



A Perspective on the 21ST Century Cures Act: Patient-Focused Drug Development

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Background

The 21ST Century Cures Act (Cures Act) includes several mandates designed to provide the U.S. Food and Drug Administration (FDA) the opportunity and resources to modernize their scientific and regulatory programs. The provisions address topics such as patient-focused drug development (PFDD); adaptive designs and statistical modeling in new drug applications; the use of real-world evidence to help support new indications for previously approved drugs and/or for post-approval study requirements; and, formalizing mechanisms for the Drug Development Tools Qualification program, among others. The Cures Act was signed into law December 13, 2016, and authorizes \$500 million in funding specifically for use by the FDA to carry out these and other provisions that fall within their purview.

The “Patient-Focused Drug Development” section of the Cures Act (Title III, Subtitle A) emphasizes the need for patient engagement in drug development, and includes

provisions designed to define and standardize the use of patient experience data in regulatory programs.

Patient experience data is defined as “data collected by any person (including patients, family members, and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers) that are intended to provide information about patients’ experiences with a disease or condition”.¹ The term specifically includes data regarding:

- a. The impact of the disease or condition, or a related therapy, on patients’ lives; and
- b. Patient preferences with respect to treatment of the disease or condition.”

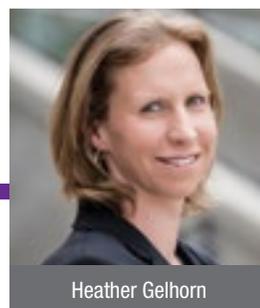
The legislation mandates that as of June 13, 2017, all new drug approvals include a brief statement summarizing any patient experience data that was submitted and reviewed as part of the application. The legislation does not specify the format or location in which the brief statement will be communicated to the public. The legislation does, however, require the FDA to release a series of new guidance documents that delineate methods, approaches, standards, and expectations for the use of patient experience data. It is reasonable to expect that the format and location of the brief statement for the patient experience summary may be defined in the guidance. In response to the mandate to develop the PFDD guidance, the FDA developed a plan for the issuance of seven new guidance documents related to the use of patient



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experience data over the next five years, and presented the plan to the FDA Science Board in May 2017.² With the approval of the Science Board, the FDA submitted their final plan for addressing the provisions of the Cures Act, including PFDD, to Congress in June 2017.³

Purpose

This paper is designed to provide an overview of the FDA's plan for issuance of the PFDD guidance² and discuss considerations for stakeholders related to the inclusion of patient experience data in drug development programs.

Model of Patient-Focused Drug Development

Patients who live with a disease are the ultimate stakeholder and are well-positioned to contribute to the comprehensive drug development process. The FDA's plan outlines a model for PFDD, which is designed to center the focus of drug development efforts on the patient (*Figure 1*). Patient perspectives should systematically be gathered to:

1. define the burden of disease, burden of treatment, and unmet needs,
2. identify the holistic set of impacts that are important to patients within a specific disease area,
3. identify and select meaningful clinical outcome assessments (COAs) based on the holistic set of patient-identified impacts,
4. define change in COAs that are meaningful to patients, and
5. characterize patient-acceptable benefit-risk ratios (*Figure 1*).

Historically, regulatory standards for patient experience data have centered on the use of patient-reported outcome (PRO) endpoint data in pivotal clinical trials. The content outlined in the FDA's plan for PFDD suggests that the new guidance will address alternate methods to gather patient experience data (e.g., patient stakeholder input, advisory boards, surveys, preference data) that may be used across the drug development cycle (i.e., pre-clinical through post-marketing).

The topics for the seven new PFDD guidances outlined in the FDA's plan describe patient experience data

as it relates to burden of illness, burden of treatment, impacts, meaningful clinical outcomes assessments, and patient-acceptable benefit-risk ratios. A description of each guidance document, as outlined by the FDA, is summarized below, followed by considerations for stakeholders.

Perspectives on the FDA's Plan for the Patient-Focused Drug Development Guidances

Guidance 1

Guidance 1 will be focused on methods and approaches to "collect meaningful patient input throughout the drug development process, and methodological considerations for data collection, reporting, management, and analysis."²

Considerations

As described in the FDA's plan, this first guidance is expected to highlight approaches to engaging with patients and collecting patient input throughout the entire drug development process. The proposed scope of this guidance highlights the importance of engaging with patients throughout a product life cycle through patient consultant services, surveys, advisory boards, interviews, and other research activities. This type of evidence may become acceptable information for regulatory submissions, so sponsors starting clinical programs need to consider engaging patients early and often.

Figure 1. Model for Patient-Focused Drug Development



In the absence of a guidance with defined acceptable approaches, sponsors need to focus on empirically-based methodology for collecting patient perspectives, and document any patient experience activities in a manner consistent with the rigor expected for regulatory submissions. Previous experience with the various types of FDA patient engagement work streams⁴ will likely inform the initial framework of this draft guidance. External stakeholders are encouraged to participate in discussions to help shape the guidelines. Feedback from stakeholders on methods used and associated challenges and successes can be communicated to the FDA during the public workshop and comment period. The first workshop to discuss the development of this guidance is December 18, 2017,⁵ and registration is currently open for in-person and web-based participation.

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Guidance 2

Guidance 2 aims to delineate methodological approaches to “collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy.”²

Considerations

Although there is some degree of conceptual overlap between this second guidance with the first, the fact that a separate guidance will be released specifically to address methods and approaches for capturing the burden of disease and treatment suggests this may be an area of particular interest. The FDA’s PFDD “Voice of the Patient” meetings⁶ are designed to systematically collect patient perspectives on the burden of illness, burden of treatment, and key impacts of disease. The initial framework for this guidance is likely to be influenced by the FDA’s experience with these Voice of the Patient meetings.

Sponsors are encouraged to refer to the publicly available Voice of the Patient meeting materials, which include audio files, transcripts, and reports, for disease areas in which these meetings have been conducted; leverage these materials when making decisions regarding medical product development programs; and, document these decisions. In disease areas where meetings have not been conducted, consider sponsoring an externally funded Voice of the Patient meeting⁷ to gather this information systematically in a manner that is consistent with the FDA’s methodology. Alternative approaches to consider collecting these perspectives include patient survey studies, burden of illness studies, patient journey maps, interviews, and focus groups.

Guidance 3

Guidance 3 will be focused on approaches to identifying a “holistic set of impacts that are important to patients” with a specific disease.²

Considerations

Again, there is some degree of overlap with this topic and the outline of the first guidance. The focus on “holistic” impacts suggest that the guidance may extend the range of outcomes and concepts considered in regulatory submissions beyond the traditional symptoms and physical impacts. The legislation requires the FDA to make a brief statement summarizing what, if any, patient experience data was submitted and reviewed as part of the application, but it is not clear where this information may appear. For example, will it appear in the product label? If not, what alternatives might be appropriate for communicating patient experience data?

The answer to these questions may not be addressed until the release of the guidance, but the FDA issued a draft Medical Product Communications guidance in January 2017⁸ that suggests PRO data may be used promotionally even when it is not in the product label, assuming it is for the approved/cleared indication in its approved/cleared patient population. This more flexible approach to the dissemination of PRO data is one indication that there may be a place for patient experience data in the era of PFDD that extends beyond the product label.

To capitalize on potential opportunities following the release of the guidance, sponsors should ensure that the impacts evaluated in medical product development programs are expanded to include critical targets of treatment as defined by patients. Sponsors should also leverage existing patient-defined core impact sets⁹ when available, and, when unavailable, consider partnering with other stakeholders to conduct patient workshops, surveys, Delphi panels, etc., to identify core impact sets that are important to patients.

Guidance 4

Guidance 4 is designed to define standards for the selection, design, and development of clinical outcome assessments and “will as appropriate, revise or supplement the 2009 Guidance to Industry on Patient-Reported Outcome Measures (2009).”²

Considerations

The plan for a new guidance on COAs that will be designed to either replace or supplement the existing PRO guidance¹⁰ may represent an expansion in regulatory thinking beyond the traditional PRO to broader patient-identified meaningful endpoints, which could be a performance-based measure, observational measure, PRO, or something else. The intent is to ensure that the COA is meaningful to patients.

The rigor of the evidence required to support a COA – the content validity, other validity, reliability, ability to detect change, and interpretation thresholds – is not likely to change. The FDA's outline for this guidance suggests rather an expansion to include other types of COAs, as well as specifications related to technologies that may be used for the collection, capture, storage, and analysis of electronic COA data. Sponsors with submissions including PRO endpoints may have the opportunity to negotiate certain aspects of their planned PRO strategy in the interim period.

Guidance 5

The fifth guidance aims to provide stakeholders with information required to “develop and submit proposed draft guidance relating to patient experience data for consideration by FDA” on patient experience related topics, for example “planning and conduct of clinical trials to be more patient focused, enhancing patients’ ability to enroll and continue to sustain participation in clinical studies, and the quality of their experiences as participants in such studies.”²

Considerations

The FDA has a recent history of working with disease foundations on disease-specific draft guidance documents and drug development tool qualifications.^{11,12} The new PFDD guidance is anticipated to leverage this experience and provide a formal guidance for stakeholders invested in defining best practices related to patient-centered drug development generally, as well as to those interested in undertaking efforts to develop and/or qualify endpoints in a precompetitive environment. This guideline seems to signal the FDA's readiness to continue to engage a broad range of stakeholders in the development of disease specific guidelines. In this context, collaborations of sponsors and stakeholders especially in the area of rare disease, may present new opportunities.

Guidance 6

Guidance 6 will outline how the FDA intends to respond to patient experience submissions, and timeframes for response to submissions made for the drug development qualification program for COAs and PROs.

Considerations

One challenge that stakeholders have encountered when engaging with the FDA outside the context of a drug development submission is the lack of a specified timeframe for response. The PFDD section of the Cures Act requires the FDA to issue guidance on how the Agency intends to respond to submissions related to patient experience data, including a timeframe for submissions that are not part of a regulatory application. Ideally, attaching specific timelines to precompetitive submissions will facilitate increased access to qualified measures for use in the drug development process.

Guidance 7

The final guidance is expected to define how the FDA intends to use “relevant patient experience data and related information, including with respect to the structured benefit-risk assessment framework” to “inform regulatory decision-making.”²

Considerations

This critical guidance is expected to define how the FDA will utilize the expanded patient experience data in the new PFDD regulatory framework. Although the specific requirements related to the use of patient experience data are currently unknown, the considerations outlined above provide a starting point for sponsors to consider as the guidance is developed.

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The FDA's outline for this particular guidance highlights benefit-risk assessment framework. Although the methodologies acceptable by the FDA are not yet specified, it is reasonable to assume that developments in other areas of the FDA may be indicative of the potential direction of future initiatives. In the case of benefit-risk assessment, it is worth noting that the Center for Devices and Radiological Health (CDRH) recently released a guidance on the use and voluntary submission of patient preference information during the review process.¹³ This guidance was intended to acknowledge that patients and caregivers have their own perspectives and insights on diseases which may be important to consider from a regulatory perspective. The guidance also outlines preferred approaches and methodologies to gathering these types of data. It is conceivable that other FDA Centers such as the Center for Drug Evaluation Research (CDER) and Center for Biologics Evaluation and Research (CBER) may adopt, adapt, and/or expand this guidance to suit their needs, and that the current recommendations may be an excellent starting point for those wishing to capitalize on any potential opportunities early on.

The timeline for releasing the various PFDD guidance documents as outlined in the FDA's plan² is summarized in Table 1. The FDA will be holding several public workshops in advance of the release of draft guidance documents, and stakeholders are encouraged to actively engage in the process to help shape the PFDD regulatory guidance.

Conclusions

The issuance of this PFDD plan suggests that we have entered a new era of drug development where systematic inclusion of patients’ perspectives and experiences across the drug development cycle are an integral part of the

drug development and approval process. Going forward, methods and approaches for achieving PFDD are expected to be defined, and all new product approvals will be required to include a brief statement concerning what, if any, patient experience data were submitted and reviewed as part of an application. By leveraging empirically-based methods and approaches for capturing patient experience data, and by documenting the methods and approaches used, sponsors will be equipped to respond to and capitalize on the opportunities offered by the new PFDD guidance. Finally, by actively participating in the process planned by the FDA for the development of these guidance documents, all stakeholders can be satisfied that their perspective is considered in the development of these important documents. ■

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Table 1. Timeline for Issuing the FDA's Patient-Focused Drug Development Guidance

Guidance	Workshop	Draft Guidance	Final Guidance
1	December 18, 2017	Q2 2018	Q1 2020
2	Q4 2018	Q2 2019	Q1 2021
3	Q4 2019	Q2 2020	Q4 2021
4	Q2 2019	Q2 2020	Q2 2021
5	N/A	Q1 2018	Q4 2019
6	N/A	Q4 2019	Q4 2020
7	Q2 2019	Q2 2020	Q4 2021

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