Biotechnology Innovation Organization

September 11, 2018

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

Re: Docket No. FDA 2018-D-1893: FDA Draft Guidance Patient-Focused Drug Development: Collecting Comprehensive and Representative Input.

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(BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance on Patient-Focused Drug Development: Collecting Comprehensive and Representative Input.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 applauds the FDA's initiative to continue to advance the use of patient experience data (PED) to inform drug development and regulatory review. BIO appreciates the FDA's organization of a public dialogue on the topic through the public workshop "Patient-Focused Drug Development: Guidance 1 – Collecting Comprehensive and Representative Input," on December 18, 2017 as well as the associated discussion document (and accompanying appendices and glossary). Furthermore, BIO appreciates the FDA's efforts to develop the first Draft Guidance addressing comprehensive and representative input as required by section 3002 of the 21st Century Cures Act, and commitments made by FDA under the sixth authorization of the Prescription Drug User Fee Act (PDUFA VI).

BIO sees this first Draft Guidance, addressing comprehensive and representative input, as an important tool for strengthening our collective understanding of the relevant evidence needed to support the FDA regulatory process with PED. The Draft Guidance is well-written and provides discussion of standard research methods and study designs used to collect PED as well as utilizable suggestions as to whom to obtain PED from as well as why and how the information could be collected.

The Draft Guidance presents approaches that adhere to established standards for good research practice and provides enough information to gain insight into what is needed to compose an appropriate research study. However, BIO strongly believes that in order for a broad adoption of PED, the upcoming guidance documents should emphasize the FDA's willingness to exercise regulatory flexibility and acceptance of innovative designs and approaches for collecting PED. For example, the Draft Guidance is highly focused on statistical requirements for collection of subjective measures and although representation of the population is paramount, there is also a need to balance such representativeness with statistical validity, as the requirement of many strata for representation could have a

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negative impact on statistical power. The Draft Guidance also lists several sampling methods along with their inherent limitations, however, such sampling methods may not be feasible under all circumstances and thus flexibility on the part of the FDA will be needed. The FDA also 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. To not discourage the collection of PED in the context of rare diseases, we also ask the FDA to exercise flexibility and acceptance of innovative designs and approaches for collecting such data, especially in cases where there are limited patient populations.

We also note FDA's use of the term "ultra-rare disease populations" in the Draft Guidance (Line 708); to our knowledge, the term has not been defined in statute, regulations, or existing FDA guidance.[1] As such, we encourage the Agency to continue to employ the established terminology and definition of a rare disease (e.g., affecting fewer than 200,000 persons in the United States) until there have been sufficient opportunities to discuss with all stakeholders; including industry Sponsors and patient organizations; and establish definition or terminology based on scientific evidence.

We have included additional comments below as well as proposed specific line edits for the FDA's consideration as they work to finalize the Draft Guidance.

Target Population

The Draft Guidance refers to samples being representative of the "target population," however the Draft Guidance does not define the term "target population." A "target population" could include a population similar to the disease subpopulation that would be included in the pivotal trial or it could be the population with the target disease, composed of sub-populations with different attributes (e.g., severe versus mild, advanced versus early disease, patients with comorbidities versus patients without comorbidities, or those who have prior experience participating in clinical studies versus those who do not). The Draft Guidance would benefit from additional discussion regarding what the FDA considers a "target population."

Use of Patient Experience Data

[1] While "ultra-rare disease population" is not included in statute, regulation, or guidance BIO is aware of Commissioner Gottlieb's use of the term during FDA remarks at the 11th Rare Disease Day on February 26th 2018 and the FDA's reference to "rare diseases of low prevalence" defined as "a condition affecting approximately 5,000 persons or less in the United States" in the FDA's Draft Guidance on "Slowly Progressive, Low-prevalence Rare Diseases with Substrate Deposition that Results from Single Enzyme Defects: Providing Evidence of Effectiveness for Replacement or Corrective Therapies.

It is BIO's belief that in order to truly support patient-centric drug development, PED should be considered for use throughout the drug development lifecycle. For example, appropriate fit-for-purpose tools for collecting PED have the potential to inform patient-centric decisions from protocol design and endpoint selection to benefit-risk assessments and labeling, among other considerations. To encourage all stakeholders to collect PED we request that the FDA more clearly indicate the regulatory decisions for which they will consider PED. Similarly, BIO believes that many types of PED can be used to inform drug development and review. To this end, we encourage the Agency to emphasize more broadly throughout the Draft Guidance, that "fit-for-purpose" PED collected with appropriate rigor will be used to inform regulatory decisions across the lifecycle of product development. The inclusion of examples of fit-for-purpose tools and methodologies and appropriate uses for those tools and methodologies would also be helpful to include in the Draft Guidance.

On a similar note, BIO requests that the FDA make clear in the Draft Guidance the delineation between collection of PED to inform clinical studies (e.g., development of a clinical outcome assessment tool or to inform clinical study endpoints) and PED collected within a clinical study meant for submission to the FDA to inform a regulatory decision. Collection for each of these uses may impact the choice of methodology used as the collection of all PED may not involve the same methods and standards as are currently applicable for registrational clinical trials (Lines 282-288). Holding all types of patient experience data to the same standard could place an undue burden on stakeholders in terms of data management, data standards, and reporting requirements and discourage collection of PED for some purposes. Therefore, we recommend that the Draft Guidance clarify the standards FDA expects for the collection of PED based on its intended use. Regarding FDA's statements in the Guidance (Lines 133 and 257, and 1126-1130) that the level of rigor needed for generating PED can vary across studies and will depend on the intended use, we request that the FDA clearly describe how the evidentiary standards may vary depending on the intended use of the PED. FDA's clarification of the standards in a pre-clinical stage research context such as a patient advisory board, or in exploratory, concept elicitation, hypothesis generating or instrument development research, would help clarify the appropriate standards required for PED used for regulatory decision-making and inclusion in labelling.

Stakeholder Engagement with the Food and Drug Administration

BIO appreciates that throughout the Draft Guidance (e.g., lines 152-153 and lines 293-294), the FDA stresses the importance of "obtaining feedback from the relevant FDA review division early and often," as early opportunities for stakeholders to engage with the Agency will best support the collection and use of PED for drug development and review. However, the Guidance does not elaborate on when and how Sponsors can consult with the FDA regarding the conduct of patient experience studies. BIO requests the FDA to consider the use of existing milestone meetings (Type B and C) and potentially extending the length of

milestone meetings, if necessary so that Sponsors are able to discuss PED with the FDA. The FDA should also consider providing Sponsors with opportunities to reach written agreement on aspects of the design, collection, and use of PED. Timely and specific feedback for Sponsor to understand why the FDA accepted or did not accept a particular proposal for collection of PED is also important.

To address this topic in the Draft Guidance, BIO requests the FDA consider consolidating language (e.g., lines 98-100, 152-153, and 292-295) into a single section indicating that "sponsors may request meetings with review divisions per the FDA Guidance on *Formal meetings between FDA and Sponsors or Applicants of PDUFA Products.*[2]" A statement can also be included in the Draft Guidance to direct patients and patient organizations to the Patient Affairs Staff (PAS) in the Office of Medical Products.

Patient Experience Data in Future FDA Clinical/Medical Guidance Documents
BIO requests that the FDA consider including, in future disease specific guidance documents or in guidance documents yet to be finalized, recommendations for collecting and using PED for the specific disease area addressed in the guidance document. Such recommendations could include examples of methodologies for the collection of PED, assessment with appropriate clinical outcome assessment tools, and criteria for PED to be considered in the regulatory decision-making process for the respective disease area.

Communication around Patient Experience Data and Glossary of Terms
BIO believes that appropriate communication of PED with physicians and patients will be important as they, together, determine if a treatment is right for the patient. To ensure the patient and physician have the information they need to support this dialogue, inclusion of PED in product labeling is recommended. BIO suggests the FDA provide recommendations on the content and format of PED in product labeling through an update to existing labeling guidance documents or development of a new labeling guidance document. This guidance may follow the recent precedent set in the (*Rituxan Hycela ®)* label (Section 14 Clinical Studies). BIO also requests that the FDA consider ways in which PED can be provided to patients and physicians beyond information included in labeling, as information including plain language trial results and summaries can be helpful both to the patients in those trials and to others living with the medical condition under study.

We also believe that the use of a standardized glossary across the Draft Guidance series is critical and that the glossary provides detailed information regarding relevant terminology that will be appropriate for all of the upcoming Guidance documents. BIO believes that consistent definition of terms also helps development of product labeling for physicians. Additionally, we propose that the glossary provide an additional health literate

[2] FDA Guidance on Formal Meetings between the FDA and Sponsors or Applicants of PDUFA Products.

definition of relevant terms, so that there is consistent definition for PED language in both physician and patient labeling across companies. Without a glossary of patient-friendly definitions, differences in how each company describes a particular term could cause unnecessary complexity and confusion for patients.

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

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.[3] (*Source: BEST (Biomarkers, Endpoints and Other Tools) Resource*)"

Proposed Addition: "Endpoint": A measure, which reflects a specific outcome, which 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."

Use of Social Media and other Data Sources

BIO appreciates the Agency's acknowledgement of social media as a component for helping to better understand what is important to patients and that data collected from social media sources may serve as a mechanism for patients to provide their experiences. However, the

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

Agency does not provide discussion regarding how data collected via social media may be used as a primary source of data for research studies. BIO requests that the FDA consider social media data that is fit-for-purpose and collected in a rigorous manor as an acceptable form of PED and include reference to this in the Draft Guidance while also recognizing that the use of social media for these purposes is still evolving.

In addition to the collection of PED through social media there is a growing role for the use of wearables for collecting continuous data on physical functions, self-management interventions, and impacts or outcomes. To this end, we request that the FDA further discuss in the Draft Guidance how stakeholders may use wearables to collect PED.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance, Patient-Focused Drug Development: 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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 1	Suggested editorial change.	BIO requests that the FDA consider the edit: Patient-Focused Drug Development: ~~**Collective**~~ **Collecting** Comprehensive and Representative Input Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders
A. Overview of the Series of FDA Guidance for Enhancing the Incorporation of the Patient Voice in Drug Development and Regulatory Decision Making		
Line 18	Suggested editorial change.	BIO requests that the FDA consider the edit: "Overview of the Series of FDA Guidance **Documents** for Enhancing the Incorporation of the Patient's Voice in Drug Development and Regulatory Decision Making."
Lines 37-43	Suggested editorial change.	BIO requests the FDA to consider the following edit: "Focusing on practical approaches and methods, this series will inform stakeholders of FDA's current thinking about methods that could be used **to** bridge important early-stage efforts on gaining patients' narrative perspectives on the clinical context (e.g., meetings with patients) and development and use of ***methodologically-sound*** data collection tools in clinical trials. These guidance documents will also address Agency expectations regarding what sort of analyses might be conducted as part of this work and what sort of documents might be produced **and**, when appropriate, submitted to FDA."

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Line 40	Because not all PED will be collected as part of a clinical trial, BIO requests the FDA to consider the following edit.	BIO requests that the FDA consider the edit below: "...use of methodologically-sound data collection tools in clinical trials and **in supportive studies**"
Lines 40-43	The FDA Draft Guidance states:" These guidance documents will also address Agency expectations regarding what sort of analyses might be conducted as part of this work and what sort of documents might be produced, and when appropriate, submitted to FDA." This sentence implies that FDA does not expect that all studies/analyses/data reports should be submitted to the Agency. Currently, there doesn't seem to be a mechanism which would prevent submitting PED data or a review process by which the Agency would make a determination whether these study data would be refused for filing and/or use by the Agency.	Given the implication that FDA does not expect that all studies/analyses/data reports should be submitted to the Agency, BIO recommends that FDA expand the guidance and clarify the regulatory mechanism as well as process by which PED study data could be refused for acceptance, filing and or use by the Agency. BIO further recommends that this expanded section of the guidance potentially discuss and address provisions outlined in Sections 3002 (c)(7) and 3002 (c)(8) of the 21st Century Cures Act (Pub. L. 114-255), as appropriate.
Line 67	Suggested editorial change.	For clarity, BIO requests that the FDA consider moving footnote 8 to be a footnote with "patient-focused drug development," the first appearance of a glossary term.
B. Purpose and Scope of Guidance 1		
Line 127	Suggested editorial change.	BIO requests that the FDA consider the edit: "Identify approaches to sampling **that** will ensure…"

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Lines 127-128	Suggested editorial change.	BIO requests that the FDA consider the edit: "Identify approaches to sampling **that** will ensure that the input collected...."
Lines 133-135 and lines 270-271	The Draft Guidance states in several locations that there are common elements applicable to all studies including a protocol, structured data collection, and analysis. However, if a protocol, for example, is required for all patient experience studies it may discourage Sponsors and other stakeholders from collecting PED through other means other than a clinical study.	BIO requests that there be flexibility in the "minimum requirements" depending on the methods used to capture the data. For example, we recommend that a formal protocol not be required for submission to FDA in instances when exploratory research is being conducted. BIO also requests that the FDA provide clarification of minimum data requirements for cases when using existing data and/or social media sources, which may not directly conform to a "study protocol" or "study report," are used.
Lines 140-150	For clarity, BIO requests the following edit.	For clarity, BIO requests the following edit: "Although this document presents methods and approaches for collecting patient experience data, it does not fully address methods for collecting and analyzing COAs ~~***or patient preference information***~~. **COAs, including PROs, are outside the scope of patient experience data in this guidance, as they measure outcomes, rather than experiences with a disease or condition.**"

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Line 152	For clarity and consistency BIO recommends adding "and submitting" and "to FDA" to help distinguish circumstances when a stakeholder is submitting data to the FDA.	For clarity, BIO requests the following edit: "If you are considering collecting **and submitting** patient experience data **to FDA**, FDA encourages…"
C. Patient Experience Data		
Lines 179-184	To clearly delineate patient perspectives directly from patients and patient partners versus clinicians, we request the following edit. This section would also benefit from discussion regarding the difference between input from a patient and input from a patient partner.	For clarity, BIO requests the following edit: "An understanding of that perspective may be enriched ~~**or informed**~~ by input from patient partners and clinicians**; however, the patient perspective should not be 'filtered through' clinicians, nor viewed as being of lesser importance than perspectives provided by clinicians**." BIO requests that the FDA emphasize and explain why providers cannot provide the direct patient perspective.
Line 187, Table 1	For the types of Patient Partners, under the definition of "Caregiver", parents/guardians of pediatric patients should be included.	For clarity, BIO requests the following edit: "A **caregiver** … and is not the patient's healthcare provider**. This includes a parent/guardian of a pediatric patient, who is responsible for a patient ages less than 18 years of age**."

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Line 188	This section describes a few types of "Carers" or patient partners but does not reflect the diversity of "patient" types who may be included.	BIO requests that the FDA consider adapting what is in the European Patient's Academy (EUPATI) guidance documents[4] to reflect the diversity of patient partners, including: • "Individual Patients" are persons with personal experience of living with a disease. They may or may not have technical knowledge in R&D or regulatory processes, but their main role is to contribute with their subjective disease and treatment experience. • "Carers" are persons supporting individual patients such as family members as well as paid or volunteer helpers. • "Patient Advocates" are persons who have the insight and experience in supporting a larger population of patients living with a specific disease. They may or may not be affiliated with an organization. • "Patient Organization Representatives" are persons who are mandated to represent and express the collective views of a patient organization on a specific issue or disease area.

[4] EUPATI Guidance on Patient Involvement in Regulatory Process: https://www.eupati.eu/patient-involvement/guidance-for-patient-involvement-in-regulatory-processes/

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		• "Patient Experts," in addition to disease-specific expertise, have the technical knowledge in R&D and/or regulatory affairs through training or experience, for example, EUPATI Fellows who have been trained by EUPATI on the full spectrum of medicines R&D.
Lines 191-214	The list does not mention the impact on caregiver (or care partner), family, etc.	BIO suggests including the impact on others as part of the patient experience.
Lines 204-209	In addition to 'harms or risks,' patient's perspectives on ability to tolerate the treatment/medical product should also be assessed.	BIO requests the following edit in new bullet in line 210: "**perspectives that may impact patients' willingness to continue with treatment**"
Line 216	It would be helpful to encompass the various ways in which PED can be gathered under a single term, such as 'patient experience research.'	BIO requests the following edit: "… patient experience data**, and efforts to gather patient experience data will be referred herein as patient experience research**."
Lines 218-220	As written, this section implies that clinicians would determine whether or not a particular outcome is important. However, we believe that if the patient	BIO requests the following edit: **"**Can data be collected from other experts as well? Where appropriate to supplement patient experience data, FDA ~~**recommends**~~ **suggests** also gathering input from clinicians

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	has identified the outcome as important, the outcome should be deemed important. This section indicates also does not provide information regarding when and how inputs from clinicians and other experts can be used.	and other experts in the given disease area to **further expand on what patients have identified as** ~~**ensure**~~ important ~~**clinical**~~ outcomes ~~**are studied**~~." BIO requests that the FDA consider further describing what "representativeness" considerations are important to consider from non-patient partners (e.g., as per Table 1) in order to speak for patient experiences. Examples of when input from clinicians and other experts can be used.
Lines 224-225	For consistency with standard terminology, we suggest the use of the term "medical product developers" instead of the term "drug manufacturers," as "drug manufacturer" can be interpreted to refer to a narrower group.	BIO requests the following edit: "… researchers, and **medical product developers**~~**, and drug manufacturers**~~."
Lines 225-226	The FDA Draft Guidance states: "It should be clear in any submission to FDA which person or group has collected the data." Study development, collection of data and submission could, and likely will be, a collaborative effort.	BIO suggests the following edit to reflect a collaborative nature of PED collection: "It should be clear in any submission to FDA which person**(s)** or group**(s)** **have engaged in conducting PED studies, including data collection**. ~~**has collected the data**~~."
Lines 237-238	For self-administration, patients/caregivers can also provide important information related to dosage and	BIO requests the following edit:

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	administration aspects of the medical product. To clarify this point, we suggest the following edit.	"… unmet medical needs**, elements for dosing and administration of medical products,** and important clinical outcomes…"
Line 240	The last sentence of this section implies that only clinical outcome assessments will be used to inform a B/R assessment. It should be clarified that any type of patient experience data may inform any type of regulatory decisions, if collected with the appropriate rigor.	BIO requests that the FDA clarify that any type of patient experience data may inform a regulatory decision if collected with the appropriate rigor. There are multiple type of decisions that may be informed by PED (i.e., trial design, endpoint selection, subpopulation identification, approval decisions and labeling) and the Draft Guidance should be strengthened with the addition of commentary that addresses some of the differences that might be observed in studies required to inform specific types of decision as well as the level of certainty that might be required.
Line 242	The term "patient stakeholders" should be replaced with "patients" or "patient partners" to avoid confusion, particularly since this Guidance is intended for Industry, FDA Staff and Other Stakeholders.	BIO requests the following edit: "When should patient ~~**stakeholders**~~ **partners** be involved…"
Lines 242-246	It would be helpful to provide examples of how patient partners can be involved at early, mid and late stages of product development. Additionally, the current text doesn't answer the specific question	BIO requests the FDA to include a figure to highlight key opportunities for patient involvement across product development (e.g., Geissler J *et al*. Therapeutic Innovation & Regulatory Science 2017 vol. 51(5) 612-619).

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	"When should patient stakeholders be involved in product development?"	
Lines 248-253 and Line 260	Clarification is needed to clearly delineate what information will be included in each guidance document.	BIO suggests the text be clarified or rewritten to clarify what is meant by "methodological approaches" for Guidance 1 (vs. "Methods of generating patient experience data," which are to be discussed in Guidance #2 as stated in Line 260).
Lines 255-263	In this section the FDA provides examples such as surveys and interviews, however, additional examples beyond surveys and interviews would be beneficial for stakeholders.	BIO requests that the FDA provide additional examples, and should mention surveys, and patient preference studies, among other methods. It would also be helpful if the table included examples from social media or other digital information.
Table 2, Row 1	The descriptions in the cells in Row 1 do not adequately describe the typical/common research objectives.	BIO requests the following edits: Row 1, column 1: change "~~**Description**~~" to "**Descriptive**" Row 1, column 2: change "~~**Numerical description**~~" to "**Numerically descriptive**" Row 1, column 3: **there can be multiple objectives in Qualitative and Quantitative research.**

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Table 2, row 1	In the row titled "Common Research Objectives" and the column titled "Quantitative Research," the FDA lists "casual explanation and prediction," however only a certain type of study design (i.e. longitudinal) is able to provide causal explanation and predication.	BIO requests that the FDA provide clarification that causal explanation and predication can only achieved through a specific study design. Quantitative research on its own is not sufficient to provide casual explanation and prediction.
Table 2, row 1	In the row titled "Common Research Objectives" and column titled "Mixed Methods Research," the FDA references "understand multiple perspectives," however, understanding of multiple perspectives can be achieved only through inclusion of study subjects that represent the full spectrum of the target population, not through mixed methods research on its own.	BIO requests that the FDA clarify what is meant by the use of mixed methods to understand multiple perspectives.
Table 2, row 2	In the row titled "Common Study Characteristics" and the column titled "Quantitative Research," the FDA lists "study behavior under controlled conditions," however not all quantitative research is designed or able to study behavior under controlled conditions and therefore not all quantitative research is able to isolate the causal effect of single variables.	BIO requests that the FDA clarify that randomized clinical trials facilitate the study of behavior.
Table 2, row 5	In the row titled "Data Analysis" and the column titled "Quantitative Research," the FDA should also indicate that in addition to identifying statistical	BIO requests that the FDA include reference to descriptive analysis in this section.

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	relationships among variables, quantitative research also allows for descriptive analysis of the data (e.g., frequencies, mean, SD, median).	
Line 264	The title "How can external stakeholders submit patient experience data to the FDA?" is not described in Section B of the Guidance.	BIO requests that the FDA provide information regarding how external stakeholders can submit patient experience data to the FDA in this section of the Guidance.
Lines 270-273	Suggested editorial change.	BIO recommends the following edit: "At ~~the~~ **a** minimum, when patient experience data are submitted to the agency, a study report and protocol from the research study should be submitted to FDA, as well as additional information including the primary data capture (see **Section IV** and **Appendix 2)**."
Lines 275-280	This section indicates that Sponsors should interact with the appropriate review division and clearly delineate the intended purpose of the patient experience data being submitted to the Agency, however the section does not include examples of potential intended purposes that the FDA may consider.	BIO requests that the FDA provide specific examples of the intended purpose and the associated data needed for that intended purpose. Because FDA is expanding the potential use of PED (beyond patient reported outcomes and patient preference), additional examples and guidance on the other potential uses of patient experience data would be useful for all stakeholders.

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Lines 282-288	This section indicates that many existing FDA regulations, guidance documents, and other standards and requirements also apply to patient experience data, but it does not clearly delineate that not all the regulations, guidance documents, and other standards and requirements will apply to all patient experience data.	BIO requests that the FDA clarify that all regulations listed in appendix 2 do not apply to all studies collecting patient experience data.
Lines 290-293	With respect to labeling and "other communications" it is unclear how descriptive patient experience information, (distinct from comparative safety and efficacy data derived from the patient perspective), will be allowed and interpreted for use in promotional materials.	BIO encourages the FDA to elaborate on how PED will be treated from a promotional perspective. If PED is included on the label or is consistent with the FDA approved indication, we assume that sponsors will be able to rely on this information for promotional purposes.
Lines 290-295	This section indicates that the FDA values the use of PED but the section does not indicate for what decisions the FDA may consider such data.	BIO requests that the FDA consider providing information regarding how patient experience data will be used by the Agency.
Line 292	Section 3001 of the 21st Century Cures Act establishes a process for documenting and publicly communicating how patient experience information was used in NDA/BLA reviews, but this "brief statement" is not referenced in the section of the Draft Guidance.	BIO requests that the FDA consider making the following addition: "**FDA will document the patient experience information used to inform the approval decision in the "Statement of Patient Experience" included with the summary basis of review." (Sec. 3001 of the 21st Century Cures Act**).

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Line 292	Section 3002 of the 21st Century Cures Act directs FDA to specify "(8) how the Secretary, if appropriate, anticipates using relevant patient experience data and related information, including with respect to the structured risk-benefit assessment framework described in section 505(d) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(d)) to inform regulatory decision making." FDA's revised structured benefit risk assessment framework 5-year plan also notes that FDA intends to offer guidance by 2020 on "how relevant patient experience data and related information may be used to inform benefit-risk assessment, in accordance with the Cures Act." However, the Draft Guidance does not reference the inclusion of PED in the structured benefit/risk framework.	BIO believes that the Draft Guidance should reference the inclusion of PED in the structured benefit/risk framework to provide sponsors and patients more clarity on how this information will be formally incorporated into FDA review processes. BIO requests the following addition: "**FDA also anticipates using patient experience data and related information as part of the structured risk-benefit assessment framework and is exploring strategies for incorporating patient input (derived through both qualitative and quantitative methods) into the framework**."
II. GENERAL CONSIDERATIONS for COLLECTING PATIENT EXPERIENCE DATA		
A. Overview		
Line 313	As written, it is unclear as to which study design/implementation phase should be considered.	BIO requests the following edit: "The **patient experience** research approach should be determined during the study design phase, prior to study implementation, and should be comprised of the plans for

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		your research as well as the steps to implement those plans."
Line 346	BIO suggests using the term patient experience research studies to encompass the various ways in which patient experience data can be gathered under a single term.	BIO requests the following edit: "Figure 1: General Steps for Conducting ~~**Studies about**~~ Patient Experience **Research Studies**" BIO also recommends that this change be reflected in the "TABLE OF FIGURES" (page prior to Draft Guidance page 1).
B. Defining the Research Objectives and Questions		
Lines 359-360	This section outlines potential subject matter experts who may be consulted when defining research objectives and questions. We believe that patient advocates are subject matter experts in their own disease and therefore should to be considered when conducting research.	BIO requests that the FDA consider the follow edit: "...other relevant research literature along with subject matter experts (e.g., clinicians, social scientists, **patient advocates**)."
Lines 262-263, Table 2	Adding examples for each component presented in the table would be helpful to elucidate differences for all stakeholders.	Concrete examples may help delineate the difference between the different methodological approaches. BIO requests that the FDA consider including examples for each component.
C. Who to Collect Information From		
1. Defining the target population		
Lines 393-396	Suggested editorial change.	BIO requests the following edits:

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		"Characteristics of the target population should inform ~~**both**~~ the ~~**type of**~~ research methodology, ~~**including the**~~ data collection mode, ~~**that you choose for your study. It is important to tie the target population characteristics to the**~~ and study sample and inclusion criteria."
2. Determining who will be providing patient experience data		
Lines 412-418	This section describes who should provide patient experience information under circumstances when the patient cannot reasonably be expected to reliably self-report and includes a couple of such circumstances, however it does not detail cases when a patient is at the end-of-life. Additionally, depending on marital status, age, culture and other contingencies, more than just the patient partners can provide valuable information and we recommend to capture that, adding other stakeholder groups closely related to the patients.	BIO requests that the FDA include reference to circumstances regarding input from patients at the end-of-life. BIO also requests the follow edit: "Patient partners**, siblings, parents, other relatives or friends and caregivers** can also provide valuable information about the patient experience."
Line 428	We believe that self-reported data from low health literacy patients should also be collected.	BIO requests the following edit: "~~**Health literacy**~~…"

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Line 429	Clarity is needed to better understand what is meant by "Insight" in this context.	BIO requests that the FDA define what is meant by "insight" in this context.
Lines 450-451	Please see edits to line 359-360.	BIO requests the following edit: " (e.g., clinicians, social scientists, **patient advocates**)"
3. Subgroups		
Line 463	It would be helpful if this section included a sampling schedule.	BIO requests that the FDA include a sampling schedule.
D. Determining the Study Design and Research Setting		
1. Sampling methods		
Table 3	For clarity, BIO requests the follow edit.	BIO requests the following edit: "Similar to snowball sampling. The chain of referrals is often longer than snowball sampling and**,** under certain conditions, estimates can be generalizable to the target population."
Lines 543-544, Table 3	To improve readability, BIO requests that Table 3 be omitted from the text or moved to an Appendix.	BIO recommends moving Table 3 to an Appendix.
2. Representativeness		
Line 549	By definition, PED are subjective.	BIO requests the following edit: "patient experience data that are not only relevant, ~~**objective**~~, and accurate…"

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Lines 562-564	This section describes when a sample is representative of a target population, however, this section does not address representativeness in the context of rare diseases, where the heterogeneity of the target population is greater. Additionally, in the context of rare diseases, the convergence of real world experience can be better reflected compared to those addressing more widespread diseases with larger target populations because for rare diseases, a larger proportion of the target population can be included in a patient experience study.	BIO requests that the FDA consider further discussing patient experience and representativeness in the context of rare diseases. The peculiarities of collecting such information for rare diseases could be better highlighted in the document. Greater flexibility in what constitutes representativeness is needed.
3. Sample size		
Line 581	Effect size and level of confidence also drive sample size. While confidence is mentioned, effect size is not.	BIO requests the following edit: "**Effect size and level of confidence**"
Lines 583-586	The statement "...(e.g., rare diseases), the research objectives should be adjusted accordingly and noted as a limitation in the study report." may potentially discourage the collection of patient experience data for rare diseases, making them appear of lesser value.	BIO requests that the FDA consider rephrasing the sentence, taking into consideration the peculiarities of rare diseases, as to avoid discouraging the collection of patient experience data in the context of rare diseases.
Line 621	For clarity, BIO request the following edit.	BIO requests the following edit: 80%, if the **specified** effect (or more extreme) exists.

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E. Constructing a Sample Frame		
Lines 633-643	The information about registries is a particular example of how sampling frameworks can be applied. BIO recommends simplifying the text to avoid implying that the framework is just for registries.	BIO requests the following edit: "~~**To the extent that disease registries.... the sampling frame.**~~"
A. Additional Considerations		
1. Sufficient representation		
Lines 665-684, including Figure 3	For clarity, BIO suggests that this text be moved to the section on representativeness.	Move text from Lines 665-684, including Figure 3 to Section II.D.2 (*Representativeness)*, line 547.
Lines 672-673	This sentence fails to highlight how for rare diseases, albeit small, the study sample can offer very good representativeness of the target population.	BIO requests that the FDA consider adding a sentence to highlight the particular advantages of collecting patient experience data for rare diseases and how these data can be particularly representativeness of the target population.
2. Missing data/Non-response		
3. Leveraging existing data		
Lines 707-708	The FDA Draft Guidance indicates: "Sometimes engaging in primary data collection methods is not practical or feasible (e.g., collecting patient experience data from ultra-rare disease populations)." Because the term "ultra-rare disease" has not been defined in statute, regulations or existing FDA guidance, we encourage the Agency continue to	BIO requests the following edit: "Sometimes engaging in primary data collection methods is not practical or feasible (e.g., collecting patient experience data from ~~ultra-~~rare disease populations)".

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	employ the established terminology and definition of a rare disease (e.g., affecting less than 200,000 persons in the United States) until there have been sufficient opportunities to discuss and establish any additional scientifically-based definitions.	
Lines 707-713	This section describes circumstances when other data may be leveraged, however the section does not provide context around circumstances when the data are not owned/ controlled by a study sponsor, but collected by another party. These data are likely to have been collected for different objectives and may not be available in their original source form to further explore for the planned research objectives/questions.	BIO requests that the FDA provide additional guidance on acceptable methods to leverage existing data (e.g., literature reviews, social media, and other secondary sources).
III. METHODS FOR COLLECTING AND ANALYZING PATIENT EXPERIENCE DATA		
Line 716	To clearly delineate this section from the section that starts at Line 910, BIO requests the following update.	BIO requests the following edit: "**Patient Experience Research Methodologies**".
A. Qualitative Research Methods		
Lines 734-735	For clarity, BIO recommends the following edit.	BIO requests the following edit: "… research questions, ~~**whether it is**~~ to better understand **either** burden of disease…"

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1. Analyzing qualitative data		
B. Quantitative Research Methods		
Table 4	In step 4 – Represent & Visualize data, there is the potential to identify patients or subgroups of patients.	BIO requests that the FDA explicitly note the need for de-identification of personal information from data.
Lines 763-764	Quantitative research can be reported descriptively and does not always require the "application of statistical methods to summarize the collected data."	BIO requests the following edit: "…the collection of quantifiable data (e.g., numerical data) ~~**and the application of statistical methods to summarize the collected data**~~."
1. Analyzing quantitative data		
Line 777	The Table 13 referred to in the text is not in Appendix 1.	BIO requests that the FDA consider adding Table 13 or replacing it with another table that is referenced in lines 777.
Lines 782-787	To improve flow and readability, Table 4 could be moved to an Appendix.	Recommend Table 4 be moved to the appendices.
2. Additional considerations for data obtained under probability sampling		
3. Additional analytical considerations for missing data and non-response		
C. Mixed Methods		
Lines 831-840	The FDA references "simplest approach to a mixed method study involves the use of both qualitative and quantitative data," however, the FDA does not include an example of such an approach.	BIO requests that the FDA provide an example of a simple mixed method approach.

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Lines 831-863	Mixed methods is critical to PED research and we request that the guidance should emphasize this point.	BIO requests that the Draft Guidance include description and examples of mixed methods approaches.
1. *Analyzing data from mixed methods*		
IV. OPERATIONALIZING AND STANDARDIZING DATA COLLECTION AND DATA MANAGEMENT		
A. Standard Approaches to Consider for Collecting and Managing Data		
1. *Locating patient/sites*		
Line 880	For clarification, BIO requests the following edit.	BIO requests the following edit: "…identify the appropriate **target population,** sample and/or sites…"
2. Human subjects protection		
Lines 890-893	In the Draft Guidance, the FDA indicates that a full discussion of the laws which may apply to collection methods is beyond the scope of this guidance. However, the Draft discusses use of highly innovative technologies (e.g., digital health technologies) for collection of PED.	BIO requests that the FDA expand the guidance to address and discuss policy implications surrounding interpretations of data-protection regulations, particularly as they apply to highly innovative technologies (e.g., digital health technologies) for collection of PED.
Lines 894-895 and 897-899	FDA does not indicate types of PED that will need IRB review. This section refers to the CFR section generally, but it would be more helpful to reference the specific sections regarding circumstances when IRB review is required, exemptions from IRB	BIO requests that the Draft Guidance indicate the types of PED research that will and will not need IRB approval.

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	requirement, and waiver of IRB requirement as applied to the different contexts of gathering patients experience data.	
3. Sampling strategy		
4. Collecting data		
Line 921	The sentence notes "four data collection methods" and points to Table 5., but Table 5 has 7 data collection methods listed.	BIO requests the following edit: "**...seven data collection methods...**"
Lines 926-930, Table 5	To improve flow, Table 5 can be moved to the appendices.	BIO recommends that Table 5 be moved to the appendices.
Lines 935-937	This section states that "The method of interviewing (e.g., in person, telephone or by video chat) may vary depending on the goals of the interview."	BIO requests that the FDA also indicate that the method of interviewing may also be dependent on the availability of the person (e.g., orphan disease where a limited number of individuals are distributed across the country/world and it is not feasible to conduct face-to-face interviews) and in what context the experience would be collected (e.g., heart failure patient and exercised-induced fatigue).
Lines 964-965, and 996	In line 996 the FDA indicates "Each participant in a sample is asked the same set of questions to the extent possible," in lines 964-965 indicates "but can	BIO requests that line 996 is updated to reflect that in circumstances when computerized adaptive testing is used, not all participates may be given the same questions.

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	be administered via computerized adaptive testing…". These two statements conflict, as with computerized adaptive testing all participants in the sample are asked the same questions.	
Lines 1055-1057, Table 6	To improve flow, Table 6 can be moved to the appendices.	BIO recommends that Table 6 be moved to the appendices.
Table 6	For clarity, BIO requests the following edit.	BIO requests the following edit: "Must have authorization to obtain ~~**identifiable information (e.g., Personal Health Information (PHI))**~~ **personal health information**"
5. *Recording information*		
6. *Resolving site/field issues*		
Line 1103	The header should clarify that this section pertains only to PED collection in the context of a clinical study, if that is what is intended by FDA.	BIO requests the following edit: "Access to **clinical study** patients/sites"
Line 1103	The issues described for paper questionnaires can also be problems with electronic questionnaires.	BIO recommends combining the sections for Paper and Electronic Questionnaire Administration.

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Line 1103	Under "Ethical Issues," "Coercion" and "Mishandling/falsification of data" are factors that should be included.	BIO requests the following edits: Under "Ethical Issues," add bullets: "**Coercion**" and "**Mishandling/falsification of data**"
7. Data management		
8. Data standards		
Line 1118	For consistency, BIO suggests deleting "External."	BIO recommends the following edit: "~~**External s**~~**S**takeholders should use appropriate data standards…"
9. Monitoring and quality assurance		
Line 1134	For consistency, BIO suggests deleting "external."	BIO recommends the following edit: "FDA expects that ~~**external**~~ stakeholders…"
10. Storing data		
11. Confidentiality		
V. CONCLUSIONS		
Lines 1162-1164	For clarity, BIO requests the following edit.	BIO requests the following edit: "This document **provides a comprehensive but not exhaustive** ~~**has provided an**~~ overview of methods to collect robust, meaningful, and sufficiently representative

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		patient input to inform medical product development and regulatory decision making."
VI. REFERENCES		
GLOSSARY		
Lines 1589-1601	The definition of social media in lines 1598-1601 of the guidance defines such tools as "web-based" tools used for "computer-mediated communication." However, not all such tools are web-based and computer-mediated. We propose the term "virtual platforms" to replace "social media" in the guidance, wherein "virtual platforms" may include "social media." Further, the definition of "social media" should be modified to remove references to "web-based" tools and "computer-mediated communication."	We propose the use of the term "virtual platforms" to replace "social media" in the guidance, wherein "virtual platforms" may include "social media." Further, the definition of "social media" should be modified to remove references to "web-based" tools and "computer-mediated communication."
APPENDICES		
Appendix 2. Standards and Requirements Pertaining to Submission of Data		
Appendix 3. Considerations for Data Management		