the zinc levels present *in vivo*.
- This study may result in the modification or refinement of the current methods for *in vitro* antimicrobial susceptibility testing and the protocols for the selection of effective treatment for patients with MBL-producing *Enterobacterales* infections.
- This study aligns with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.

Expanded Metabolomic Interrogation of an Intestinal Microbiome Disruption Model.

- Interagency Agreement between FDA and Centers for Disease Control and Prevention (FY 21: 75F40121S30022).
- The overarching goal of this study is to create an experimental culture system that identifies agents that disrupt or protect the human intestinal microbiome. This study expands upon initial successes (FY19, CDC) to identify additional markers of microbiome disruption by monitoring different metabolite types and by using a broader array of disrupting antimicrobial agents. This work will

improve system reliability and interpretability, and will distinguish qualitatively different modes of disruption.

- Data from these studies will be important to develop a standard test that predicts adverse events from antimicrobial use. This knowledge will help identify where preventative or restorative interventions, as well as new narrower-spectrum antibiotic development, can help to mitigate risks for patients taking antibiotics

Assessment of Residual Needs for Novel Gram-negative Active Agents: A Real-world Post-Approval Pharmacoepidemiologic Analysis, U.S. Hospital, 2019-2020

- Interagency Agreement between FDA and National Institutes of Health (FY 21: 75F40121S30021).
- This study will aim to confirm and validate previous work conducted (FY18, NIH) by using the Premier Inc. database. Study Aims include: 1) quantify the opportunities for empiric and targeted treatment with antibacterial therapy for inpatients between 2019-2020 with suspected or confirmed infections secondary to Gram-negative isolates displaying high level resistance, 2) Assess the impact of the FDA approved gram-negative active antibiotics since 2015 with activity against carbapenem-resistant gram-negative infections on current market estimates.
- This study will provide information to help better understand the current landscape for novel gram-negative antibiotics during 2019-2020 and assess the impact of recently approved antibiotics on potential future market size.

A Critical Look at Cefepime Breakpoints *In Vivo*: An Assessment of Cefepime Activity against Carbapenemase-producing *Enterobacterales* with Unexpected Cefepime-Susceptibility and Cefepime Susceptible-Dose Dependent Phenotypic Profiles

- Awarded to Hartford Hospital (FY21: 75F40121C00128)
- The overall objective of this study is to advance the science of susceptibility testing and reporting as well as breakpoint determination as it pertains to cefepime activity against bacteria that produce prevalent carbapenemases such as *Klebsiella pneumoniae* carbapenemase (KPC).
- Results from this study will determine the therapeutic implications of administering cefepime when the infecting isolate demonstrates discordance between its genotype and phenotype, as well as provide insights on the appropriate phenotypic test that can resolve this discrepancy when encountered in the clinic.
- This study aligns with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.

Ampicillin-Sulbactam against *Acinetobacter baumannii* infections: Pharmacokinetic/Pharmacodynamic Appraisal of Current Susceptibility Breakpoints and Dosing Recommendations

- Awarded to Hartford Hospital (FY21: 75F40121C00184)
- The objective of this study is to assess the pharmacokinetics and pharmacodynamics of ampicillin-sulbactam against *A. baumannii* infections in the murine pneumonia model. The outcomes from the infection model will be correlated to the ampicillin-sulbactam *in vitro* susceptibility interpretive criteria (breakpoints) to assess the capability of these breakpoints to predict *in vivo* outcomes.

- This study represents the first comprehensive assessment of the PK/PD of ampicillin-sulbactam against *A. baumannii* infection which aims to provide insights to assess the suitability of the current established breakpoints.
- The study aligns with section 2.4.4 of the Broad Agency Announcement: advance the science of antibacterial drug susceptibility testing to ensure that up to date susceptibility testing criteria (breakpoints) are available for patient care and antimicrobial stewardship.

β-lactam Continuous Versus Intermittent Infusion and Associated Bacterial Resistance and Therapy Outcomes in Critically ill Patients with Severe Pneumonia

- Awarded to University of Florida (FY21: 75F40121C00157)
- The goal of this study is to conduct a randomized, controlled clinical trial that aims to identify the benefits and risk of β-lactam continuous versus intermittent infusion in critically ill patient with severe pneumonia caused by gram-negative pathogens who have been admitted to the ICU. The study will compare the clinical, microbiological, and safety outcomes between the two groups of patients.
- This study will attempt to fill a current knowledge gap concerning the development of antimicrobial resistance between different infusion strategies of β-lactam antimicrobials. Results may guide future dosing recommendations of the antimicrobials and help identify patients who could benefits from prolonged infusion to achieve better drug exposure and therapy outcome.
- This study aligns with section 2.4.2 of the Broad Agency Announcement: Advance the science of in-vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction

Continuous versus Intermittent Infusions of β-lactam Antibacterial Drugs: Impact on Resistance and Outcomes in Sepsis

- Awarded to The University of Queensland (FY21: 75F40121C00126)
- The aim of this study is to explore the relationship between β-lactam antibacterial exposure (accounting for antibacterial concentration, bacterial susceptibility, and method of administration) and clinical outcomes (e.g., all-cause 90-day mortality, clinical cure at day 14 post-randomization) of sepsis patients observed in the BLING III clinical trial (NCT03213990). This study is a sub-study of the BLING III clinical trial and is a prospective observational study only.
- The goal of this study is to provide data to better understand the optimal dosing method and method of exposure of β-lactam antimicrobials that lead to better clinical outcomes in patients with sepsis.
- This study aligns with section 2.4.2 of the Broad Agency Announcement: Advance the science of in-vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction

Evaluating the Impact of Extended-Infusion B-lactam Administration Strategies on Improving Clinical Outcomes and Reducing the Subsequent Emergence of Antimicrobial Resistance

- Awarded to Johns Hopkins University School of Medicine (FY21: 75F40121C00127)
- The overarching objective of this study is to determine whether prolonging the infusion time of B-lactam therapy for the treatment of Gram-negative bloodstream infections improves patient outcomes while reducing the emergence of subsequent resistance to the B-lactam agent initially administered.
- This study will provide needed information regarding the association between extending antibiotic administration and reducing the emergence of resistance. Results from this study may help inform clinicians of treatment strategies to better optimize patient outcomes.
- This study aligns with section 2.4.2 of the Broad Agency Announcement: Advance the science of in-vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antimicrobial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction

Development of Pulmonary Nontuberculous Mycobacterial Disease Symptom Scale (NTM-SS), Pulmonary NTM Infection

- Awarded to Oregon Health and Science University (FY21: 75F40121C00120)
- The objective of this study is to develop, test, and validate a disease-specific patient-reported outcome (PRO) measure in well-characterized population of patient with NTM
- Clinical trials for NTM treatment have been limited by the lack of validated measures (e.g., PROs) to assess clinical benefit. This study intends to develop a NTM-specific PRO in order to improve clinical trial design and identify more effective treatments for patients with NTM pulmonary disease.
- This study aligns with section 2.4.1 of the Broad Agency Announcement: Evaluate potential innovations in clinical trial design for new drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches.

Creation and Validation of a Patient Reported Outcome (PRO) Instrument for the Assessment of Health-Related Quality of Life (HRQOL) in Patients with Coccidioidomycosis

- Awarded to F2G, Ltd. (FY21: 75F40121C00145)
- The objective of this study is to develop and validate a PRO measure for the management of chronic disseminated coccidioidomycosis (Valley Fever).
- Currently, there are no well-defined and validated endpoints for use in coccidioidomycosis clinical trials. The PRO instrument under development in this study aims to accurately assess the efficacy of anti-fungal treatments for coccidioidomycosis.
- This study aligns with section 2.4.1 of the Broad Agency Announcement: Evaluate potential innovations in clinical trial design for new drugs such as enrollment strategies, data collection streamlining, drug development tools, clinical endpoints, and new statistical analytic approaches.

Previously Funded Studies:

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 (FY16: HHSF223201610070C)
- The objective of this project was 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 populated 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 addressed 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.
- Study Outcomes:
    - Publication: Fabre V, Amoah J, Cosgrove SE, Tamma PD. Antibiotic Therapy for Pseudomonas aeruginosa Bloodstream Infections: How Long Is Long Enough? Clin Infect Dis. 2019 Nov 13;69(11):2011-2014. doi: 10.1093/cid/ciz223. PMID: 30882137; PMCID: PMC7320076. (Link)
    - Publication: Fox MT, Amoah J, Hsu AJ, Herzke CA, Gerber JS, Tamma PD. Comparative Effectiveness of Antibiotic Treatment Duration in Children With Pyelonephritis. JAMA Netw Open. 2020 May 1;3(5):e203951. doi: 10.1001/jamanetworkopen.2020.3951. PMID: 32364593; PMCID: PMC7199115. (Link)

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 (FY16: HHSF223201610100C)
- The objectives of this contract were 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 may be submitted for qualification in accordance with both the FDA PRO guidance and the FDA drug development tool (DDT) qualification draft guidance.
- These objectives addressed 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 were 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 (FY16: HHSF223201610082C)
- The overall goal of this project was to develop and evaluate a new paradigm for evaluating CNS penetration of antibacterial drugs in human neonates. The objectives of this project were: (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 (FY17: HHSF223201710112C)
- The objectives of this contract were 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 aligned 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.
- Study Outcomes:
    - Publication: Nguyen NTQ, Gras E, Tran ND, Nguyen NNY, Lam HTH, Weiss WJ, Doan TNM, Diep BA. Pseudomonas aeruginosa Ventilator-Associated Pneumonia Rabbit Model for Preclinical Drug Development. Antimicrob Agents Chemother. 2021 Jun 17;65(7):e0272420. doi: 10.1128/AAC.02724-20. Epub 2021 Jun 17. PMID: 33972247; PMCID: PMC8218622. (Link)

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

- Awarded to Lovelace Biomedical & Environmental Research Institute (FY17: HHSF223201710130C)
- The objective of this contract was 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 aligned 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 (FY18: 224183008S)
- Project aims were: (1) quantify the opportunities for empiric and targeted antibacterial therapy for patients within the *Cerner Healthfacts* dataset with infections secondary to Gram-negative (GN) 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.

- This study will provide an understanding of the real-world market size for new agents with activity against resistant GN pathogens with limited treatment options could inform appropriate use, mitigate over-reliance on carbapenems, and ensure balance in aligning both incentives and investments.
- Study Outcomes:
    - IDSA Abstract: Jeffrey R Strich, MD, Sarah Warner, MPH, Yi Ling Lai, MPH, Cumhur Y Demirkale, PhD, John H Powers, MD, Robert L Danner, MD, Sameer S Kadri, MD, MS, 2251. Estimating the Need for Novel Gram-Negative Active Antibiotics in US Hospitals, *Open Forum Infectious Diseases*, Volume 6, Issue Supplement_2, October 2019, Pages S769–S770, (Link)
    - Publication: Strich JR, Warner S, Lai YL, Demirkale CY, Powers JH 3rd, Danner RL, Kadri SS. Needs assessment for novel Gram-negative antibiotics in US hospitals: a retrospective cohort study. Lancet Infect Dis. 2020 Oct;20(10):1172-1181. doi: 10.1016/S1473-3099(20)30153-5. Epub 2020 Jun 4. PMID: 32505231; PMCID: PMC7272178. (Link)

MIC Breakpoints

- Interagency Agreement between FDA and National Institutes of Health (FY19: 75F40119S30002; FY20: 75F40120S30046)
- The project aims are to: (1) develop an approach using *Cerner Healthfacts* dataset to determine whether there is a correlation between patients stratified by existing *in vitro* MIC breakpoints and those stratified by clustering of risk-adjusted clinical outcome, (2) identify the strengths and limitations of this approach, and (3) compare findings from this approach with any relevant published literature concerning MIC breakpoints for the same drug-bug combination analyzed.
- The FY20 study will focus the MIC breakpoints and clinical outcomes analysis on *Stenotrophomonas maltophilia* and various relevant antimicrobial agents.
- The expected outcome from this study is an adjusted odds ratio of in-hospital mortality stratified by existing MIC breakpoints. Data from this study will help to further define the relationship between MIC breakpoints and risk-adjusted clinical outcomes.

Natural Language Processing (NLP) of Electronic Health Records (EHRs) to Advance Understanding of Antimicrobial Resistance (AMR)

- Awarded a Task Order to the MITRE Corporation (FY19: 75F40119F80474).
- This proof of concept study aimed to: (1) demonstrate a tightly focused application of Natural Language Processing (NLP) on a set of Electronic Health Records (EHRs) using a database to understand the utility of NLP analysis of EHRs for antimicrobial resistance (AMR) relevant information, (2) conduct NLP that analyzes unstructured notes in EHRs, such as anonymized hospital admission and discharge notes, and assess whether we can train the machine to recognize in notes that certain events took place, such as a patient had an abscess drained or had infected hardware removed from their body.

- The purpose of this study was to conduct a NLP proof of concept study on a single topic (i.e. source control) and a single use case to assess the benefits and limitations of NLP in automating analysis of information relevant to AMR in EHRs. This information will be the basis to build a full NLP annotation study in the future.

A Human Microbiome Disruption Model

- Interagency Agreement between FDA and Centers for Disease Control and Prevention
- In FY19 (75F40119S30012), CDC will continue to support studies to understand the microbiome disruption potential for antibiotics. Specifically, CDC will fund a study, using both FDA-CDER IAA and CDC AR funds to identify and validate biomarkers of microbiome disruption in a microbiome model to measure antimicrobial disruption of gastrointestinal (GI) microbiome. This project will advance the science of measuring antibiotic-specific human microbiome disruption.
- Data from these studies will be important to develop a standard test that predicts adverse events from antimicrobial use. This knowledge will help identify where preventative or restorative interventions, as well as new narrower-spectrum antibiotic development, can help to mitigate risks for patients taking antibiotics.

Additional Publications by FDA Staff and Fellows Supported by CARB Funding:

- Dheman N, Mahoney N, Cox EM, Farley JJ, Amini T, Lanthier ML. An Analysis of Antibacterial Drug Development Trends in the US, 1980 - 2019. Clin Infect Dis. 2020 Jun 25:ciaa859. doi: 10.1093/cid/ciaa859. Epub ahead of print. PMID: 32584952. https://pubmed.ncbi.nlm.nih.gov/32584952/

- Bart SM, Farley JJ, Bala S, Amini T, Cox E. Geographic shifts in antibacterial drug clinical trial enrollment: implications for generalizability. Clin Infect Dis. 2020 Mar 12:ciaa246. doi: 10.1093/cid/ciaa246. Epub ahead of print. PMID: 32161946. https://pubmed.ncbi.nlm.nih.gov/32161946/

- Waack U, Weinstein EA, Farley JJ. Assessing Animal Models of Bacterial Pneumonia Used in Investigational New Drug Applications for the Treatment of Bacterial Pneumonia. Antimicrob Agents Chemother. 2020 Apr 21;64(5):e02242-19. doi: 10.1128/AAC.02242-19. PMID: 32122895; PMCID: PMC7179594. https://pubmed.ncbi.nlm.nih.gov/32122895/

- Bart SM, Nambiar S, Gopinath R, Rubin D, Farley JJ. Concordance of early and late endpoints for community-acquired bacterial pneumonia trials. Clin Infect Dis. 2020 Jun 25:ciaa860. doi: 10.1093/cid/ciaa860. Epub ahead of print. PMID: 32584969. https://pubmed.ncbi.nlm.nih.gov/32584969/

- Bart SM, Rubin D, Kim P, Farley JJ, Nambiar S. Trends in hospital-acquired and ventilator-associated bacterial pneumonia trials. Clin Infect Dis. 2020 Nov 11:ciaa1712. doi: 10.1093/cid/ciaa1712. Epub ahead of print. PMID: 33173946. https://pubmed.ncbi.nlm.nih.gov/33173946/

- Byrne JM, Waack U, Weinstein EA, Joshi A, Shurland SM, Iarikov D, Bulitta JB, Diep BA, Guina T, Hope WW, Lawrenz MB, Lepak AJ, Luna BM, Miesel L, Phipps AJ, Walsh TJ, Weiss W, Amini T, Farley JJ.

FDA Public Workshop Summary: Advancing Animal Models for Antibacterial Drug Development. Antimicrob Agents Chemother. 2020 Oct 26:AAC.01983-20. doi: 10.1128/AAC.01983-20. Epub ahead of print. PMID: 33106262.
https://pubmed.ncbi.nlm.nih.gov/33106262/

- Waack U, Joshi A, Jang SH, Reynolds KS. Variations in pharmacokinetic-pharmacodynamic target values across MICs and their potential impact on determination of susceptibility test interpretive criteria. J Antimicrob Chemother. 2021 Aug 4:dkab282. doi: 10.1093/jac/dkab282. Epub ahead of print. PMID: 34347077.
https://pubmed.ncbi.nlm.nih.gov/34347077/

More information on the research activities and future research opportunities can be found on FDA's Office of Infectious Diseases Research webpage: https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-infectious-diseases-research-activities