Research Funding Opportunity to Evaluate the Utility of In Vitro Models to Characterize the Urine-Specific Antibacterial Pharmacokinetics and Pharmacodynamics through the FDA Broad Agency Announcement

The FDA Broad Agency Announcement (FDABAA-23-00123) is an open solicitation for research and development to support regulatory science and innovation. The BAA solicitation can be viewed at: https://sam.gov/opp/52766923970840219c29d0ba2f0f4711/view#attachments-links

In fiscal year 2023, the following research area under FDABAA-23-00123 has been identified as a priority area by the Office of Infectious Diseases in FDA's Center for Drug Evaluation and Research:

- Charge Area: **III. Invigorate public health preparedness and response of the FDA, patients, and consumers.**
- Regulatory Science Topic Area of Interest: **B. Antimicrobial Resistance**
- FDA-Regulated Areas: **1. Drugs**
    - **1b - Advance the science of in vitro, animal model, pharmacokinetic studies, and/or real- world evidence studies to facilitate drug development, including studies focused on antifungal and antibacterial resistance and drug development for special populations such as patients with unmet need, children and patients with renal or hepatic dysfunction**

Specifically, research proposals focused on evaluating the utility of in vitro models to derive urine-specific antibacterial pharmacokinetic/pharmacodynamic parameters in support of drug development for uncomplicated urinary tract infections will be prioritized.

Depending on the scientific merit of the Full Proposals, the Agency anticipates awarding 1 research contract on or before September 30, 2023, to address this priority area. The funding for this priority area will not exceed $400,000.

Information regarding proposal preparation and submission is available at the link above. **To ensure consideration for awarding of research contracts by September 30, 2023, please submit the Quad Chart and White Paper no later than January 23, 2023.**

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

Uncomplicated urinary tract infections (uUTIs) are highly prevalent and can lead to significant medical sequelae and poor quality of life. These infections are often recurrent, and their treatment contributes to increasing antibacterial resistance. The standard of care antibiotic treatments for uUTIs include older antibacterial drugs that were developed prior to the use of modern pharmacokinetic/pharmacodynamic (PK/PD) methodologies, and better PK/PD characterization of some of these drugs may further inform their dosing recommendations and susceptibility test interpretive criteria (breakpoints).

Non-clinical PK/PD infection models play a critical role in optimizing clinical dosage regimens, susceptibility breakpoint determination, and "go or no go" drug development decisions. The antibacterial PK/PD index and target associated with efficacy derived from the non-clinical PK/PD infection models are conventionally established in blood or plasma. However, for uUTIs, PK/PD parameters based on antibacterial drug concentrations in urine may be more informative for the evaluation of drug efficacy, dosage optimization, and determination of urine-specific susceptibility breakpoints.

Typically, antibacterial PK/PD parameters are derived from animal infection models (e.g., neutropenic murine thigh infection model). Although murine UTI models are available, there are several challenges such as technical challenges of collecting urine, inoculation issues, highly variable urine PK, and obvious anatomical differences between mice and humans. For these reasons, in vitro models (e.g., hollow fiber infection model) may be of more utility to characterize the urine-specific PK/PD parameters since these models can be adjusted to mimic human PK profiles in urine and simulate urodynamics to directly evaluate exposure-response relationships and resistance suppression for uUTIs. These in vitro models do not come without their own limitations, such as failure to account for host factors (e.g., the immune system) or tissue environment, and extrinsic factors that can affect the results of the model (e.g., media, starting inoculum and urodynamics). Despite these limitations, data from in vitro models are needed to characterize the urine-specific PK/PD of antibacterial agents for the treatment of uUTI.

Research Proposal Objectives

FDA is interested in advancing the science of in vitro models to facilitate antibacterial drug development for the treatment of uUTI. Specifically, FDA is interested in evaluating the utility of in vitro models to characterize the urine-specific antibacterial PK/PD.

FDA will prioritize White Papers submitted in response to the FDA Broad Agency Announcement by the **January 23, 2023** deadline that propose studies to evaluate the following:

- Use of in vitro infection model(s) to determine the urine-specific PK/PD parameters (in comparison to plasma PK/PD parameters) associated with bacterial killing and suppression of resistance
- Influence of urinary parameters (e.g., pH, glucose) on the activity of antibacterial agents
- Influence of simulated urodynamics on the activity of the antibacterial agents
- Correlation of in vitro results to clinical and microbiological outcomes

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 the in vitro methodology to characterize urine-specific PK/PD in advancing drug development for uUTIs.

The Full Proposal should include sufficient detail regarding planned studies including a description of the in vitro PK/PD model(s) to be studied, data analysis plan, and criteria for validation of the in vitro PK/PD model(s). Sufficient detail should be provided including the uropathogens and antibacterial drugs to be

studied, human PK data (plasma and urine) to be simulated in the model, the urine-specific PK/PD parameters to be evaluated, and the endpoints to be assessed.

Proposed activities could include:

- Microbiologic studies to select specific uropathogen strains to be studied in the in vitro model(s)
- Development of in vitro infection model(s) to characterize the urine-specific PK/PD parameters associated with bacterial killing and suppression of resistance
- Validation of the in vitro model(s) with clinical and/or microbiological data, if available
- Application of the urine-specific PK/PD parameters generated from in vitro model(s) for dose selection/optimization

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.

Proposals also must include a plan to make research findings publicly available.

Further information on how to submit the quad chart and white paper by the **January 23, 2023, deadline** can be found at (starting on pg. 39 of the PDF):
https://sam.gov/opp/52766923970840219c29d0ba2f0f4711/view#attachments-links

Contact Information for Questions:

Thushi Amini, Ph.D.
Associate Director for Research
Office of Infectious Diseases, Center for Drug Evaluation and Research, FDA
Thushi.Amini@fda.hhs.gov

Office of Infectious Diseases' Research Webpage Link:
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