FY2025 Office of Infectious Diseases Funding Announcement to Facilitate Development of Susceptibility Test Interpretive Criteria (STIC or Breakpoints) for Enterococci through the FDA Broad Agency Announcement

In fiscal year 2025, 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 $325,000 (direct and indirect cost).

Background

Informing appropriate selection of antibacterial drugs is critical to individual patient care and public health. The selection of an appropriate antibacterial drug is guided by breakpoints, the criteria to interpret antimicrobial susceptibility testing (AST) results. Enterococci are important clinical pathogens with limited treatment options, especially for infections resistant to first line therapies such as ampicillin and vancomycin. While nonclinical pharmacokinetic-pharmacodynamic (PK-PD) data relying on animal models of infection are instrumental in establishing breakpoints, existing animal models of enterococcal infection are limited. In the frequently used murine thigh infection model, Enterococci exhibiting poor growth characteristics may confound the interpretability of a drug's antibacterial activity. As a result, reliable nonclinical PK-PD data for antibacterial drugs used to treat resistant enterococcal infections, such as daptomycin, are limited. [1]

Research Proposal Objectives

FDA has previously awarded the following proposal:

- Development of Modernized Susceptibility Guidance for Ampicillin and Vancomycin for Enterococcus Species Using Pharmacometric Approaches

FDA is interested in advancing the science of antibacterial drug susceptibility testing for daptomycin in the treatment of enterococcal infection. Proposals are requested to develop and evaluate, among other characteristics, the following:

- Develop an in vivo model demonstrating predictable and reproducible growth characteristics of *E. faecium* and *E. faecalis*
- Test dose ranges equivalent to daptomycin human doses of 6, 8, 10, and 12 mg/kg/day

Research Proposal Preparation Considerations

Concept 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

[1] Kidd JM, Abdelraouf K, Asempa TE, Humphries RM, Nicolau DP. Pharmacodynamics of Daptomycin against Enterococcus faecium and Enterococcus faecalis in the Murine Thigh Infection Model. Antimicrob Agents Chemother. 2018 Sep 24;62(10):e00506-18.

to justify the specific research being proposed including the public health priority regarding breakpoints for the proposed drug-bacteria combination and any relevant information available regarding clinical response.

The Full Proposal should include sufficient detail regarding planned microbiologic and pharmacokinetic studies and analyses. The proposed activities could include:

- Providing daptomycin MIC against enterococcal surveillance isolates collected in the preceding 3 years including isolates with various known resistance phenotypes and details on specific strains (i.e., ATCC or CDC) used in experiments, e.g., susceptibility and virulence factors (presence of known resistance genes)
- 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:
    - *In vivo* PK/PD animal infection model findings including confirmatory assessments of bacterial growth of the selected strains under no treatment
    - *In vivo* animal infection model findings utilizing human-simulated antimicrobial exposures at the infection site
    - Human pharmacokinetic data of the drugs in plasma
- 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[1]. The contractor will also be responsible for subcontracting with institutions and other collaborators.

It is anticipated that research contract awards will be made through the FY25 FDA Broad Agency Announcement (BAA). Information regarding proposal preparation and submission as well as specific due dates will be announced in **Fall 2024** on Sam.gov website as well as on the Office of Infectious Disease Research Webpage Link at:

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-infectious-diseases-research-activities

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

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