FY2024 Office of Infectious Diseases Funding Announcement to Facilitate Development of Urine-Specific Susceptibility Test Interpretive Criteria (Breakpoints) through the FDA Broad Agency Announcement

The FDA Broad Agency Announcement (FDABAA-24-00123) 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/26fa501e9b4d4f1ba8e1c2a8314343cb/view

In fiscal year 2024, charge area **IIIb1a** (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) 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 microbiologic and pharmacokinetic data that could be utilized by standards development organizations and the FDA to update susceptibility testing criteria (breakpoints) will be prioritized.

Depending on scientific merit of Full Proposals, the Agency anticipates awarding one research contract to address charge area IIIb1a. The total funding for this priority area will not exceed $250,000 (direct and indirect cost).

Background

Enabling physicians to select appropriate antibacterial drugs is critical to individual patient care and public health. The selection of an appropriate antibacterial drug is informed by breakpoints, the criteria to interpret antimicrobial susceptibility testing (AST) results. Breakpoints are conventionally established based on serum concentrations of antibacterial drugs regardless of the anatomical site of infection. However, for uncomplicated urinary tract infections (uUTIs, also referred to as acute cystitis[1]) which are characterized in women with normal anatomy by pyuria, a microbial pathogen on urine culture, local signs and symptoms and the absence of systemic symptoms, pharmacokinetic-pharmacodynamic (PK/PD) parameters based on concentrations of antibacterial drugs in urine may be informative for evaluation of their efficacy. Consequently, urine-specific breakpoints for common bacterial causes of uUTI could be developed to guide safe and effective treatment of uUTI. Moreover, the use of urine- specific breakpoints may facilitate the use of drugs to treat pathogens that are deemed resistant based on serum concentrations, which may facilitate antimicrobial stewardship.

However, simple findings of urine concentrations of antibacterial drugs above Minimum Inhibitory Concentration (MIC) of uropathogens may not be sufficient to evaluate the urine-specific PK of antimicrobial agents and support urine-specific breakpoints. Additional data including from *in vitro* dynamic models (e.g., hollow-fiber) and non-clinical *in vivo* uUTI infection models, are needed to provide better understanding of PK/PD characteristics of antimicrobial drugs in the treatment of uUTI and to re-evaluate the currently recognized susceptibility breakpoints[2].

Research Proposal Objectives

FDA is interested in advancing the science of antibacterial drug susceptibility testing in the treatment of uUTI specifically through the evaluation of urine-specific breakpoints.

[1] FDA Guidance for Industry on Developing Drugs for Treatment Uncomplicated Urinary Tract Infections
[2] Development Considerations of Antimicrobial Drugs for the Treatment of Uncomplicated Urinary Tract Infections

Proposals are requested to evaluate, among other characteristics, the following:

- Exposure-response approaches to define urine-specific breakpoints (in comparison to plasma) in *in vitro* and/or *in vivo* animal models of infection associated with bacteriological efficacy (killing, suppression or resistance development) in the presence of the antibacterial agent
- Traditional PK/PD parameters (%fT>MIC, AUC/MIC, Cmax/MIC) versus urinary PD parameters (AUIC, AUBT etc.). PK/PD parameters for the treatment of complicated UTI may not necessarily be similar or appropriate for uUTI
- Bacterial characteristics and growth (e.g., virulence, strains, biofilms, pili) of uropathogens (e.g. the Enterobacterales)
- Influence of urinary parameters (e.g., pH, osmolality, specific gravity, presence of blood, white blood cells, protein including immunoglobulins, glucose) on the activity of antibacterial agents

FDA will prioritize proposals that provide a rationale for the proposed approach to evaluate urine-specific breakpoints and selection of particular drug-bacteria combinations (especially those accounting for the most common bacterial causes of uUTI), propose to synthesize or obtain relevant microbiologic data, propose to generate urinary drug pharmacokinetics data and bactericidal activity data in patients with uUTI or healthy adult women using state-of-the-art methodologies (e.g., population PK modeling), propose to utilize relevant human pharmacokinetic data and animal model studies to conduct probability of target attainment analyses, and/or incorporate any clinical response data available in the public literature or other sources to justify any proposal for using urine-specific breakpoints based on the research findings. Consistent with the FDA Guidance[1], it is expected that initial work will focus on uUTI in women with normal anatomy.

FDA has previously awarded the following proposal:

- Development of Modernized Susceptibility Guidance for Oral Sulfamethoxazole-Trimethoprim Using Pharmacometric Approaches

<u>Research Proposal Preparation Considerations</u>

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 breakpoints for the proposed drug-bacteria and any relevant information available regarding clinical response.

The Full Proposal should include sufficient detail regarding planned microbiologic studies, PK/PD studies, and the pharmacometric approach to define a breakpoint. For example, when appropriate, include: (i) sources and details to gauge the quality of PK, PD, or PK/PD data that will be utilized; (ii) data analysis plan for PK, PD, or PK/PD modeling, Monte Carlo simulations, and probability of target attainment analyses; (iii) strategy to handle behavioral factors (e.g., degree of bladder emptying and voiding patterns) in the target patient population that impact drug concentrations in urine; (iv) criteria for nonclinical infection model validation.

Proposed activities could include:

- Providing MIC and zone diameter distributions (if relevant) against the bacterial isolates of UTI pathogens collected in the preceding 3 years; categorical agreement between MIC and zone diameter breakpoints (if relevant); details on specific strains (i.e., ATCC or CDC) used in experiments, e.g., susceptibility and virulence factors
- Nonclinical infection models to characterize PK/PD efficacy and emergence of resistance

relationships, identify the PK/PD index, and select target values to be used to bridge this information to humans. Relevant information may include:
    - Static and/or dynamic PK/PD *in vitro* infection model findings
    - *In vivo* PK/PD animal infection model findings
    - *In vivo* animal infection model findings utilizing human-simulated antimicrobial exposures at the infection site
    - Human pharmacokinetic data of the drugs in plasma and urine
- PK/PD modeling, Monte Carlo simulations, and probability of target attainment analyses.

Offerors should include a description of their qualifications, capabilities, related experience, and past performance, and describe their plan to make research findings publicly available for consideration by the FDA and standards development organizations. For example, FDA has opened a public docket for information and data relevant to updating breakpoints[3]. The contractor will also be responsible for subcontracting with institutions and other collaborators.

New Submission Process for the FY24 FDA BAA

It is anticipated that research contract awards will be made through the FY24 FDA Broad Agency Announcement (BAA) with the following deadlines:

- **Early Concept Papers are due November 6, 2023.**
- **Concept Papers and Full Proposals are due February 19, 2024.**

Please note that there is a new submission process for the FY24 FDA BAA:

- **Therefore, we highly recommend that potential Offerors attend the upcoming 2023 FDA Broad Agency Announcement Day on October 25, 2023.**
    - Information regarding this event can be viewed at:
        - https://www.fda.gov/science-research/2023-fda-broad-agency-announcement-day-10252023.

- Information regarding proposal preparation and submission can be found at: https://sam.gov/opp/26fa501e9b4d4f1ba8e1c2a8314343cb/view

Office of Infectious Disease Research Webpage Link:

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

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[3] https://www.regulations.gov/docket?D=FDA-2017-N-5925