October 8, 2018

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

Re: Docket No. FDA-2018-D-2382: FDA Draft Guidance on Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the FDA Draft Guidance, *Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment.*

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 nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial, and environmental biotechnology products.

BIO supports the FDA's work to develop the Draft Guidance, *Opioid Use Disorder: Endpoints for Demonstrating Effectiveness of Drugs for Medication-Assisted Treatment* as BIO sees the Draft Guidance as an important step in clarifying to Industry Sponsors and FDA reviewers the FDA's thinking as it relates to endpoints used to demonstrate efficacy for therapies developed to treat opioid use disorder (OUD). BIO commends the FDA for recognizing the need and interest in expanding primary and secondary endpoints used in clinical trials for medications used to treat OUD, including outcome measures important to patients and their families, clinicians, and the public, including through the April 17th, 2018 public meeting on *Patient-Focused Drug Development for Opioid Use Disorder*. BIO also appreciates the Agency's willingness to meet early in the drug development process with Industry Sponsors to discuss such use of endpoints in clinical trials for OUD therapies.

BIO requests the FDA clarify in the Draft Guidance how it defines relapse to illicit opioid use. In particular, BIO suggest the FDA consider using the terms "persistent relapse to illicit opioid use" and consider definitions used for clinical trials for medication assisted therapy,[1] such as four consecutive weeks of any non-study use by urine toxicology or self-report, or seven consecutive days of self-reported use.

Throughout the Draft Guidance, BIO also requests that the FDA consider reductions in public resource utilization as other possible endpoints used to demonstrate effectiveness of drugs for medication assisted treatment. Such reduction in public resource utilization may include

[1] Lee et al., Comparative Effectiveness of Extended-Release Naltrexone Versus Buprenorphine-Naloxone for Opioid Relapse Prevention (X:BOT): A Multicentre, open-label, randomized Control Trial.

reduction in emergency or hospital visits, use of child protective services, or incarcerations or arrests. Furthermore, the FDA should consider using patient reported assessments of treatment effectiveness (i.e., whether the patient feels/perceives that they are in recovery as a result of medication assisted treatment use) as a potential patient-reported outcome to demonstrate effectiveness of medication assisted treatments.

Finally, BIO recommends that the FDA provide additional detail within the Draft Guidance regarding Phase III studies for medication assisted treatments, such as the duration of treatment in a Phase III study, similar to what is outlined in the FDA's Guidance for Industry on Alcoholism: Developing Drugs for Treatment would be Informative for Industry Sponsors. In addition, further information on the number of Phase III studies would be helpful for Industry Sponsors developing mediation assisted treatments.

BIO appreciates this opportunity to submit comments regarding the FDA's Draft Guidance. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Danielle Friend, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
II. BACKGROUND		
Lines 51-53, 55-56	The Draft Guidance indicates: *"For medications intended for use as initial therapy, patients are generally new entrants to treatment (i.e., actively ill and not currently receiving other drug treatments for OUD), and these trials employ active controls with a superiority or noninferiority design. Designs generally incorporate standard-of-care nonpharmacologic treatments as well as active medications available on a rescue basis, with patients requiring rescue transferred out of the protocol to standard care. For medications intended to reduce the risk of relapse, patients already stable on other treatments are studied, and in general, the comparator should be an approved therapy.* However, completing trials with an active comparator may not always be feasible.	In lines 51-53 and 55-56, BIO requests that the Agency provide regulatory flexibility in its guidances to allow for innovative clinical trial designs, and to not use otherwise limiting language such as those recommending active comparators. Use of innovative clinical trial design can decrease unnecessary and unethical patient exposure to clinical procedures and experimental products while still advancing clinical development.
Line 64	The Draft Guidance indicates: "The responder definition is prespecified and takes into account the schedule of assessments and may incorporate a grace period. Efficacy analyses include comparison of responder rates, continuous responder curves, and graphic displays of individual patient responses."	BIO requests that the FDA clarify that the observation period for remission can be reduced with the grace period.

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	However, it is unclear whether the "grace period" described in line 64 can reduce the observation period for remission.	
III. CLINICAL ENDPOINTS		
A. Adverse Outcomes of OUD		
B. Change in Disease Status Using Diagnostic Criteria for OUD		
Line 107	The Draft Guidance indicates: *"Diagnostic criteria for OUD encompass both drug use and its effect on patient well-being. If all trial patients meet the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM5) criteria for moderate-severe OUD at baseline, the sponsor could use the proportion of patients meeting DSM-5 criteria for remission of OUD at the end of the trial as a primary or secondary efficacy endpoint."* However it is unclear if "early" (3 months) is acceptable or if "sustained" (12 months) remission is required.	BIO requests that the FDA clarify that "early" remission (3 months) is acceptable as a primary or secondary endpoint.
C. Patient-Reported Outcomes		
D. Change in Drug Use Pattern		
Lines 156	This section indicates: *"In addition, to support a drug use pattern as a response-defining threshold, the sponsor should evaluate and submit evidence from clinical trials, longitudinal observational studies, or other sources of information to show that such reduction in drug use predicts clinical benefit (i.e., better health outcomes or psychosocial function). Sponsors should discuss with the division approaches to measure change in*	BIO recommends that the FDA consider accepting any reduction in drug use as a clinical benefit to the patient rather than requiring Sponsors to demonstrate that the reduction in drug use predicts clinical benefit, a hurdle that will discourage drug development for the treatment of opioid use disorder.

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	drug use patterns and how evidence of clinical benefit could be generated." This section seems to contradict lines 70-71 which indicate that "*FDA accepts drug use patterns as surrogates for the benefits of abstinence from drug taking or presumed benefits of reduction of drug taking*."	
GENERAL COMMENTS		