Research Funding Opportunity to Facilitate Development of Urine-Specific Susceptibility Test Interpretive Criteria (Breakpoints) through the FDA Broad Agency Announcement (FDABAA-22-00123)

FDA Broad Agency Announcement (FDABAA-22-00123)

The FDA Broad Agency Announcement (FDABAA-22-00123) is an open solicitation for research and development to support regulatory science and innovation. The BAA link can be viewed at: https://sam.gov/opp/c00c56895d2c45b1895ea60d0e4e4747/view

In fiscal year 2022, research area **2.4.4** (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 1 research contract on or before September 30, 2022 to address priority area 2.4.4. The funding for this priority area will not exceed $250,000.

Information regarding proposal preparation and submission is available at the link above. **To ensure consideration for awarding of research contracts by September 30, 2022, please submit the Quad Chart and White Paper no later than January 21, 2022.**

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

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 urinary tract infections (UTI), especially for uncomplicated UTI (uUTI), 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 could be developed to guide safe and effective treatment of uUTI. Moreover, the use of urine-specific breakpoints may allow using the drugs to treat pathogens that are determined 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.

Research Proposal Objectives

FDA is interested in advancing the science of antibacterial drug susceptibility testing in the treatment of uUTI. Specifically, FDA is interested in evaluating urine-specific breakpoints and requesting proposals evaluating, 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
- Influence of urinary parameters (e.g., pH, osmolality, specific gravity, presence of blood, WBCs, protein including immunoglobulins, glucose) on the activity of antibacterial agents

FDA will prioritize White Papers submitted in response to the FDA Broad Agency Announcement by the **January 21, 2022** deadline that provide a rationale for the proposed approach to evaluate urine-specific breakpoints and selection of particular drug-bacteria combinations, 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 adults 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, 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.

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 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.

Offerors should 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 (https://www.regulations.gov/docket?D=FDA-2017-N-5925).

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 21, 2022 deadline** can be found at (page 33):
https://sam.gov/opp/c00c56895d2c45b1895ea60d0e4e4747/view

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Office of Infectious Disease Research Webpage Link:

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