Advancing the science of patient input throughout the regulatory decision-making process

Million A. Tegenge | Megan M. Moncur | Robert Sokolic | Richard A. Forshee | Telba Irony

1 Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research (CBER), US Food and Drug Administration, Silver Spring, Maryland
2 Office of Tissues and Advanced Therapies, CBER, US Food and Drug Administration, Silver Spring, Maryland

Correspondence
Megan Moncur, Office of Biostatistics and Epidemiology, CBER, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20993
Email: megan.moncur@fda.hhs.gov

Abstract
The US Food and Drug Administration (FDA) understands the value of patient input in the regulatory decision-making process and has worked to enhance meaningful engagement. In recent years, there has been an increased scientific demand for more systematic and quantitative approaches to incorporate patient input throughout the medical product lifecycle, including to inform regulatory benefit-risk assessments. The use of patient preference information (PPI), elicited using established scientific methods, is a promising strategy for accomplishing this. Although much of the science behind PPI is not new, its application in a regulatory setting will require adapting and advancing the science of identifying, collecting, and evaluating patient input for informing regulatory decision making. Patient input and empowerment are foundational to a learning healthcare system. A learning healthcare system paradigm can also help us better understand and continuously improve the incorporation of the patient perspective in regulatory decision making. In this article, we highlight the Food and Drug Administration’s Center for Biologics Evaluation and Research experience and current initiatives on advancing the science of patient input in a regulatory setting, in particular, PPI. We provide a use case that explores how the principles and benefits of PPI applied in shared clinical decision making can be realized and leveraged to enhance regulatory evaluation of innovative therapies. To further advance the application of the science of patient input in our regulatory framework, we compiled a list of example resources that support stakeholders in designing and conducting PPI studies. More collaborative research among stakeholders is needed to establish best practice approaches, ensure scientific validity, and continuously learn and improve the systematic incorporation of scientific patient input throughout the regulatory decision-making process.

KEYWORDS
patient perspective, patient preference, benefit risk, science of patient input

1 | INTRODUCTION

A patient-centered healthcare system that aligns care with individual patient needs and values has the potential to improve the quality of care delivered and health outcomes not only at the patient level but also at the population level.1,2 Multiple cultural and political forces have been moving this vision forward.2-4 One area that has received significant attention is that of incorporating the patient perspective into all aspects of the medical product development paradigm, including the regulatory framework for review and approval of new products.5,6 The US Food and Drug Administration (FDA) understands the value of patient input in the regulatory decision-making process and has regularly sought patients’ input.7 Over time, FDA’s approach for engaging patients has been evolving from a more reactive to proactive approach. For example, in the late 1980s, AIDS patients and advocacy groups actively engaged FDA to express their concerns over the lack of treatment options and the slow pace of the approval process. This
engagement helped FDA expedite the implementation of regulations that provided wider and timelier access to AIDS treatments and subsequently to treatments for other serious and/or immediately life-threatening diseases.8

FDA also sought more proactive patient engagement strategies. For example, in the late 1970s, FDA added consumer representatives to its prescription drug advisory committees; however, initially their participation in committee deliberations was limited. In 1991, FDA included a patient representative as a voting member of the Antiviral Drugs Advisory Committee, thereby formally incorporating the patient perspective into regulatory decision making.9

Although FDA’s efforts have become more systematic over time, recently there has been a call to do more.9,10 FDA has responded by launching multiple efforts that support the capture of the patient perspective qualitatively, such as through the Patient-Focused Drug Development initiative, as well as efforts to capture the patient perspective quantitatively, by commissioning a study to elicit patient preferences for weight-loss devices and subsequently finalizing the 2016 Guidance for Industry on Patient Preference Information—Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling.11-13 As part of the agency’s efforts to incorporate patient input in medical product development and evaluation, FDA’s Center for Biologics Evaluation and Research (CBER) has recently launched the Science of Patient Input (SPI) initiative, which includes patient preference information (PPI) and patient-reported outcome measures.

In this article, we describe some of our activities to incorporate PPI in medical product development, share an example from CBER’s SPI initiative of how PPI can inform clinical and regulatory decision making, and discuss opportunities for advancing SPI in the future.

2 | SCIENCE OF PATIENT INPUT

FDA’s engagement of patients as key stakeholders in regulatory decision making has been evolving over the past several decades.

In recent years, the demand for more systematic incorporation of patient input throughout the medical product lifecycle, including for informing regulatory decision making, has been increasing. Multiple factors have encouraged and supported this call for greater patient engagement and empowerment, including legislative initiatives and the availability of structured social platforms (e.g., online patient communities) for patients to express their concerns about and share their experience with their health condition and treatment options.9,10

CBER is one of several FDA centers with efforts focused on more systematically incorporating the patient perspective throughout the medical product development paradigm. Table 1 includes links to information about some of the efforts that have been launched across the agency.

As part of the agency’s overall efforts, CBER has recently launched the SPI Initiative. In this context, CBER defines SPI as scientifically valid qualitative and/or quantitative methods for eliciting patient perspective information, such as through PPI and patient-reported outcome measures, on the benefits and risks of medical products and incorporating this information into regulatory decision making. The initiative focuses on advancing SPI by (1) building CBER internal review capacity and expertise, (2) by collaborating with our colleagues in other FDA centers and external stakeholders, and (3) by exploring existing and new ways to effectively integrate scientific patient input information into our regulatory framework. We are also tracking our experiences to inform continuous improvement of our SPI efforts.

Collaboration with external stakeholders, both domestically and internationally, is an important component of our SPI effort. For example, our staff regularly participate in external meetings and symposia to understand new scientific developments and to exchange ideas. Staff have also participated in working groups that include international regulatory authorities, both as part of a revision of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use guideline on Enhancing the Format and Structure of Benefit-Risk Information revision and an Innovative Medicines Initiative project called, PREFER: Patient Preferences in benefit-risk assessments during the drug life cycle.14,15

3 | EXPLORING THE USE OF PATIENT PREFERENCES IN CLINICAL AND REGULATORY SETTINGS

The Medical Device Innovation Consortium (MDIC) defines a preference-sensitive decision as “a decision in which there are multiple diagnostic or treatment options, and the decision of which option to pursue depends on the particular preferences of the decision maker”.16 In the clinical setting, the optimal treatment choice for a patient facing a preference-sensitive decision should be based on a patient’s values and preferences. Shared decision making, described in the literature as “an approach which seeks to fully inform patients about the risks and benefits of available treatments and engage them as participants in decisions about the treatments,” has been suggested as a means for informing treatment decisions at the point of care.17 One of the aims of CBER’s SPI initiative is to understand how some of these same principles could be leveraged to inform the regulatory decision-making process.

An example of a preference-sensitive condition from CBER’s experience is sickle cell disease (SCD). SCD is a disorder of hemoglobin that leads to unusually rigid red blood cells, prone to obstruction of
small vessels and breakdown. Patients with SCD have a shorter lifespan than patients who do not have SCD. Furthermore, such patients can expect a poorer quality of life marked by frequent pain crises and other medical sequelae, including anemia, stroke in childhood, kidney disease, and immune deficiency.

Using SCD as an example, we explore how PPI can inform the treatment decisions facing SCD patients and their caregivers and how it can inform the benefit-risk assessments facing regulators.

### 3.1 Clinical setting

The treatment options available to SCD patients and/or their caregivers are limited. Transfusions and hydroxyurea are treatments that can ameliorate the symptoms of SCD. With appropriate and aggressive management, patients with SCD can live for many years with fewer symptoms. Cellular therapy for SCD, in the form of allogeneic hematopoietic cell transplantation (commonly referred to as “bone marrow transplantation” or BMT), is the only known curative treatment, but this treatment often carries a significant risk of morbidity and early mortality. The choice of whether to submit to BMT (or to submit one’s child to BMT) or to instead aggressively treat the symptoms of the disease involves some considerable trade-offs between benefits and risks. For example, in a young patient, without end-stage damage from SCD, the treatment most likely to lead to a normal lifespan is BMT. At the same time, the treatment most likely to lead to an increased chance of a serious, sometimes fatal, adverse effect is also BMT. Patients and their caregivers are faced with a choice between a shorter lifespan with decreased quality of life with supportive therapy versus undergoing a BMT procedure that may potentially cure the condition but with a reasonable chance of early death (Table 2). Different patients may value these outcomes and tolerate these risks differently. Hence, the treatment choice for SCD patients is preference-sensitive and consequently should incorporate their preferences and values.

### 3.2 Regulatory setting

Patient input can be valuable to regulators at many points throughout the regulatory decision-making process. For example, it can be used to better understand novel treatments that involve difficult trade-off decisions. We use SCD to explore how patient preferences could inform regulatory decision making for a novel, hypothetical therapy, Therapy X.

Therapy X has been shown to cure SCD in preclinical models. Therapy X has less theoretical toxicity than the alternative curative treatment, BMT. However, in other settings, Therapy X has been implicated in causing serious adverse effects, which have been fatal in some cases.

If Therapy X were submitted for regulatory review, regulators would weigh the benefits and risks to patients of using the product, as for any other medical therapy. Regulators will have to decide if the potential benefits of Therapy X outweigh its risks. Historically, regulators have made such decisions based on an evaluation of the available effectiveness and safety data, multidisciplinary expertise, clinical judgment, and other information such as patient input.

Incorporation of patient input can be enhanced through a rigorous, patient preference study that is representative of the patient population. Patient preferences that have been captured using scientifically designed experimental methods allow regulators to understand how preferences differ across patients and how patients make benefit-risk trade-offs that align with their specific health condition and personal values. It is important to note that some SCD patients would opt for a potential cure with Therapy X whereas others will opt for noncurative disease management—both are reasonable decisions. For example, some SCD patients, whose

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### TABLE 2

Exploring the use of patient preferences for SCD in clinical and regulatory settings

| Clinical setting | Currently available therapies: | Example topics for discussion with an individual SCD patient at the point of care: |
|------------------|--------------------------------|----------------------------------------------------------------------------------|
| Exploring patient preferences for currently available SCD therapies | | |
| | * Hydroxyurea can reduce SCD-related complications; interindividual variability in effectiveness | Given your current SCD status and the therapy(ies) you are using to manage your disease symptoms... |
| | * Other therapies for symptom management including pain management, blood transfusion | |
| | * BMT can be curative; substantial risks include potential for serious adverse effects that are sometimes fatal; limited by availability of a donor | |

| Regulatory setting | About Therapy X: | Example questions that could be asked as part of a rigorous patient preference study in SCD patients: |
|-------------------|-----------------|---------------------------------------------------------------------------------------------------|
| Exploring patient preferences for an innovative SCD therapy, Therapy X | * Can be curative; risks include potential for developing serious adverse effects that are sometimes fatal | Given your current SCD status and available therapies for managing your disease... |
| | Note: Detailed, qualitative patient input from patients living with SCD has been collected as part of the PFDD initiative. | * Would you be willing to enroll in a clinical trial for Therapy X? |
| | | * Would you be willing to accept the potential significant risks of Therapy X in exchange for potential cure of your disease? |
| | | * Which treatment attributes of Therapy X are most important to you? |

SCD indicates sickle cell disease; BMT, bone marrow transplantation; PFDD, Patient-Focused Drug Development.
symptoms are well controlled using available therapies, may opt to stay with their current therapies, whereas others who are not currently benefiting from available therapies may prefer to accept a higher risk with Therapy X. In the presence of such preference heterogeneity, scientifically collected patient input can enable regulators and other stakeholders to understand how patients make benefit-risk trade-offs.

A patient preference study for Therapy X could be designed to capture qualitative and/or quantitative information about how different patients value the benefits (potential SCD cure) and risks (serious adverse effects that are sometimes fatal) of Therapy X (Table 2). Patients in this type of study will have to decide if the serious risk of Therapy X is worth the benefit of a cure. The qualitative results of the patient preference study may help provide an environmental scan of the patient experience and how they view the benefits and risks of this novel treatment for their SCD. Moreover, this scientifically collected patient input can provide insight into the attributes of Therapy X that are meaningful to patients, and it could potentially link these attributes with clinically relevant end points. The quantitative results of the patient preference study may provide information on the relative importance that patients assign to treatment attributes via preference scores and a characterization of the statistical variability in these scores across patients. Finally, scientifically valid quantitative patient input data can inform regulators that there are subgroups of patients who would choose a riskier treatment in exchange for a potential, higher benefit. Such information could be incorporated into the regulatory decision-making process.

### TABLE 3 Resources that encourage and/or inform the conduct of PPI studies during medical product development

| Resource | Description |
|----------|-------------|
| The Voice of the Patient: A Series of Reports from the PFDD Initiative | A compilation of qualitative patient input reports for over 20 different disease areas |
| Revision of M4e Guideline on Enhancing the Format and Structure of Benefit-Risk Information in ICH: Efficacy-M4E(R2)/M4E(R2) (effective 2016) | Harmonized definition for benefit, risk, and recommended format of benefit-risk assessment of medical product, including potential for incorporating patient perspectives |
| ISPOR conjoint analysis task force reports: | Recommended good research practices for certain PPI elicitation methods |
| • Checklist for conjoint analysis | |
| • Experimental design for DCE | |
| • Statistical methods for analysis of DCE | |
| MDIC Patient Centered Benefit-Risk Project Report: A Framework for Incorporating Information on Patient Preferences Regarding Benefit and Risk into Regulatory Assessments of New Medical Technology | Definitions, concepts, and catalog of methods and factors to consider for eliciting patient preferences for assessment of medical technology |
| FDA CDRH/CBER guidance document on PPI | Key definitions of concepts and methods; encourages early interaction with FDA and voluntary regulatory submission of PPI studies for medical devices |
| Incorporating patient-preference evidence into regulatory decision making | Utility of PPI in regulatory decision about medical devices used in the management of obesity |
| FDA-NIH Biomarker Working group BEST (Biomarkers, Endpoints and Other Tools) | Harmonized terms used in translational science and medical product development |
| Quantifying benefit-risk preferences for new medicines in rare disease patients and caregivers | Example of a patient preference study for hypothetical therapeutic options in rare diseases, quantifying benefit-risk preferences. The study was conducted in rare disease patients (n=721) and caregivers (n=152). |

PFDD indicates Patient-Focused Drug Development FDA, Food and Drug Administration; CDER, Center for Drug Evaluation and Research; CBER, Center for Biologics Research; CDRH, Center for Device and Radiological Health; ICH, International Council on Harmonisation; PPI, patient preference information; DCE, discrete choice experiment; MDIC, Medical Device Innovation Consortium, ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

### 4 | OPPORTUNITIES AND AVAILABLE RESOURCES

PPI can be useful in informing regulatory decision making at various stages of medical product development. Patient perspectives can be elicited during early development to help identify the attributes of a novel medical product that are most important to patients. Further, this information can provide insights into the entire landscape of the disease and may be used to help identify relevant clinical end points. During the later stages of development, when the benefits, risks, and their magnitude are better understood, patient preference studies can be helpful to assess the benefit-risk trade-offs. In the future, other potential applications of PPI can be explored.

Much of the science behind the design and conduct of patient preference studies is not new; however, the application of this science in the regulatory evaluation of medical products is new. As we work to advance the SPI, there are some limitations that we will need to overcome. It will be important to consider multiple factors, such as a patient’s baseline characteristics (e.g., age, gender, cognitive levels, and disease severity), sample sizes, scientifically plausible and meaningful benefit-risk attributes of therapy, and appropriate quantitative preference elicitation methods. More importantly, preference research requires active patient engagement and therefore researchers should ensure that their survey methods are clear and easy for patients to understand and minimally burdensome to complete.

Collaboration among the various stakeholders is needed to advance both qualitative and quantitative methods for identifying, gathering, evaluating, and incorporating meaningful patient input in
medical product development. Important collaborations already exist, and additional collaboration will be needed. Table 3 includes example resources that are available for encouraging and informing the conduct of scientifically valid patient preference studies. The FDA PPI guidance encourages sponsors to engage FDA early in the development of PPI studies and to voluntarily submit PPI. CDRH has also conducted a PPI study and elicited the benefit-risk profiles of medical devices intended for weight loss. The result of this obesity study informed regulators how patients make benefit-risk trade-offs and has been successfully incorporated into regulatory decision making. The MDIC, a public-private partnership between FDA, National Institutes of Health, Center for Medicare and Medicaid Services, patient groups, and multiple medical device companies developed a report. The MDIC report explains several concepts of benefit-risk assessment of new medical technologies and outlines 14 available methods for eliciting patient preferences. The International Society for Pharmacoeconomics and Outcomes Research has recently published three important research practice documents for designing, conducting, and statistically analyzing PPI.

5 | CONCLUSION

The systematic incorporation of the patient perspective in the medical product development paradigm has been evolving, driven in part by social change, legislative initiatives, and by patients themselves. We provided an overview of historical and ongoing efforts to incorporate the patient perspective in a regulatory setting. There has been considerable progress in quantitative methods, both within the agency such as through the PPI Guidance, as well as through public-private partnerships, such as the MDIC framework report. We provided a hypothetical scenario showing how PPI for SCD can be incorporated in clinical and regulatory decision making. SPI is a nascent science; we are ready to learn and advance effective application in a regulatory setting. Work continues to identify best practices and opportunities for improving the methods for eliciting PPI and enhancing its application in our regulatory framework. Stakeholders across the healthcare system will need to continue to collaborate to further improve the SPI and enhance its application in medical product development. Further, a learning healthcare system paradigm can help us better understand and continuously improve the incorporation of patient input in regulatory decision making.

DISCLAIMER

This article reflects the views of the author and should not be construed to represent FDA’s views or policies.

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