BIO WHITE PAPER ON FDA'S STATEMENT OF PATIENT EXPERIENCE

I. Introduction

In September 2017, FDA implemented the Patient Experience Data table (PED Table) to be completed by reviewers and included in NDA/BLA review documents. While the PED Table was an initial step toward transparency for PED considered during product review, there is an opportunity to enhance the PED Table so that it can be a meaningful source of information for various stakeholders. For example, the PED Table and related sections of the review could provide detailed rationale and a concise summary to better inform patients, caregivers, patient organizations, and drug developers about how the submitted PED is considered in the context of product reviews and criteria FDA reviewers apply to determine if PED can be considered as evidence to inform regulatory decisions. This paper outlines opportunities to enhance the PED Table to ensure that PED that informs regulatory decisions are adequately captured in review documents produced by FDA Review Staff, and are useful, meaningful, and transparent for both FDA and other stakeholders.

II. Background

In 2012, under PDUFA V, FDA launched the Patient-Focused Drug Development (PFDD) initiative to capture and meaningfully incorporate patients' experiences, perspectives, needs, and priorities more systematically into drug development and evaluation.[1] As part of this initiative, FDA conducted over 25 disease-specific Patient-Focused Drug Development

[1] CDER Patient-Focused Drug Development. U.S. Food and Drug Administration website. https://www.fda.gov/drugs/developmentapprovalprocess/ucm579400.htm. Updated December 20, 2018. Accessed April 24, 2019.

meetings and encouraged patient groups to conduct similar, externally-led Patient Focused Drug Development meetings in which the Agency participates. [2]

Under PDUFA VI (FDARA),[5] and as mandated in the 21st Century Cures Act,[3] FDA continues to advance the incorporation of patient experience in medical product development and review. The 21st Century Cures Act, (Section 3001[4]) directed FDA to "make public a brief statement regarding the PED and related information, if any, submitted and reviewed as part of such applications."[5] In September 2017, FDA developed and implemented the PED Table for inclusion in FDA review documents (**Figure 1**). In the PED Table included in FDA review documents, FDA reviewers can identify PED that were submitted as part of the application (e.g., COA data, qualitative /quantitative data, natural history data) as well as any other PED that were not submitted in the application but were considered in the review of the marketing application. In the PED Table, FDA Review Staff can also link to other sections of the review document to provide additional detail regarding the PED (e.g., description of PED, analyses, conclusions).

FDA issued its first multidisciplinary review document that included the PED Table in November 2017.[6] By 2019 the PED Table was included for most approved original applications;[7] however, there remains an opportunity to increase the utility of the PED Table by enhancing the content and consistency of the information included to effectively communicate FDA's conclusions about the reviewed PED (**Figure 2**).

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[2] Food and Drug Administration Voice of the Patient: A Series of reports from FDA's Patient-Focused Drug Development Initiative.
[3] 21st Century Cures Act.
[4] Ibid
[5] Ibid.
[6] Multidisciplinary Review Document: Hemlibra.
[7] Focusing on the Patient: Implementation of 21st Century Cures Provisions and Recommendations for the Future. Manetto, N., Bloch, L., Kennedy, A., and Franson T. (2020).

The following pages outline recommendations and key considerations for enhancement of the PED Table in FDA review documents. We believe that the approaches outlined below will also allow both FDA Staff and other stakeholders to understand the precedent and rationale for regulatory decisions informed by PED, in turn encouraging more patient-focused drug development and review.

I. Core Information Should be Included in the Statement of Patient Experience or Other Sections of the Multidisciplinary Review Document

Consistency in completeness of the information that FDA Review Staff include in the PED Table and other sections of the multidisciplinary review documents assists all stakeholders in better understanding the standards required for PED to be considered for different regulatory decisions (e.g., endpoint development or selection, benefit-risk assessments, inclusion in professional or patient labeling or other patient communication). This can increase the understanding of the quality of PED submitted to FDA and the degree to which patients' perspectives and experiences are considered in the context of drug development and review. Currently, there is substantive variation across product reviews in how the PED Table is completed and the level of detail included in the PED Table or in sections of the multidisciplinary review documents, including how it was considered in the context of the review. BIO has identified examples of drug approval multidisciplinary review documents (**Figure 5**) where the PED Table is fully completed with a thorough description of the PED and includes references to other sections of the multidisciplinary review documents where additional information can be found (e.g., study design, analysis, limitations and an explanation of how the PED were considered).

To support consistency in how the PED Table is populated by FDA Review Staff and to ensure the inclusion of the minimum amount of information that would make the PED Table informative and meaningful to a wide range of stakeholders, FDA may consider identifying a

core set of information that reviewers should include in the populated PED Table and related sections of the multidisciplinary review documents (**Figure 4**). BIO recommends the following **three core areas** of information regarding PED used in application review for inclusion in the multidisciplinary review documents:

1. Description: A brief description of the type(s) of PED, study objective, design, and methods for collection (e.g., focus group, advisory boards, listening sessions, testimonials, survey, one-on-one interview, clinical outcome assessment, patient stakeholder meeting, FDA-led patient stakeholder meeting, patient organization engagement), including a description of who submitted or collected the data (e.g., sponsors, patient organization, FDA);
2. Assessment Considerations: Information on how FDA considered the PED and to what extent.
    a. Information on what aspects of the review and regulatory decisions the PED informed (e.g., benefit-risk assessment, review of the clinical study design, endpoint selection, other aspects of drug development, labeling or other patient communication), how the data was weighed in relation to other data considered, and where the discussion of the decision process can be found in the review document (e.g., benefit-risk framework, section of product label);
3. Exclusion Rationale: If PED were not considered in the context of a regulatory decision, provide rationale as to why the PED were not considered and what criteria were applied by reviewers to assess the utility of PED (e.g., PED were not representative of the patient populations, PED did not meet regulatory rigor).

Prompting Questions: To help guide FDA reviewers, FDA may consider providing reviewers with prompting questions to ensure that the core information described above is appropriately captured in the PED Table or other sections of the multidisciplinary review

documents (e.g., in the benefit-risk assessment). FDA uses a similar approach for encouraging FDA Review Staff to include key information in the benefit-risk framework.[8]

Such prompting questions may include:

1. Description: A description of the PED considered, including, the underlying study objectives, design, and methods used for collection, and who submitted the data.
    a. What type of PED were submitted or considered in the context of this review (e.g., patient-reported outcome data, patient preference information)?
    b. What was the study design, study objective, and research questions that were used to guide the collection and analysis of the PED?
    c. Which methods or mechanisms were used to collect the data (e.g., focus group, one-on-one interview, listening sessions, surveys, clinical outcome assessment)?
    d. Who collected or submitted the data (e.g., the sponsor, patient advocacy organizations or another entity, via stakeholder meeting such as FDA Patient-Focused Drug Development Meetings or listening session)?
2. How the PED were considered to inform drug development and/or regulatory decisions?
    a. Were the PED considered in the context of:
        i. The therapeutic context (severity of condition and unmet medical need)
        ii. Endpoint development or selection
        iii. Study design
        iv. Benefit-risk assessment
        v. Professional or patient labeling, other patient or physician communication
        vi. Other?

[8] FDA Center for Devices and Radiological Health and Center for Biological Evaluation and Research Guidance for Industry and Food and Drug Administration Staff, Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications.

b. If PED were considered, where can the information discussing the rationale for the use and role of that PED on the review decision be found?
c. How were the PED weighed in relation to other submitted clinical data?

3. If the data were not considered, why? What criteria were used to make that determination? (e.g., data were not representative of the patient population or context of use, data were not deemed to have the sufficient level of evidence required to inform a decision)

These prompting questions could be provided to FDA Reviewer Staff in MAPPS or SOPPs or, as appropriate, within the PED Table Review Templates. In addition to the prompting questions above, FDA could consider including additional questions in the PED Table with clear "yes" or "no" response options to ensure that reviewers can clearly indicate whether data were submitted and if so, what data were considered in the review (**Figure 2**).

Update manuals of policies and procedures (MAPPs) and standard operating procedures and policies (SOPPs): Under PDUFA VI, FDA committed to "revise existing MAPPs and SOPPs to include suggested approaches for incorporating an increased patient focus in other ongoing or planned FDA public meetings (e.g., FDA scientific workshops). In addition, as appropriate, FDA will develop and implement staff training related to processes, tools, and methodologies described in this section." In alignment with this commitment, FDA could consider including reference to the "core information" and prompting questions in FDA MAPPs, SOPPs, and review templates to assist FDA Review Staff when populating the PED Table or multidisciplinary review documents. Some or all of the core information could either be included in the PED Table or in the other sections of the multidisciplinary review document, as appropriate, with reference to the PED Table. FDA could consider adding two specific, direct yes/no questions for clarity about whether data were or were not submitted or considered in the multidisciplinary review document (**Figure 3**).

Repository of examples: FDA might also consider providing FDA Review Staff with examples of PED Tables and other sections of the multidisciplinary review that contain core information as outlined above. BIO has provided a table of select approved products where the PED Table and multidisciplinary review documents have addressed core sets of information outlined above (**Figure 5**). BIO considers these examples as illustrative of a strong link between the PED Table and explanatory information in the review documents.

Incorporate PED into FDA benefit-risk assessment: While we are anticipating the release of FDA's guidance on the Structured Benefit-Risk Assessment, FDA could consider approaches to better support the consideration of relevant PED in the benefit-risk assessment. When appropriate, PED should also be reflected and described in the relevant benefit-risk sections of multidisciplinary review documents. FDA's discussion document on "Benefit-Risk Assessment Throughout the Drug Lifecycle,"[9] includes a table on "Key Considerations for FDA's Premarket Benefit-Risk Assessment of New Drug Applications." This table references key considerations related to PED such as benefit and risk values and tradeoffs, including the patient perspective.[10] FDA could include this table in the upcoming FDA Benefit-risk Guidance and update internal MAPPs and SOPPs, to help guide FDA Reviewer Staff on what PED information should be included in the benefit-risk assessment of multidisciplinary review documents.

II. Other Mechanisms for Communicating Patient Experience Data to Key Stakeholders

While the PED Table is routinely located in section 1.4 of the multi-disciplinary review documents, discussion of the analysis and ultimate utility of the PED is distributed

[9] Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document.
[10] Benefit-Risk Assessment Throughout the Drug Lifecycle: FDA Discussion Document.

throughout the multidisciplinary review documents. FDA should consider including an additional row in the PED table titled "Patient Experience Data Summary and Impact on Regulatory Decision-making" to highlight FDA's conclusions on how the PED were or were not considered in the context of the review. This is not meant to be an exhaustive section, but rather a short summary of FDA's key considerations with further details in the respective sections of the review document. This summary would allow stakeholders to readily access and understand, in brief, FDA's thinking without going into detail about each type of PED. This approach would be similar to the "Benefit-Risk Conclusions" section in the Benefit-Risk Framework (**Figure 6**). FDA may consider developing training or MAPPs or SOPPs to assist FDA reviewers in developing the brief summary statement. All stakeholders would benefit from clear, concise, and readily accessible information on PED. Over time, FDA may also consider drafting this summary using plain language to support comprehension of the summary statement by all stakeholders.

To ensure that information on PED considered in the context of a review is accessible to stakeholders, we also recommend that FDA:

1. Consider developing an online repository of PED Tables and brief summary extracted from the multidisciplinary review documents, to be housed on FDA's website (e.g., CDER's External Resources or Information Related to Patients' Experiences[11] and/or the New Drugs at FDA website.[12]). The repository should include PED Tables and summaries for CDER, CBER, and CDRH approved products.
2. Over time, applying health literacy-based practices[13] to brief, plain-language summaries highlighting what PED were reviewed, whether the PED were relevant to FDA's decision-making, and how and why FDA used the PED in the context of their

[11] FDA webpage on External Resources or Information Related to Patients' Experiences.
[12] New Drugs at FDA: CDER's New Molecular Entities and New Therapeutic Biological Products
[13] *See supra*, note 7.

review near or in the PED Table in the multidisciplinary review documents (see example summary statement below)The prompting questions described above could help facilitate in the development of these the brief summaries. This summary statement would complement the efforts initiated by FDA's Oncology Center of Excellence Project Patient Voice pilot, a web platform to present patient-reported symptomatic side effects data from cancer trials.[14]

3. While FDA may consider PED in the context of the review of supplemental applications, including new uses of an approved therapy, currently review documents are not consistently made publicly available for supplemental applications. If PED are considered in the context of the review of a supplemental application, it would be beneficial to have a summary statement (similar to that recommended above for newly approved therapy review documents) made public for all stakeholders to access.

[14] FDA Oncology Center of Excellence Project Patient Voice.

III. Conclusions

FDA implemented the current PED Table to fulfill requirements outlined in the 21st Century Cures Act and to track and report better on the use of PED in regulatory decision making. Further, enhancements to the PED Table based on the recommendations outlined above would help support more transparent and meaningful communication between FDA and key stakeholder groups (e.g., medical product developers, healthcare providers, patients and patient organizations) regarding the utility of PED in regulatory decision-making. While the PFDD guidance series[15] released by FDA has helped inform stakeholders who are collecting PED, a more informative PED Table and associated multidisciplinary review documents have the potential to provide important information on how PED are actually being used in the context of drug and biologic review. Further elaboration about how PED are used by FDA may result in the generation of more valuable PED by Sponsors and patient organizations, thereby advancing patient-focused drug development.

Currently, the PED Table and associated sections in the multidisciplinary review documents are not easily located. The development of a brief summary of the PED data considered in the context of the review in a location that is more accessible to physicians and patients has the potential to improve communication and facilitate shared decision-making.

In summary, to strengthen the utility of the PED Table, BIO recommends the following:

- The FDA should consider including core information on PED in multidisciplinary review documents to provide greater transparency, consistency, and clarity on the review process for PED. This would include integrating additional information that are centrally located in review documents to outline how FDA is considering PED in the

[15] FDA Patient-Focused Drug Development Guidance Series for Enhancing the Incorporation of the Patient's Voice in Medical Product Development and Regulatory Decision Making.

context of review as well as the evidentiary standards being used for PED and evidentiary standards used to inform regulatory decisions.

- FDA could consider making information readily accessible to all stakeholders via online communication tools (e.g., repositories, making review documents for supplemental review applications) and PED summaries that are written in plain language within review documents to improve communication and promote understanding of FDA's consideration of PED.
- FDA could consider developing or updating MAPPs and SOPPs to include examples where FDA Review Staff have included adequate information on the PED that were considered in the context of the review and how FDA considered the data.

Figure 1. Current Statement of Patient Experience. Current Statement of Patient Experience used by FDA Review Staff when reviewing an application. Staff populate the chart to provide information on what PED were submitted to FDA and/or considered in the context of the review of a therapy. The chart is included in the multidisciplinary review and clinical reviews of approved products.

Patient Experience Data Relevant to this Application (check all that apply)				**Section of review where discussed, if applicable**
☐	The patient experience data that were submitted as part of the application include?			
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient-reported outcome (PRO)	
		☐	Observer-reported outcome (ObsRO)	
		☐	Clinician-reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review?			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
		If none checked, check here to confirm that patient experience data that were not submitted in the application were not applicable, available, or considered in this review		
☐	Patient experience data were not submitted as part of this application			

Figure 2. Suggestions for an Updated Statement of Patient Experience that includes question prompts for FDA Review Staff. Text in red indicates possible adjustments that could be made to the chart in order to make the information included clearer.

Patient Experience Data Relevant to this Application (check all that apply)						**Section of review where discussed, if applicable**
	Was patient experience data submitted as part of this application? ☐ Yes ☐ No					
☐	The patient experience data that were submitted as part of the application include?					
	☐	Clinical outcome assessment (COA) data, such as				
		☐	Patient-reported outcome (PRO)			
		☐	Observer-reported outcome (ObsRO)			
		☐	Clinician-reported outcome (ClinRO)			
		☐	Performance outcome (PerfO)			
	☐	Qualitative (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)				
	☐	Patient-focused drug development or other stakeholder meeting summary reports				
	☐	Observational survey studies designed to capture patient experience data				
	☐	Natural history studies				
	☐	Patient preference studies (e.g., submitted studies or scientific publications)				
	☐	Other: (Please specify):				
	Was additional patient experience data, beyond what data were submitted as part of this application considered in the context of this application? ☐ Yes ☐ No					
☐	Patient experience data that were not submitted in the application, but were considered in this review?					
	☐	Input informed from participation in meetings with patient stakeholders				
	☐	Patient-focused drug development or other stakeholder meeting summary reports				
	☐	Observational survey studies designed to capture patient experience data				
	☐	Other: (Please specify):				

Figure 3. Three Core Areas of Information that Should be Included in FDA's Statement of Patient Experience. BIO has identified three core areas of information pertaining to the PED information submitted and/or considered in the context of a medical product review. It would be helpful for FDA to include consistently in multidisciplinary review documents across divisions.

Description of the Information	Reasoning for Including this Information
A brief description of the PED objective, design, and methods for collection (e.g., focus group, advisory boards, testimonials, survey one-on-one interview, clinical outcome assessment, patient engagement meeting, via FDA patient stakeholder meetings) of PED that were submitted or considered, including a description of who submitted or collected the data (e.g., sponsors, patient organization, FDA, etc.).	This information will provide stakeholders with a better understanding of the type of PED that were considered, how the data were collected, and whether the data were collected by the product developers, patient organizations, or FDA.
Information on how FDA considered the PED and to what extent. • Information on what aspects of the review and regulatory decisions the PED informed (e.g., benefit-risk assessment, endpoint selection, labeling or other patient communication) along with where the discussion of the decision process can be found (e.g., benefit-risk framework, section of product label).	This information will provide stakeholders with a better understanding as to how FDA considered the PED, for which regulatory decisions, and in relation to other data submitted pertaining to the product. This information will assist stakeholders who are considering the collection of PED while also informing physician and patients about what the PED means in relation to the medical product.
If PED were not considered in the context of a regulatory decision, provide rationale as to why the PED were not considered and what criteria were applied by reviewers to assess utility of PED (e.g., PED were not representative of the patient populations).	This information will provide stakeholders with a better understanding as to why FDA did not consider the PED, including the evidentiary standards required for consideration of these data, in the context of the review. This information will assist stakeholders in their collection of PED for submission to the FDA, reducing burden on both data collectors and FDA.

Figure 5. Examples of FDA's Statement of Patient Experience that Highlight Good Practices for FDA Review Staff

Product Name	Examples from the Multidisciplinary Review Documents Where Core Information about Patient Experience Data were Included
Takhzyro	The PED Table (Section 1.4) associated with the Takhzyro product review clearly outlines sections of the multidisciplinary review document where additional information can be found (i.e., on the use patient reported outcome instruments, patient-focused drug development or other stakeholder meeting summary reports, and patient experience data that were not considered in the application but that were considered in the context of the review). This PED Table also clearly and accurately references the HAE PFDD Meeting held in 2017, highlighting overarching themes from the meeting and how the workshop informed FDA's thinking in the context of the application.
Rinvoq	This PED Table (Section 1.4) clearly outlines sections of the clinical review document where additional information can be found (i.e., clinical outcome assessment data and clinician reported outcomes). Additionally, Section 1.2 of the multidisciplinary review (Conclusions on the Substantial Evidence of Effectiveness) also indicates that the study was designed to capture clinically meaningful changes in patients' disease activity. PED (specifically PROs) informed the approval decision for Rinvoq, patient reported outcomes and clinician reported outcomes showed clinically meaningful improvement, and were referenced in the label as well as the benefit dimension of the Benefit-Risk Assessment in the Summary Review along with the Clinical Review.
Ultomiris	This PED Table (Section 1.4) clearly outlines sections of the multidisciplinary review document where additional information can be found (i.e., clinical outcome assessment data). The multidisciplinary review documents (including the PED Table) provide a brief and clear description of the PED objective, design, and methods for collection (e.g., FACIT-Fatigue and EORTC QLQ C30). In Section 1.2 of the multidisciplinary review (Conclusions on the Substantial Evidence of Effectiveness), reference to the changed observed in the population as measured using the PRO is referenced. The benefit dimension of the Benefit-Risk Assessment also references the FACIT-fatigue PRO, indicating that it informed the benefit aspects of the review. Importantly, page 21 of the multidisciplinary review document provides information to the public as to why the PRO data were of limited interpretability.

Figure 6. Potential draft PED Table with summary statement.

The FDA reviewed the following PED as part of this application for **DRUG XX**:

Patient Experience Data Relevant to this Application (check all that apply)				**Section of review where discussed, if applicable**
X	The patient experience data that were submitted as part of the application include			
	☐	Clinical outcome assessment (COA) data, such as		
		X	Patient-reported outcome (PRO)	Section 1.3 (B-R Assessment), Section 6 (Review of Relevant Individual Trials Used to Support Efficacy), Section 7 (Integrated Review of Effectiveness)
		☐	Observer-reported outcome (ObsRO)	
		☐	Clinician-reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	X	Qualitative (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Section 2 (Therapeutic Context)
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	X	Patient preference studies (e.g., submitted studies or scientific publications)		Section 2 (Therapeutic Context)
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review?			
	X	Input informed from participation in meetings with patient stakeholders		Section 2 (Therapeutic Context)
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
		If none checked, check here to confirm that patient experience data that were not submitted in the application were not applicable, available, or considered in this review		
☐	Patient experience data was not submitted as part of this application			

[New Row in PED Table] Patient Experience Data Summary and Impact on Regulatory Decision-making

FDA reviewed a range of patient experience data (see above) highlighting the patient experience (e.g., burden of illness, unmet need, treatment outcomes, benefit-risk tradeoffs) with Disease YY as part of the application. COA data was submitted by the Applicant supporting the secondary endpoint (i.e. improved physical function). Drug XX-treated subjects experienced a clinical benefit compared to control subjects for the secondary endpoint, improved physical function, which was chosen to assess potential treatment benefits to patients with Disease YY.

PROMIS Physical Function was used to measure the change from baseline for the improvement of physical function. Analyses showed a clear additional clinically meaningful benefit with Drug XX treatment and statistically significant improvement on physical function compared to the lower dose in these studies.

The Applicant also submitted a Patient Advisory Board summary report highlighting the patient perspectives regarding Disease YY as part of the application. The patient narratives (n=10) from the Patient Advisory Board summary report enhanced FDA's understanding of Disease YY and the unmet medical need, mainly patient considerations related symptoms AA and BB and its impact on patients' daily lives. Additionally, FDA participated in an FDA-NORD listening session with patient stakeholders with Disease YY, where they highlighted the severe impact of the disease. However, FDA notes that the patient narratives from the Patient Advisory Board and listening session were not fully representative of the patient population. Also, due to concerns regarding the methodology used in the Applicant's patient preference study to elicit patient trade-offs, FDA did not take the patient preference data into consideration.