February 16, 2018

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

Re: Docket No. FDA–2017-N-5896: Public Workshop: Patient-Focused Drug Development: Guidance 1- Collecting Comprehensive and Representative Input.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding Patient-Focused Drug Development: Guidance 1- Collecting Comprehensive and Representative Input.

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 appreciates the FDA's initiative to hold the public workshop "Patient-Focused Drug Development: Guidance 1 – Collecting Comprehensive and Representative Input," on December 18, 2017. We also commend FDA's efforts to develop and make available the discussion document (and accompanying appendices and glossary) to stakeholders to provide a basis for discussion that will inform the development of guidance to facilitate collection and submission of usable patient experience data (PED) for medical product development and regulatory decision-making. The discussion document, including the appendices and glossary, are informative and serve as a basis for drafting the additional planned guidance documents. We also appreciate FDA's willingness to be flexible and open to innovative methods and practices, as the science is evolving every day and new ideas and approaches will continue to emerge.

While BIO also agrees that the upcoming guidance documents should be complementary to the FDA guidance on Patient Reported Outcomes (PRO), we believe that the PRO guidance is too restrictive and thus has not led to an increase in qualified or validated PRO tools for use in labeling. To this end, we ask the FDA to consider some of the broad implementation challenges that make the PRO guidance more restrictive, in order to keep the PFDD guidance documents broadly applicable and flexible, and maximize their utility. BIO strongly believes that in order for a broad adoption of PED, the upcoming guidance documents should emphasize the FDA's willingness to exercise flexibility and acceptance of innovative designs and approaches in collecting such data. We have included additional comments below for the FDA's consideration as they continue to develop the patient-focused drug development (PFDD) guidance documents.

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Guidance 1 Discussion Document Questions (Lines 68-77):

Question #1. What level of detail do you think is appropriate for this FDA guidance series?

As part of this FDA guidance series, BIO advocates that FDA provide clarity on how to engage with the agency on collection and submission of PED for medicinal drug product development and regulatory decision making. In addition, FDA should clarify at what time points sponsors/stakeholders can approach FDA to discuss research design and methods and the level of evidence that is expected. The FDA should also empathize that there is likely a need for collecting PED at different stages during drug development and how these data are linked to possible uses.

Question #2. What document structure and content would be most useful for this first guidance?

As this FDA guidance series is intended to be used by a variety of stakeholders, unlike others released by the agency, BIO recommends the inclusion of graphical representations and visuals illustrations. Examples include: (i) the types of PED and how these data are linked to possible uses, (ii) timeline where critical agency meetings occur in the drug development process and applicability of PED, (iii) a grid tailored to different stakeholders summarizing roles and responsibilities associated with collection of PED, and (iv) a graphical representation of the benefit-risk grid. Below, we have also included several other suggestions for the FDA to consider when determining content of the guidance documents.

- BIO requests that future guidance documents provide more examples and details to clarify FDA's expectations regarding how the guidance is envisioned to be implemented. One such example that may be important to highlight is the scenario in which an existing primary endpoint has regulatory precedent and is used in regulatory clinical practice, but according to the patient population may not necessarily represent true patient need. Such an example could show acceptability of an established primary endpoint in addition to secondary endpoints supported by PED. Similarly, and as mentioned during the public workshop, BIO believes that including examples or 'best practices' collected from various stakeholders would also be beneficial. We recommend that in addition to a set of 'best practices,' described in the guidance documents, the FDA should provide online resources with such information. BIO also requests examples of different types of PED that might reasonability be analyzed and provided to the FDA.

- Although the intention of the guidance is to incorporate more patient insights and experiences into drug development and regulatory decision making, BIO believes that the discussion document should provide more detail to emphasize this point. Additionally, and in several sections, the need for patient partner contribution is not firmly articulated. For example, when defining the general steps for conducting studies (e.g., in Section 2, page 13), the discussion document does not specify the inclusion of the patient perspectives in the actual design of the study. To better incorporate this concept, for example, figure 3 of the discussion document could show the steps in a study where patient expert input is recommended. BIO also

suggests including discussion as to how patient organizations and companies could work together to reduce burden on patients and patient organizations.

- In an effort to ensure global harmonization when collecting and using PED, BIO requests that the FDA include information in the guidance documents regarding how international studies/patient engagement data might be addressed/accepted by the FDA. Additionally, information regarding how work generated from other international organizations and projects such the Innovative Medicines Initiative patient preference information work[1] is complementary to the FDA guidance, would also be helpful.

- BIO asks that the discussion document also include information regarding patient representativeness that may be specific to rare diseases or circumstances where there may be a limited population. For example, many rare genetic diseases are pleotropic and the same disease may manifest differently in different patients. Collecting such multi-faceted data can lower the power of the contribution of each single observation or data set. Thus there may be circumstances when analyzing data on a per-patient basis would allow sponsors to examine a spectrum of symptoms and behaviors. Additional guidance on these circumstances would be helpful. The guidance should include some detail around PED as it relates to disease state and the unmet need and how that factors into the benefit-risk assessment.

- In various sections of the discussion document, the language changes from patient and caregiver, to patient stakeholder. BIO requests that the language throughout the document remain consistent in order to support clarity of the items discussed. BIO agrees with the language used in the section on patient partners (line 193) and suggests that the FDA use that language consistently through-out the discussion document.

- The discussion guide recognizes and acknowledges the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health's guidance on patient preference information in the discussion document. BIO requests that the FDA clarify whether the guidance is also endorsed by the Center for Drug Evaluation and Research and how staff training and MAPPS will be updated in accordance with this guidance.

With regards to the content, BIO believes that the guidance series should also focus on what is unique about collecting PED for the purposes of submitting to the FDA to support the benefit-risk assessment of a medicinal drug product. To this end, key topics that should be addressed include the following:

- What are the evidence standards for collecting PED that is intended to support a claim of clinical benefit? In addition to the quality of the data collected, what *amount* of such data are needed to make a convincing evidence package to the FDA? What types of study designs are considered acceptable or unacceptable by the FDA,

[1] http://www.imi.europa.eu/

depending on the type of PED being collected? What evidence will FDA expect/demand in regard to demonstrating that patients adequately comprehended the risk information? How should an evidence package consisting of both qualitative and quantitative studies be presented?; 2) under what regulatory vehicles/ mechanisms can such PED be submitted to FDA?; 3) at what specific time points in the drug lifecycle (both pre- and post-approval) can PED be submitted to FDA?; and 4) What types of PED can be included in the drug label?

Question #3. Many potential research methods are available and not all could be included in the discussion document. Is it clear the Agency is open to discussion of the methods described and other methods, both within medical product programs and in the pre-competitive space?

BIO advocates the use of 'mixed-methods' approaches to collecting PED. BIO also asks that the FDA be receptive to the use of both qualitative and quantitative PED for regulatory decision making. In this regard, the Guidance 1 Discussion Document is mostly devoted to outlining quantitative approaches, and gives short shrift to qualitative and mixed-methods approaches. We acknowledge and commend the FDA for demonstrating interest in working with industry to advance the science in this area, and openness to the use of new and/or different methods to collect PED.

Question #4. What are the most important time points when FDA input could be maximally helpful?

BIO's perspective is that the most important time points for FDA input would be the following:

1. FIH: Gain agreement on the scope, type and methods used to collect PED to support the filing;
2. EoP2: Review (if discussed at FIH)/gain agreement on what patient focused research should be performed either as part of or ancillary to the registrational clinical studies; and
3. Pre-filing: Review and gain agreement on the proposed data package of patient focused research and how this could impact the assessment of benefit-risk and labeling

Question #5. The PDUFA VI commitment letter calls for a glossary of standardized nomenclature and terminology relevant to all four guidance documents. Are the proposed draft definitions within the glossary clear and do they serve to facilitate dialogue?

BIO believes that the use of a standardized glossary across this FDA guidance series is critical and that the draft glossary provides detailed information regarding relevant terminology that will be appropriate for all of the upcoming guidance documents. However, BIO also believes that a benefit of creating a glossary will be a consistent definition of terms, not only for clinical research, but for later in the development of product labeling for physicians. Physicians will be able to recognize that the same term means the same thing, regardless of the company creating the labeling. Hence, we propose that the glossary also provide an additional health literate definition of each term, so that there is consistent

definition in both the physician and patient labeling across companies for each term. Without these patient-friendly definitions provided in the glossary, later there will be differences in how each company describes the same term to patients. This will create unnecessary complexity and confusion for patients. A key principle of health literacy is saying the same thing, the same way, to increase understanding.

Below are two examples of how these terms may be modified:

From the Glossary: "Disease burden": The impacts, direct and indirect, of the patient's health condition that has a negative effect on his or her health, functioning, and overall well-being. Disease burden includes (but is not limited to): the physical and physiologic impacts of the disease and its symptoms; co-morbidities; emotional and psychological effects of the disease, its management, or prognosis; social impacts; effects on relationships; impacts on the patient's ability to care for self and others; time and financial impacts of the disease and its management; and considerations on the impacts on the patient's family."

Recommended Addition: "Disease burden": The ways that a patient's condition causes problems or discomfort in their life and the lives of their families, such as: physical symptoms, risk for other medical conditions, emotional or mental health problems, social and relationship concerns, challenges in caring for self and others, and time and money concerns."

From the Glossary: "Endpoint": A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question. A precise definition of an endpoint typically specifies the type of assessments made, the timing of those assessments, the assessment tools used, and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined.[2] (*Source: BEST (Biomarkers, Endpoints and Other Tools) Resource*)"

Proposed Addition: "Endpoint": A variable, which reflects a specific outcome, that is statistically analyzed to answer a research question. The endpoint definition usually includes how and when it will be measured and sometimes other details, such as how multiple measurements for one individual are combined."

BIO appreciates this opportunity to submit comments regarding FDA's discussion document Patient-Focused Drug Development: Guidance 1- Collecting Comprehensive and Representative Input. 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

[2] BEST (Biomarkers, Endpoints, and Other Tools) Resource, FDA-NIH Biomarker Working Group

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION and Background		
Line 21	Under Guidance 2: "…questions that are well understood by a wide range of patients…" There is no mention of the concept of "plain" language in patient HCP communication. The concept of plain (simple) language is well recognized and is important when providing guidance regarding communication to a "wide range of patients".	BIO asks that the FDA include this concept in the guidance.
1.1 Introduction to the Legislation and Series of FDA Guidance for Enhancing the Incorporation of the Patient's Voice in Drug Development and Regulatory Decision Making		
Lines 133	Glossary of terms; may not be universal/standard; IMI PREFER is developing a more relevant glossary and Cochrane Collaborative may also contain relevant terms.	BIO asks that the FDA expand and provide additional references for terms, drawing from other well established glossaries.
Lines 133	This section states that it does not address methods for collecting and analyzing COAs or patient preference yet the document refers to patient preference in several areas (lines 180, 185, 191, 210, 349, 505, 520).	BIO asks that the FDA provide additional details on methods for collecting and analyzing patient preference information.
1.2 Purpose and Scope of Guidance 1: Approaches to Collecting Comprehensive and Representative Patient and Caregiver input on Burden of Disease and Current Therapy		
Lines 128	This section provides a description of the methods alone but no there is no guidance on specific applications.	BIO asks that the FDA provide scenarios for the use different methods.
1.3 Patient Experience Data		

SECTION	ISSUE	PROPOSED CHANGE
Lines 209-210	Although tolerance for harms and risks was included, we noted that there was not reference to burden of risk minimization?	BIO asks that the FDA include reference to burden of risk minimization as it can impact both risk tolerance and benefit risk tradeoffs.
Line 229	This section states that PED should be collected as early as possible.	BIO agrees that it is critical to collect PED as early as possible, we request that and this should be restated for impact within the guidance document.
Lines 248-252	It is unclear for whom this information intended.	BIO suggests that the FDA indicate that all stakeholders (industry, patient organizations, and other stakeholders) should collect the PED in a variety of settings.
II. General Considerations for Collecting Patient Experience Data		
Lines		BIO recommends changing the titles to section two to state "Methodological Considerations for Designing Studies to Collect Patient Experience Data."
2.1 Overview		
2.2 Defining the Research Objectives and Questions		
Lines 316-343		Under section 1. 'Defining Research Objective,' BIO request that information in a separate sub-section be included to describe the timeline of the development program when PED may be used as well as a separate sub-section covering study-specific considerations, which may include figures 2 and 3.
2.3 Whom to Collect Information From		
Lines 388	This section states "FDA recommends stakeholders engage with subject matter experts in that disease area when determining the appropriateness of self-report in the target population."	BIO asks the FDA to clarify who is considered a subject matter expert.
2.3.1 Defining the target population		

SECTION	ISSUE	PROPOSED CHANGE
2.3.2 Determining who will be proving patient experience data		
2.3.3 Subgroups		
2.4 Determining the Study Design and Research Setting		
Lines 454-457	Currently, the discussion document does not address or acknowledge rare or orphan diseases except briefly in section 2.4.2 (page 21, lines 454-457) and in figure 7 (page 23) on "Factors to Consider to Achieve Sufficient Representation."	We urge FDA to expressly note the challenges faced by drug development programs for rare diseases, and re-emphasize FDA's willingness to exercise additional flexibility and provide support or early advice to sponsors of drug development programs for rare diseases. Additionally, the FDA states (lines 454-457), "Having an insufficient sample size may produce unreliable and/or imprecise results. FDA recommends that if the sample size is limited due to practical considerations (e.g., rare diseases), the research objectives should be adjusted accordingly and noted as a limitation in the study report." BIO requests that the FDA include guidance regarding what challenges they predict and how such challenges should be addressed.
2.4.1 Sampling methods		
2.4.2 Sampling size		
2.4.2.1 Studies using quantitative methods		
2.4.2.2 Studies using qualitative methods		
2.5 Constructing a Sampling Frame		
2.6 Additional Considerations to Achieve Sufficient Representation		
III. Methods for Collecting and Analyzing Patient Experience Data		
Lines		BIO recommends changing the titles to section three to state "Methodological Considerations for Data Collection, Analysis and Operationalization."
3.2 Qualitative Research Methods		
3.1.1 Sources of qualitative data		
3.1.1.1 Considerations for successful interviewing and focus group moderation		
3.1.1.2 Social media		

SECTION	ISSUE	PROPOSED CHANGE
3.1.2 Selecting qualitative data		
3.1.3 Analyzing qualitative data		
3.2 Quantitative Research Methods		
3.2.1 Analyzing quantitative data		
3.3 Mixed Methods		
3.3.1 Analyzing data from mixed methods		
IV. Operationalizing and Standardizing Data Collection and Data Management		
		BIO recommends changing the titles to section four to state "Translating Best Practice into Real Practice - Developing Guiding Examples."
4.1 Standard approaches to consider for collection and managing data		
4.1.1 Locating patients/sites		
4.1.2 Access		
4.1.3 Sampling strategy		
4.1.4 Collecting data		
Lines 743-744 (also lines 795-801)	Creating and maintaining a specialized database with dedicated software is a significant proposal.	BIO requests that the FDA provide parameters needed to create such a database and how validation is to be considered.
4.1.5 Recording information		
4.1.6 Resolving site/field issues		
4.17 Data management		
4.1.8 Data standards		
4.1.9 Monitoring and quality assurance		
4.1.10 Storing data		
4.1.11 Confidentiality		
V. Conclusions		
VI. References		