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US Patient-Focused Drug Development Meetings Changing With The Times

by Sue Sutter

Meetings are now primarily hosted by external patient advocacy groups, with accelerated approval and surrogate endpoints making their way into discussions. Stakeholders want more transparency on how FDA uses PFDD reports, and one agency staffer suggests adding other types of expertise to the meetings.

As the US Food and Drug Administration's patient-focused drug development initiative hits the 10-year mark, stakeholders are eyeing ways the program has evolved and additional changes they would like to see.

Primary responsibility for organizing and leading PFDD meetings in specific disease areas has shifted from the FDA to patient advocacy groups, and participants are increasingly being asked about their willingness to participate in clinical trials, including those aimed at securing accelerated approval on the basis of surrogate endpoints, stakeholders said at a Biopharma Congress panel discussion coproduced by Prevision Policy and Friends of Cancer Research.

The PFDD program is primed for further evolution under the next iteration of the Prescription Drug User Fee Act. The PDUFA VII agreement negotiated by the FDA and industry contains several PFDD provisions, including FDA plans for new guidance on use of patient preference information and bringing in external experts to review patient experience data. (*See chart at end of story.*)

From Agency-Led To Externally-Led

Under the PFDD initiative established through the FDA Safety and Innovation Act of 2012, the FDA has conducted 30 meetings to systematically obtain the patient perspective on specific diseases and their treatments.

In the process, the agency created a template that can be used by patient advocacy groups to conduct their own meetings, and approximately 50 externally led meetings have been held to date. A summary of each meeting, often referred to as the Voice of the Patient report, is produced and made available through the agency's website.

Patients participating in PFDD meetings typically are asked to discuss several standard questions, including:

- The most significant health effects and daily impacts of their condition;
- How their condition has changed over time;
- Current approaches to disease management; and
- What they would like to see in an ideal treatment.

At some meetings, patients also have been asked to discuss factors that would influence their decision to participate in a clinical trial.

This format has "really stood the test of time and continues to provide relevant information for us," said Larissa Lapteva, associate director of the Office of Tissues and Advanced Therapies' Division of Clinical Evaluation, Pharmacology and Toxicology.

Every PFDD meeting is an important source of information that is potentially and sometimes readily applicable to drug development in a given disease area, she said. The meetings produce "truly valuable information that you can't find in regular textbooks or scientific articles or in the mainstream clinical literature."

The meetings also have served as platforms for interaction between patients, advocates and other stakeholders. "We have really elevated organized patient advocacy to an entirely different level," Lapteva said. "Patients are not research subjects anymore. They are full partners in drug development."

Although the structure of the meetings has worked well and been fruitful, there have been some innovations in the format over time, said James Valentine, an associate at Hyman, Phelps and McNamara in Washington, DC.

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PFDD meetings produce "truly valuable information that you can't find in regular textbooks or scientific articles or in the mainstream clinical literature." – FDA's Larissa Lapteva

"While largely the agendas and the discussion questions have remained pretty stable, there has been opportunity, especially in some of the externally-led meetings, for the addition of some new topics," Valentine said.

"Across some of the rare kidney conditions, one area that was added to the agenda was this discussion around acceptance of less certainty in treatment outcomes, really about surrogate endpoints to support potential accelerated approvals and actually asking patient communities to weigh in on their acceptance of that uncertainty and whether that's something that they would find valuable," Valentine said.

Voice of the Patient reports from externally-led meetings on IgA nephropathy and primary focal segmental glomerulosclerosis show that patients were asked about their willingness to participate in clinical trials designed under the accelerated approval program, and their willingness to continue in a study's extension phase to confirm clinical benefit following a drug's accelerated approval on the basis of a surrogate endpoint.

Questions around the concept of surrogate endpoints can be challenging, Valentine said.

"This is such a relatively abstract concept, to say if there's a finding on a surrogate that's only reasonably likely to predict an ultimate clinical benefit, is that something that's important? That's a little bit outside of what patients and caregivers might be thinking of every day."

Nevertheless, many different patient communities are using drugs off label, despite the lack of solid evidence to support such use. "So in a way they actually do have a lot of experience with uncertainty," Valentine said. "But I think it has taken a little bit more time to kind of hash out how that should work and how we should ask those questions."

Need For Other Areas Of Expertise

Lapteva believes it may be time to start getting other types of experts more involved in PFDD meetings.

"There could be expansion of participation in those PFDD meetings beyond that of just patient advocates, FDA, and maybe a handful of academic experts who know the disease very well, who

have maybe a natural history protocol or a registry somewhere," Lapteva said. "When planning these meetings, it might be helpful to proactively think of where the knowledge gap [is] in that particular disease area."

For example, psychometricians could be helpful if a patient-reported outcomes instrument needs to be developed, and clinical trialists or research coordinators could be helpful if there is a need to understand how to conduct a study more efficiently, Lapteva said. She also could envision getting speech and occupational therapists involved, depending upon the condition.

It is important to get "those who understand the disease in a very detailed manner" involved "so whatever issue needs to be addressed could be addressed and people could synthesize the information and maybe have some ideas of how to apply what we hear at patient-focused drug development meetings to the actual development of medical products for that condition," Lapteva said.

She also would like to see more discussion around the concept of benefit-risk at PFDD meetings. This conversation often takes place at the end of the meeting, when time is running short, she said, adding that it would be good to hear from patients regarding how much benefit they would trade for a specific risk.

Expanding and creating more specific questions on benefit-risk could help to eventually bridge from the descriptive information gathered at PFDD meetings "to a more precise data collection that often happens under the patient preference studies," she said.

Lost In Translation

While the patient testimony heard at PFDD meetings, and the resulting Voice of the Patient reports, are highly informative, there is uncertainty in how the FDA ultimately uses this information, patient representatives and advocates said.

An external consultant's assessment of the FDA's use of patient experience data in regulatory decision-making also highlighted transparency as an issue and called on the agency to more clearly explain how it uses such data in its drug and biologic approval decisions. (Also see "*US FDA Should Explain How It Uses Patient Experience Data In Drug Approvals – Report*" - Pink Sheet, 26 Oct, 2021.)

"Patient communities are a little frustrated because there's not as much transparency as they would like in seeing how that's used," Valentine said. "They're told that it's used and there's reports to kind of signal that they're being used, but I do see more and more groups trying to more proactively take on what I'll call that translational piece more directly, and some of it stems from that frustration."

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After a PFDD meeting, patient groups might request a Critical Path Innovation meeting, a listening session, or some other type of interaction with agency officials to help "connect the dots" as to how this information can aid in designing clinical trials, he said

> *"Patient communities are a little frustrated because there's not as much transparency as they would like in seeing how" PFDD testimony is used by agency, said Hyman Phelps' James Valentine.*

This persistence in follow-up was the approach taken by the Barth Syndrome Foundation following its July 2018 externally-led PFDD meeting. The group continued its dialogue with the FDA through listening sessions, patient community petitions and letters from key opinion leaders, said Emily Milligan, the foundation's executive director.

"It wasn't apparent to us how" the testimony from the PFDD was "being incorporated into internal deliberations within the agency as well as actual decision-making. I would like to have a little more transparency around that," she said.

For patient organizations, a PFDD meeting is "not a one-and-done" deal, Milligan said. "To put on one of these meetings it is very expensive. It's not trivial for small organizations. To ensure that you're getting an RoI that you can communicate back to your community is really important."

Voice Of The Patient Reports Bolster FDA Requests

FDA officials said patients' voices are being heard through the PFDD meetings. Meeting summaries are given consideration by regulators and are very helpful, even if it is behind the scenes and not publicly obvious.

"These documents are well cited within the agency and in our interaction with sponsors," said Vishal Bhatnagar, Oncology Center of Excellence associate director of patient outcomes.

For example, oncology review teams have long advocated that sponsors collect meaningful data on fatigue and physical function symptoms, "and to have the voice of the patient alongside our recommendation is very powerful," Bhatnagar said. The agency telling commercial sponsors to collect certain types of data is one thing, "but to have those reports from these very important meetings I think also has bolstered that argument."

When reviewers look at specific product development programs, they will look at the Voice of the Patient report if the condition has been the subject of a PFDD meeting, Lapteva said.

Marketing application review templates include a chart reflecting whether the application contains patient experience or PFDD data. (Also see "*'Patient Experience Data' Section Added To US FDA Drug Reviews*" - Pink Sheet, 8 Jan, 2018.)

If at some point during product development the Voice of the Patient report was not looked at but is part of the marketing application, reviewers would look at it for context in understanding the benefits measured in the clinical development program, Lapteva said.

Informing Patient Preference Studies

One of the biggest opportunities Lapteva sees for using PFDD data is informing the design of patient preference studies

Information gleaned from PFDD meetings is primarily descriptive and often not sufficient to include in product labeling, she said. However, such information can be highly useful in informing the design of patient preference studies.

“There has to be some kind of investigational component to this,” Lapteva said. “Just plain descriptive may or may not work for all product labels.”

Genentech, Inc. succeeded in getting results from a dedicated patient preference study into the labeling for Rituxan Hycela (rituximab/hyaluronidase), a subcutaneous form of the CD20-directed cytolytic antibody that previously was approved only for intravenous infusion. (Also see "*Patient Experience Data May Require Separate Label, Genentech Suggests*" - Pink Sheet, 25 Sep, 2017.)

Patient preferences is a research area still early in development, Lapteva said. “If for specific disease areas patient-focused drug development could include some information that may eventually be developed into more precise data which could inform design of these patient preference studies … that would be the type of information that would eventually make it to the product label.”

“I would dare to envision that maybe several years ahead we will see more and more of these types of studies be included in the product label where patient preference can be taken into account with regard to benefit, risk and treatment choices,” she said.

Commitment	Details
Strengthen capacity to	Expand internal staff training across review divisions, including

facilitate development and use of patient-focused methods to inform drug development and regulatory decisions	development of methodology training courses for review staff that will be conducted at least 2 times per year
	Conduct targeted outreach to industry and methodological consulting organizations to provide presentations, sessions, resources to increase understanding, acceptance and integration into development programs
	Engage external experts through the Intergovernmental Personnel Act to support the review of patient experience data
Seek public input on methodological issues, including the submission and evaluation of patient experience data in the context of benefit-risk assessment and product labeling	Issue Request for Information no later than end of June 2023
	Issue Federal Register notice summarizing input to the RFI by end of December 2023
	Conduct one workshop on methodological issues by end of FY 2024
	Conduct second workshop on methodological issues by end of FY 2025
	Based on RFI and workshop learnings, produce written summary with identified priorities for future work by end of FY 2026
Continue work to develop a virtual catalog of standard core sets of clinical outcome assessments (COAs) and related endpoints	Pursue non-user fee funding for work to develop standard core sets that will be available for public use
	Work to enhance understanding of how patient preference informs meaningful benefit or benefit-risk tradeoffs in therapeutic areas
Conduct a public input process to understand stakeholder perspectives on diseases and domains of greatest need or highest priority for development of standard core COAs and endpoints	Identify priority areas where decisions are preference-sensitive and patient preference information (PPI) data can inform regulatory decision-making
Publish draft guidance on use and submission of PPI to support regulatory decision-making	Publish draft guidance by 30 September 2026
	Work toward goal of publishing final guidance, or revised draft, within 18 months after close of public comment period