Biotechnology Innovation Organization

February 11, 2019

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

Re: Docket No. FDA-2018-D-4267: Biomarker Qualification: Evidentiary Framework; Draft Guidance for Industry and Food and Drug Administration Staff.

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(BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on Biomarker Qualification: Evidentiary Framework.

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 recognizes the FDA's efforts to provide clarity around the evidentiary standards required for biomarker qualification. The Draft Guidance outlines a stepwise process to qualify drug development tools for use in drug development. While the process that a Sponsor may follow is outlined, we find that the Draft Guidance should provide information such as timelines that the Agency will follow when making determinations regarding whether a submission will be reviewed, when Sponsors may expect to receive feedback from the Agency, and information regarding how Sponsors may interact or engage with the Agency regarding their qualification submission. Such information will be important for successful qualification of biomarkers moving forward.

BIO appreciates that the FDA indicates in the Draft Guidance that many of the principles discussed in the guidance could also be appropriate for supporting the use of a biomarker in an individual drug development program (e.g., investigational new drug application, new drug application, or biologics license application submissions). We find this language very helpful and commend the FDA for making note of this in the Draft Guidance. However, in some cases, such as in the context of rare diseases, where there are limited patient populations, it may not be feasible for a Sponsor to qualify a new biomarker. While BIO acknowledges that the Draft Guidance provides a few examples (e.g., lines 385-387), where the Agency may provide flexibility for rare diseases, it would be helpful for the Draft Guidance to make note of other such areas where flexibility may be provided in the context of rare diseases, both in the context of qualification but also in the context of biomarker use for an individual drug development program. Additionally, information in the Draft Guidance regarding how qualified biomarkers may be used to support drug labeling and/or individualized/personalized medicine would also be helpful to include.

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BIO also requests the FDA to consider including information in the Draft Guidance pertaining to the qualification of a biomarker that already has an established specific context of use (COU). For example, it would be helpful for the FDA to include information regarding whether a Sponsor can build upon a specific COU or whether a separate biomarker qualification submission would be required. Additionally, a single biomarker may serve multiple utilities. For example, pre-treatment levels of a biomarker may be predictive of response to a treatment and the same biomarker may also provide insights regarding treatment efficacy. To this end, we ask the FDA to clarify as to whether each proposed biomarker utility would require its own specific COU and a separate qualification submission. To encourage biomarker qualification, BIO encourages the FDA to take an approach that is not overly burdensome.

BIO also notes that the PDUFA VI Commitment Letter indicates that the Agency will establish a pilot program to engage external experts to support the review of biomarker qualification submissions. BIO views the use of such external experts as integral to ensure additional insight into emerging areas and thus the efficient review of qualification submissions and BIO encourages the Agency to use experts qualified in specific therapeutic areas, product development specialists as well as clinical researchers since they all have unique contributions to make. BIO is looking forward to hearing more from the Agency about the pilot program as well as other innovative approaches for accessing external experts for input into biomarker qualification. Additionally, the 21st Century Cures Act and FDARA Legislation include requirements that FDA share information about the biomarker qualification submissions, including those that result in qualification. This information will be extremely valuable to entities engaging in biomarker development. It will help biomarker developers better understand the range of studies needed for qualification of different types of biomarkers and different contexts of use. Therefore, we suggest that language be included in the Draft Guidance reminding readers of these requirements along with a link to the appropriate website(s). Additionally, the FDA might also consider putting some examples or case studies of successful biomarker qualification into the Draft Guidance as an appendix in order to provide additional clarity into the FDA's thinking.

In addition to the comments above, we have also included several line edits that can be found on the following pages. BIO appreciates the opportunity to submit comments regarding FDA's Draft Guidance, Biomarker Qualification: Evidentiary Framework. 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		
Page 1, footnote 5	In footnote 5, the FDA indicates that "for the purposes of the Draft Guidance, all references to drugs or drug products include both human drugs and biological drug products regulated by CDER and CBER, unless otherwise specified." However given the reference to the word "drug" it is unclear as to whether the Draft Guidance is also applicable to vaccines.	It is BIO interpretation that the Draft Guidance also applies to vaccines, but we ask the FDA to clarify this point in the Draft Guidance.
II. BACKGROUND		
III. Evidentiary Framework		
Figure 1		BIO requests that the FDA consider including "operational feasibility" as a fourth bullet in the column titled "Evidence to support qualification."
Lines 93-94	When developing a composite biomarker signature using modern statistical learning/data-mining techniques, weights often come from a mathematical optimization procedure and a clear biologic rationale for the weights may not be available.	BIO request the FDA to consider the following edit: "If individual components have differential weighting, the description should include the biologic rationale to support this decision, **if available**.
Line 94	In this section the FDA includes several items that pertain to the measurement of a particular biomarker; however, biomarker measurement also depends on the platform, specific technology, and the protocol used for measuring the biomarker. These additional items, however, are not referenced in the Draft Guidance.	BIO requests that the FDA also provide reference to the platform, specific technology, and the protocol used for measuring a biomarker.

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Line 110	BIO strongly believes that the perspective of the patient community for which the biomarker will impact drug development should be considered and thus referenced appropriately in the Draft Guidance.	BIO suggests that the FDA consider including in the Draft Guidance language similar to that was included in FDA's request for public input on clinical outcome assessments in August 2018: "Patient experiences are providing new insights for FDA reviewers and reinforce the importance of incorporating the patient's experience to inform drug development. This includes not only the clinical context for FDA decisions, but more direct evidence regarding drug benefits and risks." Or from the Commissioner's remarks in March 2018: "The Benefit-Risk Framework recognizes that when FDA reviewers conduct a benefit-risk assessment, they consider not only the submitted evidence related to the benefit and risk and effects reported in clinical studies, but also, importantly, the "clinical context" of the disease. This context encompasses two major considerations: 1) an analysis of the disease condition, including the severity of the condition; and 2) the degree of unmet medical need. As part of this work, the FDA recognizes a need to learn about the clinical context more comprehensively and directly from the perspective of the patients who live with the disease and their caregivers. "
A. Needs Assessment		
Lines 128-129	BIO strongly believes that the perspective of the patient community for which the biomarker will impact drug development should be considered and they are an important stakeholder in determining the evidentiary criteria for a biomarker thus referenced appropriately in the Draft Guidance.	BIO requests that the FDA list the patient community as stakeholders who should be consulted regarding biomarkers as public health priorities.

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B. Context of Use		
Line 146	Because Pharmacodynamic and response biomarkers may be different, these two items should be separated into two separate bullets in the list provided in the Draft Guidance.	BIO requests the FDA to consider the following edit: "Biomarkers can be disease-related or treatment-related and should be classified by the BEST biomarker category, selected from the following (see BEST Resource for discussion of each category of biomarker): • diagnostic biomarker • monitoring biomarker • pharmacodynamics **biomarker** ~~**/response biomarker**~~ (e.g., clinical trial endpoints, including surrogate endpoints) • **response biomarker (e.g., clinical trial endpoints, including surrogate endpoints)** • predictive biomarker • prognostic biomarker • safety biomarker • susceptibility/risk biomarker
Lines 166-167	This section indicates that "often, requestors do not have adequate data and/or information to support their proposed COU." Additionally, in some cases, there may be insufficient data to determine which BEST biomarker category the biomarker may fall under.	BIO requests the FDA to consider the following edit: "Often, requestors do not have adequate data and/or information to support their proposed COU, **or to determine the BEST category to which the biomarker belongs**."
C. Assessments of Benefits and Risks		
Lines 179-182	In this section the FDA indicates that the developer should provide a description of the anticipated benefits and risks; however, appropriate evaluation of risks of a potential biomarker rely on dialogue and discussion between the FDA and the developer. Views	BIO requests the follow edit: "Biomarker developers **in collaboration with the FDA** ~~**are expected to**~~ should identify ~~**provide a clear and objective description of**~~ the anticipated benefits and risks of the

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	of the people who may benefit or take risks in using therapies that rely on the biomarker, are also important inputs that should be given significant weight when evaluating the benefits and risks.	biomarker for the proposed COU, as well as any potential risk mitigation strategies. **Additionally, patient's perspectives and experiences should also be considered when identifying both benefits and risks.**"
Lines 192, 233, and Figure 2	The term **"correlation"** may be too restrictive. Some scientists may interpret this in the statistical meaning (a relationship between two continuous normally distributed measurements). For measurements with other distributions other measures of association could be used e.g. odds ratio's, adjusted associations etc.	BIO requests that the FDA consider using terminology similar to what is found in the statistical section (e.g., "degree of association") to replace the word "correlation".
Lines 224-226	In this section, the FDA states that "if the potential benefits far outweigh the potential risks and/or there are acceptable risk mitigation approaches, there could be increased tolerance for uncertainty" and this statement accurately captures the thinking for some regulatory decisions where the unmet need is minimal or the treatment options adequate. However, it does not adequately describe how benefit-risk will be evaluated in areas of high unmet need.	BIO requests that the FDA consider the following addition: "**In areas of high unmet need and patients have increased tolerance for uncertainty, the benefit-risk of qualifying a biomarker will be evaluated accordingly.**"
D. Determining Evidence that is Scientifically Sufficient to Support COU		
Lines 244	In this section the FDA indicates that "This relationship should be supported by statistical analyses (see section V.) and should come from multiple independent data sources," but the FDA does not mention different data platforms.	BIO requests that the FDA consider the following addition: "**For genomic studies, multiple data sources from the same platform may not be as compelling as data from different platforms. The totality of evidence, whether it be derived from multiple data sources, different platforms, or a combination of both, will be used in the biomarker qualification process.**"

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Line 248	In this section, the FDA indicates that "Biomarkers considered for qualification are conceptually independent of the specific method of measurement; however, a biomarker cannot be qualified without a reliable method of measurement."	While we agree that a biomarker may be qualified in a manner that is conceptually independent of a specific method of measurement, we believe that additional insight into FDA's thinking regarding the de-linking of a qualified biomarker from the methods used to generate the evidence for its qualification would be helpful. It is important that this process be clear so as to allow for innovation of methods of measurement while not losing progress made through biomarker qualification using older methods.
Line 254	This section indicates that performance characteristics of biomarker tests used in drug development should "perform as well as the tests used for biomarker qualification," however the Draft Guidance does not elaborate on the Agency's expectations for demonstrating that the biomarker tests used in drug development perform as well as tests used for biomarker qualification.	BIO requests that the FDA consider including additional detail regarding how one may demonstrate that a biomarker test used in drug development performs as well as tests used for biomarker qualification. Such clarification is particularly important given that different methods (i.e., a method used for biomarker tests in drug development versus biomarker tests used for biomarker qualification) may generate different cutoff values.
IV. ANALYTICAL CONSIDERATIONS		
Entire Section	In this section the FDA refers to both biomarker tests and biomarker assays. In the general context of this section, biomarker test and biomarker assays are not equivalent unless specifically stated.	For clarity, BIO requests that the FDA consider using the term "biomarker test" throughout this section except when providing examples of biomarker "assays" to measure different types of analytes.
Lines 281-283	This section indicates that "analytical validation for the purpose of biomarker qualification includes establishing that the analytical performance characteristics of a biomarker test such as the accuracy and reproducibility, are acceptable for the proposed COU in drug development." However,	BIO requests the FDA to consider the following edit: "Analytical validation for the purpose of biomarker qualification includes establishing that the analytical performance characteristics of a biomarker test, such as the **relative** accuracy and reproducibility, are acceptable for the proposed COU in drug development."

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	accuracy is not generally attainable for many biomarkers.	Additionally, we request that the Agency to list all of the analytical performance characteristics of a biomarker test that would need to be acceptable for the proposed COU in drug development, instead of only citing accuracy and reproducibility.
Line 282	In this section the FDA largely focuses on clinical validation, with little reference to analytical validation. However, statistical considerations should also be taken into account in the context of analytical validation as to ensure robust and meaningful data. Additionally, different analytical procedures may require different statistical procedures.	BIO requests that the FDA provide additional clarity regarding statistical considerations that may be taken into account in the context of analytical validation.
Line 287		For clarity, BIO requests that the FDA use of the term "test materials" throughout this section instead of the terms "source" and "materials".
Lines 292-293		To clarify this sentence, we request the FDA to consider the following edits: "Analytical validation of a biomarker test should ~~**consider the acceptability of the source or materials from which the biomarker is measured**~~ **evaluate pre-analytical factors and appropriate preparation of test materials prior to analysis**."
Lines 300-301		To clarify this sentence, we request the FDA to consider the following edits: "A reliable biomarker test is also contingent on all **its** components ~~**of the biomarker assay**~~, such as supplies, equipment, software, **user training** and instructions."

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IV. STATISTICAL CONSIDERATIONS		
Entire Section		We request the FDA to consider explicitly reference Real World Data as a type of data that can be used to establish the relationship between a biomarker and an outcome of interest.
Entire Section	This section mentions how methodological limitations that could lead to lack of power, control for bias, should be addressed in the statistical analysis plan; however, depending on the intended use of the qualified biomarker the statistical analysis plan may need to incorporate a robust design that includes discovery, analytical validation and clinical trial studies. Additionally much of this section emphasizes statistical aspects of the association between the biomarker and outcome of interest, but includes little information on statistical considerations for evaluating and controlling the analytical performance of biomarker test.	BIO requests that the FDA consider including reference to discovery, and analytical validation, and clinical trial studies in the analysis plan for the biomarker. BIO also requests that the FDA consider including statistical considerations for evaluating and controlling the analytical performance of a biomarker test.
Lines 443-445	In this section, the Agency indicated that when appropriate, adjusted or composite biomarkers can be considered with adequate justification, including biomarkers derived from composite measurements.	BIO requests the FDA to provide more clarity on whether analytical validation should be conducted for each individual biomarker when a composite biomarker is being qualified.
Lines 447-450	This section indicates that when continuous data will be dichotomized, the relationship between the clinical outcome and the biomarker could be initially established quantitatively. Expressing biomarker	BIO requests the FDA to consider the following edits:

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	measures quantitatively increases the statistical power compared to dichotomization when establishing such a relationship, however, In some cases, if the relationship between the clinical outcome and the biomarker is more like a step function, then dichotomization could provide more power.	"The relationship between the clinical outcome and the biomarker could be initially established quantitatively, **if doing so increases the statistical power.**" and "Expressing biomarker measures quantitatively **could potentially** increase the statistical power compared to dichotomization when establishing such a relationship."
Lines 450-453	In this section, the Agency indicates that a cutoff value may be determined by comparing the clinical outcomes of at risk subjects with each different biomarker cutoff; however there are other possible mechanisms for determining the cutoff value.	BIO requests that the guidance also mention that other methods are acceptable for determining cutoff values.
Lines 450-460	Because different methods might provide directionally similar results, but specific cutoff values may differ, in the Draft Guidance when cutoff values are referenced, it would be helpful for the FDA to indicate that cutoff values are linked to the specific method used to generate the data for the cutoff.	BIO requests that the FDA indicate that specific cutoff values are associated with the specific method used to generate the data.