August 13, 2018

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Re: Docket No. FDA-2018-D-2032: Limited Population Pathway for Antibacterial and Antifungal Drugs; Draft Guidance for Industry; Availability**

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) is pleased to submit the following comments on the Food and Drug Administration (FDA) Draft Guidance, "Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD); Draft Guidance for Industry."

BIO is the world's largest trade association representing biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other countries. Our member companies, both established biopharmaceutical companies as well as early-stage biotechnology companies, play a key role in addressing the rise of antimicrobial resistance (AMR) by developing and bringing innovative new medicines to patients. However, investment in AMR product research and development has declined significantly in recent years, both in early venture capital investment and by companies themselves. This trend clearly illustrates the economic challenges to traditional market approaches in sustainably incentivizing AMR product development.

BIO strongly supports incentives that can support a diverse pipeline of antimicrobial products, including the Generating Antibiotic Incentives Now (GAIN) Act, which introduced Qualified Infectious Disease Product (QIDP) designation to stimulate the development of new antimicrobials. BIO also applauds the leadership of FDA's Center for Drug Evaluation and Research (CDER) in continuing to examine regulatory approaches that facilitate the development of AMR products to meet unmet medical needs. This draft guidance provides welcomed clarity for sponsors that are developing antibacterial and antifungal drugs for approval under the Limited Population Development pathway created under the 21st Century Cures Act. Below we offer general comments for your consideration:

**Additional examples of products for which the LPAD approval pathway might be valuable or necessary would be helpful.**

BIO appreciates the two examples of drugs for which approval under the LPAD pathway could be appropriate, including those with a narrow spectrum of activity or those suitable for a select patient population with no other options. However, additional examples would be welcomed given that several antibacterial drugs developed under streamlined clinical

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programs described in the Guidance document Antibacterial Therapies for Patients with an Unmet Medical Need for Treatment of Serious Bacterial Diseases[1] (Unmet Medical Needs Guidance) have recently been approved with "limited use" labeling.

**Additional clarification is needed to inform clinical trial design for LPAD products**

BIO strongly believes that development options for sponsors should reflect the maximum flexibility afforded by the LPAD approval pathway. BIO encourages the Agency to be open to exploring any and all options to bring these products to patients through scientifically justified trial designs that demonstrate an acceptable benefit/risk profile for these high-risk populations with unmet needs. We welcome FDA's increased regulatory flexibility for antimicrobial development and notes that the draft guidance acknowledges that LPAD model may involve approval based on smaller, shorter, or fewer clinical trials (line 78) and FDA's willingness to accept a greater degree of uncertainty for these trials.

We also recognize that the sponsor must provide substantial evidence of effectiveness and safety for products approved under the LPAD pathway. We would welcome additional guidance beyond the Unmet Medical Needs Guidance on the design of trials that both take into account the unique challenges of studying products for limited populations and ensure that FDA standards are met. This would include additional guidance on acceptable non-inferiority (NI) margins, the size of the safety database, and novel pivotal trial designs.

For example, the Unmet Medical Needs Guidance recommends a minimum safety database for streamlined programs of approximately 300 patients at the dose and duration of therapy proposed in marketing. BIO notes that, based on sponsors' recent experience enrolling patients for multi-drug resistant infections, it may be difficult to reasonably meet this standard for drugs target limited populations and requests additional clarification from FDA on its expectations where full accrual to 300 patients by LPAD sponsors is not feasible. BIO also believes that guidance would be helpful to understand the potential role of animal studies, including robust pharmacokinetic/pharmacodynamics (PK-PD) studies, to support efficacy when clinical trial data are limited by population availability and only open label data is available from small clinical trials where no or limited statistical inference testing can be conducted.

In providing additional guidance on suitable clinical development programs, we respectfully ask the Agency to consider approaches used in other review divisions, such as the FDA Guidance on Clinical Endpoints for the Approval of Cancer Drugs and Biologics,[2] which provides flexibility for circumstances where there is no available therapy. Given the urgency of treating AMR infections with unmet needs, BIO believes FDA should consider approval under the accelerated pathway based on surrogate endpoints or early clinical endpoints, and consider ways to collect confirmatory evidence in the post-market setting. This could include disease biomarkers that assess an effect on overall clinical benefit instead of all-cause mortality for LPAD products.

BIO also notes that FDA interprets a limited population of patients as a group of patients "limited in such a way that is clinically relevant to health care providers" (lines 105-114). BIO appreciates that FDA has chosen a flexible interpretation but requests additional information or examples that further explain what is meant by "clinically relevant". We also request that FDA clarify whether or not a clinically limited population would be defined differently for different therapies (i.e. how a limited population is defined for products that

[1] https://www.fda.gov/downloads/Drugs/Guidances/UCM359184.pdf
[2] https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoyInformation/Guidance/UCM071590.pdf

treat infection, products that are preventative, or products that can diagnose infection). Finally, we ask FDA to clarify whether there is a numerical threshold that would constitute a limited population, akin to the numerical limits for orphan drug products.

Finally, the LPAD guidance also provides an opportunity for FDA to provide greater clarity with the sponsor regarding the label that they are likely to achieve with their clinical trial (i.e. the specifics related to potential differentiation, rare pathogens indicated, etc.). Given the challenges that sponsors face in LPAD trial design, it would be helpful to gain clarity regarding how these trials can be designed to inform a potential label.

**BIO requests that FDA consider how new initiatives to modernize drug development and review may be applied to LPAD products**

BIO notes that the FDA has several initiatives underway to modernize regulations for drug development, which may provide an opportunity to inform LPAD product development. For example, BIO acknowledges that Unmet Medical Needs Guidance provides flexibility for studying an antibacterial product by combining data from different body sites. However we respectfully ask the FDA to consider whether the underlying concepts or learnings from the oncology "tissue agnostic product approvals" could be extrapolated to LPAD, for example with pathogen specific indications. While this guidance specifically states that the LPAD pathway may be appropriate for antibacterials with a narrow spectrum of activity where pathogens occur infrequently at any body site, clinical development of these products has been challenging.

FDA is also moving to consider novel clinical trial concepts, including adaptive clinical trial design. BIO encourages FDA to consider how LPAD can be informed from these discussions. The use of adaptive clinical study design for AMR studies are more likely to demonstrate the safety and efficacy of the drug if one exists and would meet the LPAD stated aim of smaller, shorter, or fewer clinical trials.

Finally, BIO is encouraged by FDA's piloting of a model for informed drug development by increasing the use of modeling and simulation throughout the drug development process. BIO appreciates the flexibility in this space provided by the Unmet Needs Guidance and requests that FDA consider additional guidance for sponsors to better leverage PK/PD modeling to generate evidence for the benefits/risks of LPAD products, especially when tissue distribution in conjunction with *in vitro* and single-body clinical data could support an approval or an indication for a new body site.

**Additional guidance is requested on labeling**

With respect to labeling recommendations for the carton and immediate container label (lines 304-314), BIO believes it would likely be challenging to incorporate the recommended additional text, "See the full prescribing information for [drug name] for information about the limited population," on the principle display panel for many products.

BIO is concerned that this text, combined with the "Limited Population" statement, could to provide in a physically small label space for any product that does not have a container carton. We note that adding the recommended text to the principal display panel may cause other important information to be missed if there is a large amount of text on this panel. We ask the Agency to consider additional guidance for such situations. Regarding the immediate container label, we appreciate the Agency's acknowledgement of 21 CFR 210.10(i) for situations where packaging is too small for the additional statements.

BIO notes that LPAD products may have challenges in establishing *in vivo* antimicrobial susceptibility information for their products to support *in vitro* data. We welcome additional clarification on how FDA might identify or evaluate antimicrobial susceptibility interpretive criteria when clinical trial data are limited by population availability.

FDA indicates that it may terminate the limitations associated with the LPAD pathway approval when the Agency has determined that clinical data demonstrate that the product is safe and effective for a broader indication (Lines 400-408). BIO welcomes additional information from FDA that further explains the process for LPAD limitations would be terminated on these products, such as the timeline for this process and the termination's impact on promotional material.

**BIO requests clarity on communication of promotional material**

While the guidance emphasizes the requirement to use the term "Limited Population" in labeling (Lines 391-396), it lacks specifics on how to best communicate to both health care providers and consumers through promotional materials beyond the "limited population" identifier. Additional guidance on how to convey the limited population for which the drug is indicated and the drugs' benefit and risks in promotional materials may help build consistency across products, as well as foster a common understanding regarding this special pathway for both consumers and providers.

Regarding the review of promotional materials (Lines 391-396), we ask that the agency clarify whether the guidance is meant to align with the requirements under the accelerated review pathway (Subpart E/H). If the requirements for the review of promotional materials are the same for the LPAD and accelerated review pathways, we ask the Agency to mirror the language in existing guidance[3]. If the requirements are different, we ask the Agency to provide additional guidance on the timing and process for submission and review, including the scope of the review and whether sponsors will be notified of the outcome within 30 days.

**Conclusion**

BIO appreciates the opportunity to provide comments on the draft guidance, and once again applauds FDA CDER for its leadership in regulatory solutions to incentivize much-needed antimicrobials to combat the rise of AMR. We look forward to continued work with FDA in addressing AMR and would be pleased to provide further input or clarification of our comments, as needed.

Respectfully submitted,

/s/

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Director, Infectious Disease Policy
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[3] https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf