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1730 M Street NW, Suite 500, Washington, DC 20036-4561 ■ 202-785-3910 ■ www.nationalhealthcouncil.org ■ info@nhcouncil.org

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February 16, 2018

The Honorable Scott Gottlieb, MD
Commissioner, Food and Drug Administration
Dockets Management Staff (HFA-305)
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Patient-Focused Drug Development: Guidance 1 – Collecting Comprehensive and Representative Input; Public Workshop (Docket No. FDA-2017-N-5896)

Dear Commissioner Gottlieb:

The National Health Council (NHC) appreciates the opportunity to provide comments on the FDA's Patient-Focused Drug Development: Guidance 1 – Collecting Comprehensive and Representative Input. Patients with chronic diseases and disabilities are experts in their disease. As such, there is significant value to incorporating patient-provided information into decision-making across the healthcare continuum, including FDA's regulatory decisions regarding medical products. We applaud the FDA for its continued action to encourage and guide meaningful patient engagement, including developing guidance and tools to assist stakeholders.

The NHC is the only organization that brings together all segments of the health community to provide a united voice for the more than 133 million people with chronic diseases and disabilities and their family caregivers. Made up of more than 100 national health-related organizations and businesses, the NHC's core membership includes the nation's leading patient advocacy organizations, which control its governance and policy-making process. Other members include professional and membership associations, nonprofit organizations with an interest in health, and representatives from the pharmaceutical, generic drug, insurance, medical device, biotechnology, and communications industries.

In support of the public workshop held on December 18, 2017, FDA released a set of draft documents – the Patient Focused Drug Development (PFDD) Public Workshop on Guidance 1 Collecting Comprehensive and Representative Input Discussion Document (Discussion Document); Attachment to Discussion Document Appendices; and Draft Standardized Nomenclature and Terminologies for the Series of FDA PFDD Guidances (Glossary). Our comments below refer to the material contained in these draft documents.

I. *Overarching Comments*

1. *Guidance Development Process*

The NHC appreciates the opportunity to participate in the December 18th Public Workshop and provide comments to the FDA in response to the glossary and discussion document via the docket. As the Agency develops future guidances, the NHC recommends it consider avenues to co-develop these materials with patients and

patient organizations from the beginning of the development process in addition to seeking feedback and reaction to the FDA's work.

2. The FDA Workforce

Throughout the PDUFA VI negotiation process, the FDA acknowledged the need to be more flexible in addressing workforce shortages. The NHC appreciates the need to address workforce issues, as the skills and expertise of the staff reviewing patient experience data can differ from the traditional roles of the FDA reviewers. To this end, the NHC stands ready to support the Agency to ensure the skills and expertise of the FDA staff align with the function of their role.

II. Draft Standardized Nomenclature and Terminologies for the Series of FDA PFDD Guidances (Draft Glossary)

The NHC recognizes the importance of a single glossary of terms in ensuring that all stakeholders are using the same standard terms and definitions. Inconsistent use of terms leads to confusion and inaccurate understanding of the concepts that underlie the science of patient engagement and collection of patient-provided information. It is critical that consensus definitions be developed and used consistently. To that end, the NHC and Genetic Alliance hosted three multi-stakeholder events in 2016-2017 to inform the development of a document[1] containing suggested language for the FDA to consider for a guidance on patient engagement (final document attached as Appendix C). This document includes definitions for terms identified by stakeholders as key to patient engagement. We thank the Agency for incorporating some of the definitions developed through this work in the FDA's Draft Glossary.

However, we discuss below a few concerns regarding and suggested changes for a number of the definitions included in the FDA Draft Glossary.

1. Patient engagement

The Draft Glossary defines "patient engagement" as "[a]ctivities that involve patient stakeholders sharing their experiences, perspectives, needs, and priorities that help inform FDA's public health mission." We believe this definition is unnecessarily and inaccurately restrictive. Recognizing that these definitions are intended for use in FDA guidance, we believe that unless re-cast as "patient engagement for FDA's use," the term "patient engagement" should not be so narrowly defined. Given that FDA encourages patient engagement throughout drug development, and not solely to develop data to submit to the Agency and that other organizations (not just the FDA) are and have been involved in patient engagement for a variety of purposes, "patient engagement" should be defined as "activities that involve patients as active participants in any health-care-related process and/or decision making, including but not limited to patients as partners sharing their experiences, perspectives, needs, and priorities to help inform processes and decisions related to drug development and approval."

2. Caretaker

FDA should clarify that the term "caretaker" does not include a paid caretaker (e.g., a paid health care aide) by revising the definition to read "[a] person who helps a patient with daily activities, health care, or any other activities that the patient is unable to perform himself/herself due to illness or disability. This person may or may not have decision-making authority for the patient and is not the patient's health care

[1] The National Health Council and Genetic Alliance, Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, February 2017, available at: http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf (accessed Jan. 25, 2018).

provider *or paid health care aide*." (addition in italics). In addition, while we recognize the value of engaging with caretakers, it is important that the FDA acknowledge that a caretaker's perspectives do not necessarily align with those of the patient but may be needed when a patient is unable to provide information.

3. Patient-centered outcome

We find the phrasing of the definition, "an outcome that is important to patients' survival, functioning, or feelings as identified or affirmed by patients themselves, or judged to be in patients' best interest by providers and/or caregivers when patients cannot report for themselves" to be unclear and suggest revising it to read "[a]n outcome that is important to patients *in terms of* survival, functioning, or feelings…" (addition in italics).

4. Patient experience data; patient input; patient-provided input; patient perspective

The 21st Century Cures Act defines "patient experience data" as those that:''(1) are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers); and ''(2) are intended to provide information about patients' experiences with a disease or condition, including—''(A) the impact of such disease or condition, or a related therapy, on patients' lives; and ''(B) patient preferences with respect to treatment of such disease or condition.'' We believe the additional elements added to this definition to get to the FDA's proposed definition make the term inaccurately broad. For the term to be clearly understood, it should be limited only to patient *experience*, and not be interpreted to encompass perspectives, needs and priorities, which are not experiences.

With the term "patient experience data" defined properly to solely include patient *experience*, we suggest the FDA add the term "patient-provided information" as the umbrella term to denote the myriad types of patient-provided data. The NHC prefers the multi-stakeholder, consensus-driven definition below:

> *<u>Patient-provided information (or patient-provided input)</u>: a range of information that comes directly from patients such as, but not limited to: views, experiences, preferences, needs, opinions, and priorities. This can include their overall view of their condition, its natural history, and impact on their life (e.g., patient-reported outcomes such as symptoms, function, and quality of life); experience with available treatments; description/view on which outcomes are important; patient preferences, goals, desires, concerns, perceptions, or opinions; or the relative importance of any issue as defined by patients. Patient-provided information is relayed by the patient regarding their subjective experience and opinions. It does not include all medical information on a patient (e.g., genetic testing information, pathology results) that may be about the patient but comes from other sources*.[2]

The NHC also recommends the FDA produce a visual depiction to help stakeholders understand the differences among these terms. The NHC Venn diagram of patient-provided information may be a useful starting point in that process (see Appendix C).[2]

[2] *Id.*

To align with the recommendations above, the following corresponding revisions would need to be made to the Glossary (these and all definitional changes would also need to be reflected in the Discussion Document):

- The definition for *patient input* should be removed as no longer needed (as this term is included in the above definition as patient-provided input)
- *Patient perspective*: A type of *patient-provided information* that specifically relates to patients' attitudes or points of view especially regarding their condition or its management. Patient perspectives may include (but are not limited to): perceptions, goals, priorities, concerns, opinions, and preferences. (*italics replace "patient experience data" in the current draft definition)*

We also caution that because "patient experience data" is a term of art in the *health care delivery* context, there is a very real risk for confusion. In health care delivery, patient experience data is referred to in reference to quality-of-care and includes collecting data from patients regarding their views on their experience receiving care from a provider, hospital, or other delivery system. For example, the Agency for Health Research and Quality has supported the development of the Consumer Assessment of Healthcare Providers and Systems (CAHPS®) surveys,[3] which ask consumers and patients to report on and evaluate their experiences with health care. The CAHPS® program defines "*patient experience*" as: "the range of interactions that patients have with the health care system, including their care from health plans, and from doctors, nurses, and staff in hospitals, physician practices, and other health care facilities. The terms patient satisfaction and patient experience are often used interchangeably, but they are not the same thing."[4]

The CAHPS surveys are quality-reporting tools widely used by most hospitals, networks, insurance plans and providers. Those stakeholders familiar with the term from the care delivery context may inaccurately assume it means the same in the FDA regulatory context even though the use is clearly very different with different intended purposes. Because the term is used in context-specific ways, the FDA should be very clear about the use of this term to avoid confusion; we recommend the FDA refine its definition to do so.

5. *Patient-focused (also referred to as patient-centered)*

The NHC finds the definition of the terms "patient focused"/ "patient centered" problematic because it omits the act of actively engaging with patients. As currently drafted, the definition reads: "Ensuring that patients' experiences, perspectives, needs, and priorities are meaningfully incorporated into decisions and activities related to their health and well-being." We believe it is critical that any definition of "patient focused" or "patient centered" reflect that patients should be valued as partners in the enterprise. Patient-centered means doing things *with* patients, not *for* or *to* patients. Meaningful patient engagement can only exist as a continuous, bi-directional partnership with patients. This omission renders the current definition fatally flawed.

[3] Agency for Healthcare Research and Quality website, "About CAHPS," available at: https://www.ahrq.gov/cahps/about-cahps/index.html (accessed Jan. 31, 2018).
[4] *Id.*

We recommend the FDA use the following multi-stakeholder, consensus-driven definition:

> *Patient centered – any process, program, or decision focused on patients in which patients play an active role as meaningfully engaged participants and the central focus is on optimizing use of patient-provided information.*[5]

In addition, we understand that some stakeholders confuse the terms "patient-centered outcomes" and "patient-reported outcome" (PRO). As such, we ask the FDA to make an effort to explicitly distinguish the two terms from one another in the Glossary (and the Discussion Document, as needed). We believe this is a very important distinction that is widely misunderstood. We acknowledge that the methods used to develop PROs can be useful to collecting and analyzing all kinds of patient-provided information and there is knowledge to be leveraged. However, *not all patient-centered outcomes are PROs* and *not all PROs are patient-centered outcomes*.[6] It is important to clarify that the addition or development of a PRO does not necessarily mean that patient centeredness has been achieved. The PRO that was developed may be unimportant to patients.

III. PFDD Public Workshop on Guidance 1 Collecting Comprehensive and Representative Input Discussion Document (Discussion Document)

We appreciate the Agency's consideration of information from external sources in the FDA's PFDD Public Workshop on Guidance 1 Collecting Comprehensive and Representative Input Discussion Document (Discussion Document). To that end, the NHC formed patient-driven, multi-stakeholder working groups with the purpose of offering key stakeholders, including the Agency, all-inclusive and consensus-based recommendations on this topic (current recommendations attached as Appendices C and D). Below, we outline our comments and suggestions for the FDA to consider when finalizing the Discussion Document.

First, the NHC recommends the FDA include the following in the guidance:

- A statement that the guidance is intended not just for innovators of therapeutic biopharmaceuticals, but also for anyone that engages patients during medical product-development and review. The NHC envisions that this guidance (and all planned PFDD guidances) will be relevant and applicable to all stakeholders.
- A statement that the guidance aims to *encourage* engagement with patients (i.e., not just collecting data from patients, but partnering with them), but does not *require* it.
- A clear articulation that if patient engagement is conducted appropriately (i.e., the way envisioned by the Agency as described in the guidance), that such interaction is not promotional in nature. Such a statement would go a long way in dispelling the perception among some that meaningful engagement with patients during (at least some phases of) drug development and review is too risky to be pursued.

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[5] *Id.*

[6] FDA website, "Roadmap to Patient-Focused Outcome Measurement in Clinical Trials," available at: https://www.fda.gov/downloads/drugs/developmentapprovalprocess/drugdevelopmenttoolsqualificationprogram/ucm370174.pdf (accessed Jan. 31, 2018).

- A statement that the FDA is receptive to innovative and non-traditional methods, and that the Agency recognizes that the science of patient input is an evolving field. This is important to encourage stakeholders to use innovative methods and push the envelope when thinking about meaningful patient engagement.

Second, we agree with the FDA that the issue of representativeness is a key consideration and an important goal in any plan for collecting patient-provided information. The NHC recently released a white paper *Tackling Representativeness: A Roadmap and Rubric*[7], discussing insights from a multi-stakeholder roundtable on the topic of representativeness (attached as Appendix D). That document provides a set of consensus-based recommendations and key considerations regarding characteristics of "good" patient representativeness, offering a tool for those engaging patients to help them think about how to (as best as possible) achieve representativeness for their research objective.

The six key principles outlined in the document are:

- *Define* – Clearly define the objective(s) for each engagement effort
- *Understand* – Understand as much as possible about the full population and subpopulations and challenges to reaching them
- *Specify* – Develop a description of the minimum target(s) for representativeness for the engagement activity
- *Plan* – Develop a plan to achieve the minimum target(s) defined
- *Evaluate* – Develop an evaluation plan to assess progress on achieving target(s) or if they need to be adjusted based on new information
- *Document* – Record how patient representativeness was defined, targeted, achieved, and assessed[8]

Third, the NHC requests the FDA include discussion in the guidance to clarify the association between this guidance and clinical outcome assessments (COAs) and patient-preference information (PPI). While this guidance does not discuss COAs or PPI, we understand this guidance as relating to the "precursor" work required to develop a COA or collect PPI (e.g., collecting patient-provided information that informs the development of a COA or design of a study to collect PPI). We believe that making this relationship clear will help readers connect the dots between the series of progressive guidances and minimize any perception that the focus of this first guidance is irrelevant to COAs or PPI.

Finally, we understand the FDA plans to develop a repository of patient-experience data submitted to the Agency. We ask the FDA to clarify how this repository relates to the 21st Century Cures Act requirement that the Agency publish a brief statement of the patient-experience data submitted and reviewed for a product application. The NHC supports the development of a data repository for patient-provided information as long as posting data in the repository is voluntary and strongly encouraged, but not required of any stakeholder. The NHC also suggests the Agency clarify what does and does not constitute a minimum quality threshold for these data. We appreciate the increased transparency that making this data public brings and believe that this will lessen the "waste" of this data (as data not shared is wasted) and reduce the overall burden to patients (as patients are not providing the same information over and

[7] The National Health Council, Tackling Representativeness: A Roadmap and Rubric, available at: https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf (accessed Jan. 25, 2018).
[8] *Id.*

over to numerous stakeholders). However, as expressed above (section "5. Patient-focused"), there is no substitute for active engagement with patients as partners in the medical product development lifecycle. The FDA should specify that accessing and using data from the repository is not a substitute for meaningful engagement with patients. In considering the most useful format this information could take, the NHC requests the FDA consider issuing a standardized report template for the data in a readable format, similar to the information provided in the *Voice of the Patient* reports issued after the FDA-hosted PFDD public meetings, but with standardized formatting.

In conclusion, the NHC fully supports the FDA's public workshops and PFDD guidance documents as important opportunities for stakeholders to work with the Agency to make meaningful patient engagement in drug development and review *the norm*. With this goal in mind, the NHC continues to work with multi-stakeholder groups to develop new insights and materials to move the discussion and patient engagement forward. Our multi-stakeholder working groups recently produced two documents with suggested recommendations on "Foundational definitions in patient engagement" and "Who is involved in engagement" (Appendices A and B, beginning on page 8 of this document) related to comprehensive and representative patient input on burden of disease and current treatments. The Agency may find it useful to review these documents as it develops its guidance. The NHC recommends that in addition to requesting input through public workshops and on draft documents the Agency also consider engaging patients and other stakeholders earlier in an effort for co-development. The NHC stands ready to assist and support the FDA in its work and will continue to convene the NHC's patient and multi-stakeholder members to provide input, feedback, and assist in other ways deemed necessary to advance PFDD. The NHC will continue to develop materials to assist the FDA and other stakeholders, and we look forward to further stakeholder collaboration on encouraging meaningful patient engagement, developing tools to collect data, and more broadly integrating patient input into drug development and regulatory decision-making.

Please do not hesitate to contact Eric Gascho, our Vice President of Policy and Government Affairs, if you or your staff would like to discuss these issues in greater detail. He is reachable by phone at 202-973-0545 or via e-mail at egascho@nhcouncil.org.

Sincerely,

Marc Boutin, JD
Chief Executive Officer

Attachments
Appendix A: The National Health Council, Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: Foundational Definitions, December 2017
Appendix B: The National Health Council, Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: Who is Involved in Engagement, December 2017
Appendix C: The National Health Council and Genetic Alliance, Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, February 2017
Appendix D: The National Health Council, Tackling Representativeness: A Roadmap and Rubric, November 2017

APPENDIX A
Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: *[FOUNDATIONAL DEFINITIONS]*

Purpose of this document:
To offer multi-stakeholder, consensus-based language to key stakeholders, including the Food and Drug Administration (FDA or the agency) to help advance its work in this area. This document reflects National Health Council (NHC) patient driven, multi-stakeholder membership recommendations for consideration in upcoming patient engagement guidance documents.

Objectives for the recommended language proposed:

- Provide definitions for terms related to collecting comprehensive and representative patient input on burden of disease and current treatments

Recommended Language

I. Introduction

In developing this document for consideration by the U.S. Food and Drug Administration, the National Health Council convened a working group led by patient advocacy organizations and comprised of representatives from different sectors of the health care system to create a united voice on the approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy. This document also builds on previously submitted work by the National Health Council and Genetic Alliance.[9] This document offers consensus-based thinking on foundational definitions to assist in the agency's goals related to their commitment to develop guidance on patient engagement in the sixth authorization of the Prescription Drug User Fee Act (PFUDA VI).

II. Proposed Foundational Definitions

Comprehensive **–** To be thorough and inclusive in the collection of data from patients and caregivers on disease and treatment burden, covering the full gamut of their experiences - e.g., physical, functional, emotional, social, etc. – and includes all domains of the disease that are important to them. An effort to be comprehensive means thoroughly considering the questions needed to explore and how deeply to evaluate each aspect of burden.

Representative **–** Refers to the sufficient number and types of people included in the engagement activity to ensure that those engaged can speak for the target population. It refers to "who" and "how many"

[9] National Health Council. Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, (http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf)

individuals to include in an interaction to, as closely as possible, engage with individuals that represent the broader, targeted patient population.[10]

Meaningful Patient Input **–** Patient input refers to the contribution of a range of patient-provided information[11] contributed, directly or indirectly, at any point during the product lifecycle. Meaningful input has two attributes: the type of information collected and how it was collected. Meaningful includes patient report of their overall view of their condition and its natural history and impact on their life (e.g., patient reported outcomes such as symptoms, function, and quality of life); experience with available treatments; description/view on which outcomes are important; preferences, goals, desires, concerns, perceptions, or opinions; or the relative importance of any issue as defined by patients.[12] The data are typically collected through engagement activities that bidirectional, reciprocal, and continuous; where communications are open, honest, and clear' and where engagement goals, participants, methods, desired impacts, and actual impacts are clearly outlined and transparent.[13]

Burden of Disease **–** Refers to patient (or caregiver) perspectives on the impact of disease (not just in terms of survival, but also in terms of symptoms, function, and well-being). It serves to identify from the patient (or caregiver) the personal load they bear due to illness, their needs due to disease and whether their needs are being met by current care options. Assessment of unmet needs can also serve to identify targets for interventions.[14]

Burden of Treatment – Refers to patient (or caregiver) perspectives on the impact of treatment (not just in terms of survival, but also in terms of symptoms, function, and well-being). It serves to identify from the patient (or caregiver) the personal load they bear due to treatment, their needs due to treatment and whether their needs are being met by current care options. This includes medication management, self-monitoring, visits to the doctor, laboratory tests, lifestyle changes, etc. Coping with these health care tasks requires time, action, and cognitive effort from patients and caregivers.[15]

Unmet Medical Need **–** A condition, as defined by the patient, whereby treatment or diagnosis is not addressed adequately by available therapy; this includes immediate need for the defined population (i.e., need to treat a condition with no or limited treatment options), individual needs (i.e., need for additional treatment options due to safety or efficacy deficits of available treatments, individual preference or goals) or a broader need for society (e.g., to address the development of resistance to antibacterial drugs).[16]

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[10] National Health Council. Tackling Representativeness: A Roadmap and Rubric. (https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf).
[11] National Health Council. Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, (http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf)
[12] See footnote 2
[13] See footnote 2
[14] Biotechnology Innovation Organization, Parent Project Muscular Dystrophy. Key Considerations for Developing & Integrating Patient Perspectives in Drug Development: Examination of the Duchenne Case Study, (https://www.bio.org/sites/default/files/BIO_PPMD_Paper_2016.pdf).
[15] Tran, V.T., et al., Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. BMC Med, 2014. 12: p. 109. [https://minimallydisruptivemedicine.org/2015/06/29/burden-of-treatment-the-work-of-being-a-patient/]
[16] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics, (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf).

Drug Development Process **–** *Refers* to the activities undertaken to conceptualize, study, register, market and monitor a medicinal product during which patient engagement can take place. Not limited to the lifecycle of one specific drug, but to the overall processes and actions from earliest stages (before candidate molecule consideration to product or therapeutic obsolescence). For example, it may include understanding the natural history of a disease (or group of diseases) from the patient perspective prior to selecting candidate for pre-clinical study.)[17]

[APPENDIX B - NEXT PAGE]

[17] Proposed PFDD Conceptual Framework. Adapted from: Clinical Trials Transformation Initiative's Patient Groups & Clinical Trials Expert Meeting summary; National Health Council's Dialogue/Advancing Meaningful Patient Engagement in Drug Research, Development, and Approval; model proposed by Perfetto et al. Med Care. 2015 Jan;53(1):9-17. Accessed at http://www.pharmacy.umaryland.edu/media/SOP/wwwpharmacyumarylandedu/centers/cersievents/pfdd/mcersi-pfdd-proceedings-rubric.pdf

APPENDIX B

Approaches to Collecting Comprehensive and Representative Patient Input on Burden of Disease and Current Treatments: *[WHO IS INVOLVED IN ENGAGEMENT]*

Purpose of this document:
To offer multi-stakeholder, consensus-based language to key stakeholders, including the Food and Drug Administration (FDA or the agency) to help advance its work in this area. This document reflects National Health Council (NHC) patient driven, multi-stakeholder membership recommendations for consideration in upcoming patient engagement guidance documents.

Objectives for the recommended language proposed:

- Provide current thinking on who can and should be engaged in collecting comprehensive and representative patient input on burden of disease and current treatments.

Recommended Language

I. Introduction

In developing this document for consideration by the U.S. Food and Drug Administration, the National Health Council convened a working group led by patient advocacy organizations and comprised of representatives from different sectors of the health care system to create a united voice on the approaches to collecting comprehensive and representative patient and caregiver input on burden of disease and current therapy. This document also builds on previously submitted work by the National Health Council and Genetic Alliance.[18] This document offers consensus-based thinking on foundational definitions to assist in the agency's goals related to their commitment to develop guidance on patient engagement in the sixth authorization of the Prescription Drug User Fee Act (PFUDA VI).

Those involved in engagement for collecting information on comprehensive and representative patient and caregiver input on burden of disease and current treatment typically include the patients[18] providing information and those who are collecting the patient-provided information[18] for drug development purposes.

II. Who is Engaged: Providing Information

Those providing the patient perspective include: patients, patient advocates, patient advocacy groups/organizations, and patient experts (patients who have taken on an expert or consultant role). The perspectives of people at risk for a disease or condition (e.g., BRCA1 carriers, genetic carriers of disease, people living in regions of infectious disease epidemics) may also be considered in certain drug

[18] National Health Council. Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development, (http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA%20Feb2017.pdf)

development settings (e.g., gene therapies, vaccine development or other prophylactic treatments). Caregivers (typically unpaid, family caregivers, not paid professional caregivers) are also important sources of information about patients, especially when patients are unable to provide the information themselves or when the information provided by the patient provides an incomplete picture of the burden of disease or burden of treatment.

The context of a particular interaction (e.g., the objectives and format of the interaction; the point in product development in which the interaction occurs) will inform which entities are involved in a particular interaction or series of interactions with patients.[19] For example, an individual patients' input on what is clinically important may be more useful for some circumstances whereas a patient advocacy organization's input is needed to contextualize the patient population at large, including at certain stages of a disease or to provide early guidance on who to engage and on what issues (i.e., to avoid gaps or carryover of incorrect assumptions into future patient engagement).

The provider of patient-provided information will vary depending on the context and circumstance. For example, family caregivers may provide information on behalf of children or patients who may not have the capacity to engage.[2] Family caregivers may also engage in lieu of individual patients to provide the specific perspective of the caregiver. Similarly, patient advocacy organizations can provide a perspective that uniquely captures the heterogeneity of a patient population. They also may act as a key conduit for sponsors or researchers seeking to engage with a particular patient population.[20]

FDA recognizes that patients can assume different roles in these engagements. Patients can serve as advisors or consultants to provide input on research questions, study designs, or patient engagement plans. In addition, patient interactions can be formal or informal. Formal interactions may include arrangements that stipulate roles, responsibilities, any contractual obligations of the parties, as well as compensation. Informal interactions may consist of brief or temporary engagements (e.g., social media interactions).[20]

III. Who is Engaged: Collecting Information

Those collecting the data generally are sponsors, academic researchers, patient advocacy organizations, health care providers, professional societies, FDA, and those contracted to collect information or act as an intermediary between these entities and patients. For example, in the context of designing clinical trials for a particular drug, the sponsor of drug development program will generally be the primary entity collecting the data, or they may have a contract research organization working on their behalf. FDA may also collect patient provided-information at many points before and during drug development. Academicians conducting research, such as developing patient-reported outcome measures may also have a role.

[19] National Health Council. Tackling Representativeness: A Roadmap and Rubric. (https://www.nationalhealthcouncil.org/sites/default/files/Representativeness%20in%20Patient%20Engagement.pdf).
[20] National Health Council. Sponsor-Patient Interactions During Drug Development: Good Practice Insights on Patient Engagement. Retrieved from http://www.nationalhealthcouncil.org/sites/default/files/Sponsor-Patient%20Interactions%20during%20Drug%20Development.pdf (Accessed November 9, 2017).

APPENDIX C (NEXT PAGE)

Patient-Focused Drug Development – Recommended Language for Use in Guidance Document Development

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This document was prepared by the National Health Council and Genetic Alliance with the intent of submission to the Food and Drug Administration to encourage adoption, wholly or in part, by the Agency.

February 2017

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relationship relative to one another. The focus should be the patients view on their disease(s)/condition(s), desired attributes for treatments, experiences with treatments, benefit-risk preferences, and desired goals and outcomes. It should not be primarily focused on any one product.

PPIn includes, but is not limited to, information from patients about:

- the natural history of the disease
- the impact of the disease or condition on patients and their family caregivers, and how it affects their daily activities, physical functions, and quality of life
- outcomes that are most important to the patient, both clinical and non-clinical (e.g., goals for daily activities, symptom reduction, or a standard of quality of life)
- patients' preferences for treatment delivery methods and opinions about side effects
- experience on treatment(s) including symptoms and side effects and how the treatment impacts their daily activities, physical functions, and quality of life

As illustrated by this list, PPIn covers a wide variety of input from the patient regarding the patient's experience, preferences, and needs. However, PPIn does not include all information obtainable about a patient. For example, pathology results are "patient information" and distinct from PPIn because they are not conveyed directly by the patient.

B. What are FDA's PFDD initiative and patient-focused drug development?

FDA's PFDD initiative, a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), has allowed the Agency to more systematically gather patients' and family caregivers' perspectives on living with a disease, the symptoms that matter most to them, and their experiences with available therapies.[8] As part of this initiative, FDA has committed to holding public meetings, each focusing on a specific disease area.[9] FDA summarizes the input it receives during these meetings in a publicly reported series entitled, "Voice of the Patient."[10] The information provided by patients at these meetings is critical to the Agency's understanding of the needs and preferences of patients diagnosed with these diseases. FDA can use this patient input to inform the Agency's regulatory decision-making, especially when assessing a product's benefit-risk profile. For diseases for which a formal FDA PFDD meeting is not planned, FDA recommends patient groups consider holding their own, external PFDD meetings and has provided insights on how to do so.[11]

FDA's PFDD initiative represents just one way in which PPIn can be integrated into the product lifecycle. The broader term "patient-focused drug development" refers to meaningful engagement of patients throughout the product lifecycle, from the early stages of discovery to post-market studies, and extends beyond the Agency's recent activities.

[8] See Footnote 12 *Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017,* http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm (last visited February 16, 2016).
[9] See Footnote 12 *Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017,* http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm (last visited February 16, 2016).
[10] See The Voice of the Patient: A Series of Reports from FDA's Patient-Focused Drug Development Initiative, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm368342.htm (last visited February 16, 2016).
[11] See Externally-led Patient-Focused Drug Development Meetings, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm (last visited February 16, 2016).

C. Who is involved in patient-focused drug development?

In general, the exchange that takes place during patient interactions to collect patient-provided information involves:

> Those *gathering patient-provided information*, which can include, but is not limited to, sponsors, academic researchers, health care providers, professional societies, special interest groups, patient groups, FDA, and those contracted to collect information or act as an intermediary between another entity and patients.
>
> Those *providing patient-provided information*, which can in include, but is not limited to, individual patients, family caregivers, individual patient advocates, or patient advocacy organizations (defined as "patients", see Section IV).

The context of a particular patient interaction (e.g., the objectives and format of the interaction; the point in product development in which the interaction occurs) informs which entities are involved in a particular interaction or series of interactions with patients. For example, in the context of designing clinical trials for a particular drug, the sponsor of that drug will generally be the primary entity collecting PPIn. FDA may also collect PPIn at many points before and during drug development. Patient interaction during drug development is not limited to sponsors and FDA; academic researchers, professional societies, or patient advocacy organizations may also gather PPIn to inform their own and others research efforts. Guidance may encourage the use of PPIn in PFDD by all stakeholders.

The provider of PPIn also will vary depending on the circumstance. For example, family caregivers may provide information on behalf of children or patients who may not have the capacity to engage. Family caregivers may also engage in lieu of individual patients to provide the specific perspective of the caregiver. Similarly, patient advocacy organizations can provide a perspective that uniquely captures the heterogeneity of a patient population. They also may act as a key conduit for sponsors or researchers seeking to engage with a particular patient population.

FDA recognizes that patients can assume different roles in these engagements. Patients can serve as advisors or consultants to provide input on research questions, study designs, or patient engagement plans. In addition, patient interactions can be formal or informal. Formal interactions may include arrangements that stipulate roles, responsibilities, any contractual obligations of the parties, as well as compensation. Informal interactions may consist of brief or temporary engagements (e.g., patients responding to a survey).

D. Why include patient-provided information in disease research and drug development?

Draft guidance may include language recognizing the value of PPIn to those who are conducting disease research and drug development. Understanding from patients their experience of living with a disease over time is critical to, for example, understanding the natural history of a disease and identifying unmet medical needs. In addition, PPIn can identify the symptoms of a disease that are most bothersome to patients, the clinical outcomes patients care most about, ways to make a clinical trial less burdensome to patients, and treatment characteristics patients prefer. If integrated into decision-making and product planning, this

information can help product sponsors develop drugs that align with patient preferences and needs, and gather outcome data patients care about.

Patients can advise on any number of drug-development challenges to help ensure new drugs better meet patient needs and goals and enhance patient outcomes. Guidance may include language to encourage sponsors and other involved stakeholders to engage patients early and continuously in the drug development process to prevent avoidable misalignment between patient needs and preferences and development decisions and processes. This will help ensure study protocols reflect patient input, and the data captured are important to patients. In addition, early engagement can help produce product labeling that includes information important and understandable to patients.[12]

Sponsors and other stakeholders can better understand the heterogeneity of patient perspectives by engaging patients. Knowledge about how a disease impacts patients across age, disease severity, and disease progression (e.g., newly diagnosed or having lived with the disease for decades), as well as the heterogeneity of treatment effects across patients, can also inform drug development.

Many of the approaches and considerations for engaging patients can also be more broadly applied to research and development processes for all medical products, as well as basic disease-specific research (e.g., natural history studies). PPIn can provide value to all clinical research, and researchers should consider meaningfully engaging patients to support their studies in general.

III. Overview and Scope

This document provides FDA with recommended language of current perspectives on PPIn. This language applies in general, unless otherwise stated, to engagement with patients with regard to a disease, condition, or therapeutic area. In many instances, patient engagement happens unrelated to any specific product or products. When is does relate to a product or products, it can include research prior to discovery or development and the complete lifecycle of a drug (the “product lifecycle”). Research prior to discovery or development includes studies on the natural history of disease and identifying unmet medical need, and is typically disease- or therapeutic-area focused. It may not include any reference to any treatments as it may be too early in the development process for such discussion. The product lifecycle includes the discovery, research, and development tied to a specific product (e.g., clinical trials to demonstrate safety and efficacy of the product); regulatory review of that product for market approval or licensure; and post-approval study and development of that product (e.g., post-marketing commitments, surveillance that continues for as long as a product is available, or submission for new indications). There are nuances that differentiate the types of engagement needed throughout the product lifecycle. In this document, the term “product lifecycle” encompasses this full timeline, pre-product and post-approval. In this document, the word “research” refers to all phases of research from pre-product to post-approval, and therefore, includes research about the disease or therapeutic area alone, with or without reference to treatment.

[12] See Footnote 5 *Draft Guidance for Industry, Food and Drug Administration Staff; and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and* De Novo *Requests, and Inclusion in Device Labeling*.

This document recommends definitions of the principal concepts and key terms related to engaging patients outside of and during the product lifecycle. Information provided by patients during these interactions may inform FDA's thinking on a disease, condition, or therapeutic area, such as understanding the impact a disease has on patients' lives and the outcomes that are important to patients with that disease. It may also inform FDA premarket review of Investigational New Drug Applications (INDs),New Drug Applications (NDAs), Supplemental New Drug Applications (sNDAs), Biologics License Applications (BLAs), Supplemental Biologics License Applications (sBLAs), Investigational Device Exemption (IDEs), Premarket Approval (PMAs), (sPMAs) and ongoing safety surveillance.

Submission of PPIn to FDA is voluntary. The information submitted should inform decision making. PPIn can be useful to, among other things:

- Identify unmet medical need;
- Understand the natural history of a disease;
- Identify outcomes that patients care about;
- Develop clinical trial protocols that minimize burden to patients;
- Understand patient experiences with current treatments and daily living with their disease;
- Identify patient preferences, goals, and opinions, including those of a diverse patient population (and the heterogeneity within);
- Identify with which benefits and risks outcomes matters most to patients and the tradeoffs patients are willing to make between benefits and risks; and
- Refinement of materials such as informed consent, clinical trial recruitment materials, patient information leaflets, package inserts, PLS, etc.

This document recommends that FDA encourage product sponsors and other stakeholders to meaningfully engage patients throughout the product lifecycle. This document recommends the Agency welcomes submission of PPIn from sponsors and other stakeholders, and engage in a dialogue with the relevant review division on PPIn. This document, including the defined terminology, may be informative to other stakeholders, including patient groups and academic researchers, who collect and submit PPIn to the FDA. This document recommends the Agency encourages sponsors and other stakeholders that are considering PPIn for submission to FDA to communicate with the relevant FDA review division to discuss their plans for patient engagement as early in the process as possible. The next section consists of NHC recommendations to define key terms related to patient-focused drug development.

IV. Defining Key Terms for Patient Engagement

Patient engagement, in drug development and product review, means involving patients as active participants in these processes. Simply enrolling and following patients as passive research subjects in a clinical trial does not rise to the level of patient engagement. Instead, patients should be treated "as valued and valuable partners whose input, advice, and guidance is sought and implemented" throughout these processes.[13] FDA recognizes that patient engagement extends well beyond drug development and approval. However, for the purposes of this document, the focus is on patient engagement prior to and throughout a product's lifecycle.

[13] A. Hoos A, *et.al.*, "Partnering with Patients in the Development and Lifecycle of Medicines: A Call for Action," *Therapeutic Innovation & Regulatory Science,* (2015).

FDA recognizes the need for standard terminology regarding patient engagement in drug development and approval. Key terms are defined or described for the purposes of this guidance as follows:

> ***Patient*** – "those (people) having or at risk of having the medical condition(s) whether or not they currently receive medicines or vaccines to prevent or treat a disease" as well as "the family and those caring for those with the medical condition(s)," patient advocates, and patient groups.[14]

The definition of "patient" is intentionally broad in an effort to capture the myriad of valuable input to be gained from each of the listed individuals and organizations (i.e., individuals suffering from a condition, family caregivers, patient advocates, and patient advocacy organizations) without excluding a valuable perspective. However, we recognize that each type of individual or organization may not always be appropriate to speak for the person with the condition in all contexts and situations. When this guidance refers to the single person with the illness, the phrase, "individual patient," is used.

> ***Sponsor*** – an entity that takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, a government agency, academic institution, private organization, or other organization.[15] The sponsor may also be the entity responsible for submitting a new product application for FDA review.[16]

There are many terms to describe different types of patient information. For the purposes of this document, it is recommended FDA focuses on ***patient-provided information (PPIn)***, defined below. To distinguish patient-provided information for the purposes of this guidance, other types of ***patient information*** are defined as follows (see also Figure 1 on page 11):

> ***Patient information*** – broadly means all information regarding a patient from any source, such as patient-provided information as well as other medical information about a patient, including but not limited to: test results (e.g., genetic, pathology, imaging), identifying information, family history, provider opinion, and any other information in a patient's medical records.[17]
>
> ***Patient-provided information*** (***or patient-provided input***) – broadly means a range of information that comes directly from patients such as, but not limited to: views, experiences, preferences, needs, opinions, and priorities. This can include their overall view of their condition and its natural history and impact on their life (e.g., patient-reported outcomes such as symptoms, function, and quality of life);experience with available treatments; description/view on which outcomes are important; patient preferences, goals, desires, concerns, perceptions, or opinions; or the relative importance of any issue as defined by patients.[18]*Patient-provided is information relayed by the patient regarding their subjective experience and opinions.* It does not include all

[14] See Footnote 6.
[15] See 21 CFR 312.3(b).
[16] See 21 CFR 314.3(b).
[17] National Health Council, Genetic Alliance. Integrating the Patient into the Drug Development Process: Developing FDA Guidance, (http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf).

[18] See Footnote 10National Health Council, Genetic Alliance. Integrating the Patient into the Drug Development Process: Developing FDA Guidance, (http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf)

medical information on a patient (e.g., genetic testing information, pathology results) that may be about the patient but comes from other sources.

Patient-generated health data – health-related data created, recorded, or gathered by or from patients (or family members or other caregivers) to help address a health concern.[19]

Patient perspective information – a subset of PPIn; information regarding the attitude or the point of view of the patient, including anecdotal comments in correspondence to FDA or testimony at Advisory Committee Panel meetings[20] or Patient-Focused Drug Development meetings,[21] patient opinions expressed publicly including through social media, patient responses to qualitative, *ad hoc* surveys, quantitative measurements of patient-reported outcomes, and more.[22,23]

Patient preference information – a subset of PPIn; qualitative or quantitative assessments of the relative desirability, or acceptability of, attributes that differ among alternatives (e.g., alternative therapeutic strategies).[24] Attributes of a drug or biologic include characteristics such as effectiveness, safety, route of administration, dosing regimens, duration of effect, duration of use, and other product features about which patients express preferences.

Patient-reported information – a subset of PPIn; information that is reported directly by a patient without amendment or interpretation by a clinician, researcher, or any other entity.[25]

Patient-reported outcome (PRO) – a subset of PPIn; an outcome measure based on a report that comes directly from the patient (e.g., study subject) about the status of the patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else. A PRO can be measured by self-report or by interview provided that the interviewer records only the patient's responses.[26]

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[19] See patient-generated health data, *HealthIT.gov website, Consumer eHealth,* https://www.healthit.gov/policy-researchers-implementers/patient-generated-health-data (last visited April8, 2016).

[20] See Footnote 2 *See FDA website, About the Patient Representative Program,* (http://www.fda.gov/ForPatients/About/ucm412709.htm) (last visited February 16, 2016).

[21] See Patient-Focused Drug Development: Disease Area Meetings Planned for Fiscal Years 2013-2017, http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm (last visited February 16, 2016).

[22] See Footnote 5 *Draft Guidance for Industry, Food and Drug Administration Staff; and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and* De Novo *Requests, and Inclusion in Device Labeling*.

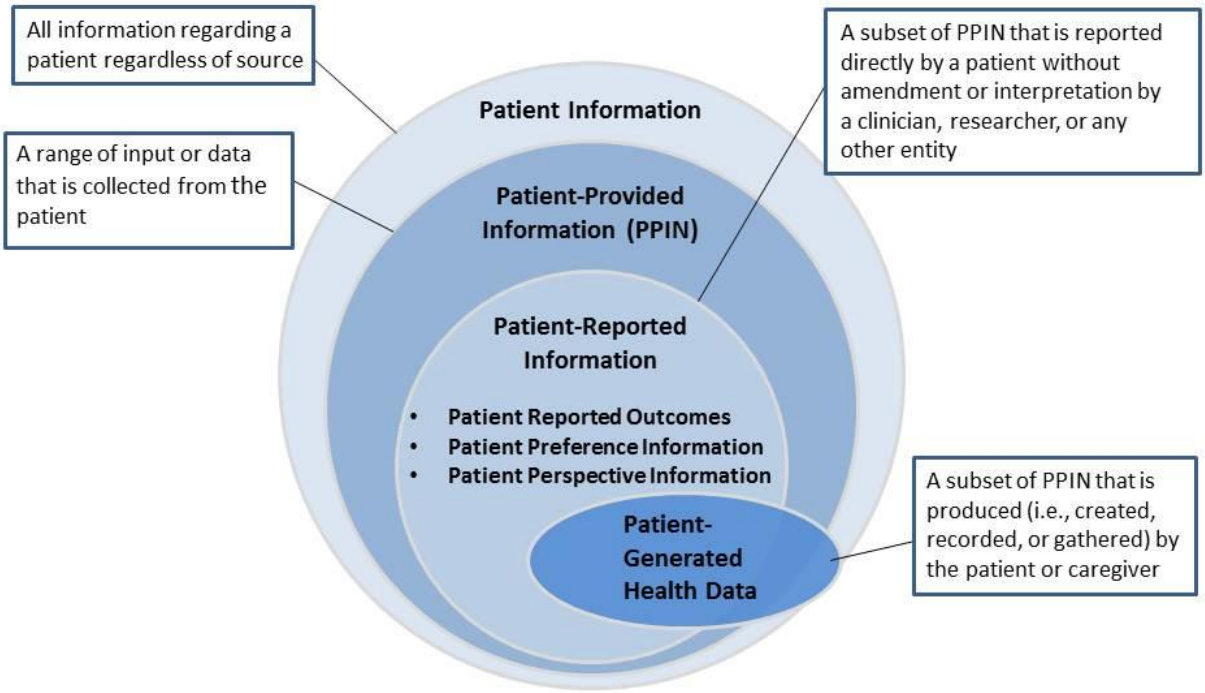
[23] See FasterCures, Enhancing Integration of Patient Perspective Data in the Drug Development Process, Proposal for PDUFA VI, (http://www.nationalhealthcouncil.org/sites/default/files/FasterCures-PDUFA-Comment-Letter-FDA.pdf).

[24] See Footnote 5 *Draft Guidance for Industry, Food and Drug Administration Staff; and Other Stakeholders; Patient Preference Information – Submission, Review in PMAs, HDE Applications, and* De Novo *Requests, and Inclusion in Device Labeling*.

[25] See Footnote 10.

[26] See the guidance for industry, *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm193282.pdf). For the most recent version of a guidance, check the FDA Drug guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (last visited February 16, 2016).

Figure 1: Relationship Among Types of Patient Information



Key terms are defined or described for the purposes of inclusion in a draft guidance document as follows:

> ***Patient voice*** – broadly refers to capturing and utilizing PPIn.[27]
>
> ***Patient involvement*** – broadly refers to patient participation or contribution in a process.[28]
>
> ***Patient engagement/interaction*** – a specific reciprocal action between a patient or patients and another individual or group for the purposes of collecting PPIn from the patient and/or communicating with the patient. Can be formal or informal; direct or indirect (i.e., through a third party such as a patient group).[23] Meaningful patient engagement requires other attributes such as continuous patient interactions on a sustained basis. (See meaningful patient engagement.)

[27] See NHC comments on FDA's Draft Guidance on Patient Preference Information, (http://www.nationalhealthcouncil.org/sites/default/files/Patient-Preference-FDA-Guidance-Comments.pdf).
[28] *See also: Patient involvement in the European Union,http://ec.europa.eu/dgs/health_consumer/dyna/enews/enews.cfm?al_id=1259.*

Patient risk tolerance – A qualitative term reflecting the extent to which a patient will accept the risk(s) of an adverse effect from a treatment for a probable benefit; risk tolerance will vary among patients, which affects individual patient decisions as to whether risks are acceptable.[29]

Meaningful patient engagement – Interactions intended to inform decision making that include direct relationships and partnerships with patients that are bidirectional, reciprocal, and continuous; where communications are open, honest, and clear; and where engagement goals, participants, methods, desired impacts, and actual impacts are clearly outlined and transparent.[30]

Patient need – a desire or requirement expressed by a patient related to their health.[23]

Patient-centered – broadly meaning any process, program or decision focused on patients in which patients play an active role as meaningfully engaged participants, and the central focus is on optimizing use of PPIn.[31]

Patient-informed drug development – generally refers to drug development that uses PPIn to guide or inform decisions but may or may not include patient involvement.[32]

Patient-focused drug development (or patient-directed drug development or patient-focused medicines development) – is the meaningful engagement of patients in the research and development of therapeutic products and the various important roles patients can play in improving the processes, from study endpoint selection that reflects outcomes meaningful to patients, recruitment and retention in clinical trials, and more effective post-marketing safety surveillance.[33]

Patient-Focused Drug Development (PFDD) initiative – refers specifically to FDA's patient-focused drug development initiative as part of FDA commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), which aims to more systematically obtain the patient perspective on specific diseases and their treatments.[34]

Product Lifecycle – the entire product development process; research prior to discovery, development, or preference, pre-product research, and throughout the complete to post approval.[35]

The terminology and concepts described here also may be useful in other contexts. Additionally, this document may be informative to other stakeholders who may wish to consider engagement with patients to inform any type of medical product development.

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[29] See CDRH guidance for industry, *Factors to Consider Regarding Benefit-Risk in Medical Device Product Availability, Compliance, and Enforcement Decisions*, http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm506679.pdf (last visited November 7, 2016).

[30] See National Health Council. The Patient Voice in Value: The National Health Council Patient-Centered Value Model Rubric, http://www.nationalhealthcouncil.org/sites/default/files/Value-Rubric.pdf.

[31] Epstein RM, Street RL. The Values and Value of Patient-Centered Care. Annals of Family Medicine. 2011;9(2):100- 103. doi:10.1370/afm.1239.

[32] See Footnote 10National Health Council and Genetic Alliance. Integrating the Patient into the Drug Development Process: Developing FDA Guidance, (http://www.nationalhealthcouncil.org/sites/default/files/NHC-GA-Patient-Engagement.pdf).

[33] See Clinical Trials Transformation Initiative, CTTI Recommendations: Effective Engagement with Patient Groups Around Clinical Trials, http://www.ctti-clinicaltrials.org/files/PatientGroups/PGCTrecs.pdf (last visited February 16, 2016).

[34] See Footnote 3.

[35] See Footnote 20 NHC comments on FDA's Draft Guidance on Patient Preference Information, (http://www.nationalhealthcouncil.org/sites/default/files/Patient-Preference-FDA-Guidance-Comments.pdf).

APPENDIX D (NEXT PAGE)