Research Funding Opportunity to Assess the Impact of Extended-Infusion of Beta-lactam Antibacterial Drugs on Development of Beta-lactam Resistance and Patient Outcomes through the FDA Broad Agency Announcement (FDABAA-21-00123)

FDA Broad Agency Announcement (FDABAA-21-00123)

The FDA Broad Agency Announcement (FDABAA-21-00123) is an open solicitation for research and development to support regulatory science and innovation. The BAA link can be viewed at: https://beta.sam.gov/opp/80543862ddf14b65a8eb2fa0072de138/view?keywords=fdabaa-21-00123&sort=-relevance&index=&is_active=true&page=1&watch=false

In fiscal year 2021, research area **2.4.2** (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) has been identified as a priority area by the Office of Infectious Diseases in FDA's Center for Drug Evaluation and Research. Specifically, research proposals focused on evaluating the impact of dosing strategies for beta-lactam antibacterial drugs for serious infections caused by Gram-negative pathogens on development of beta-lactam resistance and patient outcomes will be prioritized.

Depending on scientific merit of Full Proposals, the Agency anticipates awarding 1-2 research contracts on or before September 30, 2021 to address priority area 2.4.2. The funding for this priority area will not exceed $500,000.

Information regarding proposal preparation and submission is available at the link above. **To ensure consideration for awarding of research contracts by September 30, 2021, please submit the Quad Chart and White Paper no later than January 28, 2021.**

Following a successful review of the Quad Chart and White Paper, the Offeror may be invited to submit a Full Proposal. FDA's Office of Acquisitions & Grants Services (OAGS) will send invitation letters requesting that Full Proposals be submitted. The date for submission of the Full Proposal will be provided in the invitation letter.

Background

Gram-negative pathogens are a common cause of serious infections in hospitalized patients and are associated with significant morbidity and mortality. These pathogens commonly develop antibacterial drug resistance in the presence of antibacterial drug selection pressure. The emergence of resistant Gram-negative pathogens has outpaced the development of new antibacterial drugs, necessitating the use of innovative strategies to optimize the use of currently available antibacterial drugs. Beta-lactam antibacterial drugs demonstrate time-dependent killing. Simulations and clinical studies demonstrate

improved pharmacokinetic/pharmacodynamic outcomes with prolonged infusion to maximize %T>MIC, compared to traditional infusion.[1]

Clinical outcomes studies report conflicting findings as to whether extending the infusion times of beta-lactam antibacterial drugs improve patient outcomes.[2] As prolonged infusion does have disadvantages such as limitation of patient mobility, prolonged need for secure dedicated venous access, and drug compatibility and stability issues, understanding benefits and risks is important. Clinical outcome studies of prolonged infusion have generally not evaluated emergence of resistance to the beta-lactam prescribed as part of the outcome assessment. The impact of extended-infusion of beta-lactam antibacterial drugs on subsequent antibacterial drug resistance and other important patient outcomes warrants further investigation. While randomized studies to assess patient outcomes are preferred, proposals utilizing a longitudinal observational cohort with sufficient follow-up, microbiologic data, clinical outcomes data and other information necessary for propensity score matching or other adjustment will be considered.

Research Proposal Objectives

FDA is interested in advancing the understanding of the impact of dosing strategies of beta-lactam antibacterial drugs on development of antimicrobial resistance and patient outcomes.

FDA will prioritize White Papers submitted in response to the FDA Broad Agency Announcement by the **January 28, 2021** deadline that provide a rationale and study design to assess the association between extending the infusion time of beta-lactam antibacterial drugs and development of beta-lactam resistance and improvement in patient outcomes.

Proposals also must include a plan to make research findings publicly available for consideration by the FDA and standards development organizations.

Research Proposal Preparation Considerations

White Papers and Full Proposals will be evaluated based on program relevance to new drug development and regulatory review, overall scientific and technical merit, and offeror capability.

Offerors should provide a scientific literature review and description of research previously conducted to justify the specific research being proposed including the public health priority regarding extended infusions of beta lactam antibacterial drugs and development of beta-lactam resistance and patient outcomes.

The Full Proposal should include sufficient detail regarding planned studies including a description of the population of patients with a serious infection(s) caused by gram-negative pathogen(s) to be studied or longitudinal observational cohort to be used. Sufficient detail should be provided including the specific infection(s) to be studied, the specific antibacterial drug(s) to be studied, the feasibility of obtaining data

[1] Kim A, Kuti JL, Nicolau DP. Probability of pharmacodynamic target attainment with standard and prolonged infusion antibiotic regimens for empiric therapy in adults with hospital-acquired pneumonia. *Clin Ther*. 2009; 31:2765-78.

[2] Chen M, Buuram V, Shah M, Gahim G. Evaluation of studies on extended versus standard infusion of beta-lactam antibiotics. *Am J Heath-Syst Pharm.* 2019;76:1383-1394.

for individual patient dosing regimens, longitudinal microbiologic data that will be available, clinical outcomes (both effectiveness and safety) to be evaluated and the data available, other patient characteristics that may be associated with outcome and the data available to support propensity score matching or other methods of adjustment, and duration of follow-up. Proposed activities could include:

- Cohort identification and site agreements
- IRB/EC review and approval
- Development of the statistical analysis plan
- Database development
- Data acquisition and input
- Data analyses
- Preparation of reports of findings

Offerors should include a description of their qualifications, capabilities, related experience, and past performance.

The contractor will also be responsible for subcontracting with institutions and other collaborators.

Further information on how to submit the quad chart and white paper by the January 28, 2021 deadline can be found at (page 35):
https://beta.sam.gov/opp/80543862ddf14b65a8eb2fa0072de138/view?keywords=fdabaa-21-00123&sort=-relevance&index=&is_active=true&page=1&watch=false

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Office of Infectious Disease Research Webpage Link:

https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm536676.htm