February 15, 2018

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

Re: Docket ID: FDA-2017-D-6617: Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance titled "Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease."

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 welcomes FDA's efforts to provide clear guidance on the regulatory and scientific framework for product developers of targeted treatments and applauds the Agency for issuing guidance in a more concise and streamlined manner. This Draft Guidance is easy to read and succinctly outlines FDA's recommendations for targeted therapy development, including the types/levels of evidence to support a grouping strategy for clinical trial eligibility and benefit-risk evaluation approaches within a disease that exhibits differences in molecular subset.

BIO encourages the FDA to continue to gather stakeholder input on the topic of development of targeted therapies to ensure that FDA guidance keeps pace with scientific advances. BIO has made the following observations worthy of attention with respect to the Draft Guidance:

- BIO suggest the Draft Guidance provide further thinking on the Agency's receptivity to innovative approaches for the development of targeted therapies.

- The Draft Guidance is written with a focus on grouping multiple molecular alterations in a [single] clinically defined disease. BIO recommends the Draft Guidance also reflect the scenario where one or more molecular alterations occur across multiple "diseases" (*e.g.*, a single genetic mutation which occurs in tumors of different tissue types).

- BIO appreciates the Agency's directive to ideally design clinical trial assays to detect all possible molecular alterations that comprise the group expected to respond to a targeted therapy. However, the scope is very broad. BIO proposes that the Agency provide examples that help clarify what defines a group. For example, can the group

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be defined by a specific gene, or by a group of related genes (such as an immune panel)? Further, detecting all molecular alterations of clinical significance in a particular indication can be difficult in the absence of whole genome or whole exome sequencing which may not always be practical. Even if such techniques are pursued, clinically validating a molecular alteration can be challenging (*i.e.,* clearly establishing that a specific molecular alteration is of clinical significance in that particular disease). For example, in oncology, distinguishing between passenger and driver mutations or in cases of exceptional responders who can respond to treatments because of unknown or yet to be validated secondary mutations. Therefore, BIO requests that the Agency acknowledges these practical challenges and develop a regulatory pathway that allows a flexible path to approval of a targeted therapy for all patients who may benefit. We note that this pathway would be distinct from post-market requirements to confirm findings of the initial clinical study or to gather additional information regarding risks and benefits of the drug.

- BIO suggest that the Agency provide clarity on how these outlined principles could be interpreted in a "complementary diagnostic" situation, for example an all-comer population where patients with a range of mutations in a defined gene may respond to the targeted therapy.

BIO appreciates this opportunity to submit comments and have provided additional detailed comments to improve the clarity of the Draft Guidance in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION AND BACKGROUND		
Line 19 footnote 2	Clinically defined diseases should acknowledge that a "disease" may (at least for the purposes of this Draft Guidance) be characterized by the molecular alteration itself and not by the tissue of origin.	BIO suggest the following edit: "For the purpose of this guidance, a *targeted therapy* is defined as a drug intended for populations that are subsets of one or more clinically defined diseases and that may be ~~are~~ identified by using diagnostic testing."
Lines 27 – 29	The document does not include case studies or examples of evidence that can be used across disease indications that share a molecular alteration.	BIO suggests that the Agency provide details on the level of evidence that is acceptable to demonstrate efficacy across molecular subsets not only within a disease, but also across disease indications governed by the same molecular alteration.
II. DEVELOPMENT AND REGULATORY CONSIDERATIONS		
***A.* Identification of Patients for Inclusion in Clinical Trials**		
Lines 61-62	The ordering of evidence by strength presents a risk to the durability and broad applicability of the Draft Guidance as science advances and innovative approaches to drug development and evidence generation are pursued. For example, under certain circumstances, *in vitro /in silico* data may be a more sensitive or reliable way to address potential differences in activity (*e.g.,* target binding) than a preclinical animal model.	Types of evidence that could support a grouping strategy are listed below ~~in general order of decreasing strength, although other sources of evidence may also be appropriate~~ with clinical data being considered the strongest evidence and other types of evidence also considered appropriate to support a totality of the evidence approach
Lines 83-86	The category of "phenotypic characterization of molecular alterations" provides an example of evaluation of a nonclinical, molecular phenotype (*i.e.*, assessment of molecular activity), but does not include an example of a clinical phenotype.	BIO suggest the Agency provide a range of examples for this category and the other categories in this section (lines 66-86). Specifically, for this category, it would be helpful to understand how FDA views clinical genetic analysis of case reports from a strength of evidence perspective.

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B. **Generalizability of Findings**		
Lines 97-105	The Draft Guidance discusses FDA's view that low numbers or the absence of patients with rare molecular alterations in a clinical trial population will generally preclude meaningful empirical inferences about treatment benefits or risks in patients with those rare or unstudied alterations. While historical regulatory approvals reflect the FDA's stated view (*i.e.*, requiring a genotype-by-genotype approach to the study and approval of therapies), BIO believes that it is no longer scientifically appropriate to assert that this approach is needed in "most settings" (line 100-101). The combination of unmet medical need and the availability of strong genetic information (including case reports) for a disease should allow for inferences about treatment benefits and risks in patients with molecular alterations represented in low numbers or absent from the clinical trial population. The recommendations presented in lines 97-105 create a negative impression of FDA's receptivity to this approach and are somewhat contradictory with the recommendations presented in lines 107-120.	BIO encourages the FDA to emphasize the recommendations in lines 107-120 and to clarify FDA's willingness to work with drug developers and to consider the totality of evidence when evaluating molecular subsets and the ability to extrapolate to unstudied subsets. Specifically, BIO recommends the following edit to lines 100-102: "low numbers or the absence of such patients would in ~~most settings preclude~~ in some settings may preclude meaningful empirical inferences."
Lines 116-120	The Draft Guidance could benefit from additional details regarding how to address a "substantial scientific issue" beyond the possibility that "the indicated patient population may be narrower than the clinical trial enrolment criteria.	BIO suggests the following edit: "If after trial enrolment the FDA or sponsor newly identifies a substantial scientific issue essential to determining the safety or effectiveness of the drug in some molecular subset included in the trial, the indicated patient population may be narrower than the clinical trial enrolment criteria. The FDA or Sponsor are

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		encouraged to discuss proposed trial modifications prior to implementation."
C. **Benefit and Risk Determination and Labeling**		
Lines 142-146	The Draft Guidance read: "The FDA may grant exceptions when the drug is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists, and FDA determines that the benefits from the use of the drug outweigh the risks from the lack of an approved or cleared in vitro companion diagnostic device."	BIO supports the inclusion of this sentence and the recognition that it is important to allow for exceptions where the benefit outweighs the risk.
D. **Refining the Target Population/Indication After Initial Approval**		
Lines 154-157	Clarification is needed.	BIO suggests the following edit: "Similarly, if emerging data from studies (i.e. substantial evidence, whether from observational or randomized trials) indicates lack of efficacy in certain molecular subgroups for which the drug was initially indicated, then, the FDA will consider narrowing the intended population in collaboration or with input from the Sponsor.
Lines 159-163	Clarification is needed.	BIO suggests the following edit: "In some cases, generating data in the postmarket setting may be necessary to provide additional information regarding the risks and benefits of the drug in subsets of patients with limited or no enrolment in clinical trials. Real world evidence (e.g. from observational studies or registry data), traditional controlled trials, or data from other sources (including trials already ongoing) may be appropriate and sufficient."
Lines 159-165	Use of real-world evidence.	While the Draft Guidance acknowledges indication expansion in this section, the majority of the discussion is focused on

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		narrowing of an indication or post-marketing study requirements. BIO recommends that FDA include the Agency's views of use of real-world evidence and other non-traditional data sources for expansion of an indication in the post-market setting. For genetic conditions for which genotype-phenotype relationships are still being identified and for which the majority of new information will emerge from clinical practice, BIO strongly encourages the FDA to propose flexible and efficient mechanisms to incorporate new data in the post-market setting.