SOCIETY FOR WOMEN'S HEALTH RESEARCH

POLICY PRINCIPLES: PATIENT-FOCUSED DRUG DEVELOPMENT

Background

The Society for Women's Health Research (SWHR) strongly supports Title III Section 3002 of the *21st Century Cures Act* and the sixth authorization of the *Prescription Drug User Fee Act (PDUFA VI)*, which give the U.S. Food and Drug Administration (FDA) new directives to advance medical innovation that addresses unmet patient needs.[1]

SWHR commends FDA for its significant milestones to date across the agency to implement the Patient-Focused Drug Development (PFDD) Program. By coordinating resources developed by the Center for Device and Radiological Health (CDRH), the Center for Drug and Evaluation Research (CDER), and the Office of Medical Products and Tobacco (OMPT), this program will better ensure the systematic collection and use of patient experiences to inform the research and development of new therapies and their regulatory review by FDA.

SWHR is committed to ensuring the PFDD Program **addresses patient population diversity (including sex and gender)** and obtains **meaningful input from women**.

- Women comprise more than half (51%) of the U.S. population.[2]
- Women provide the majority of caregiving.
    - An estimated 66% of caregivers are female.[3]
    - Women assume multiple roles while caregiving: hands-on caregiver, case manager, companion, surrogate decision-maker and advocate.
- Women make more than 80% of health care spending decisions.[4]

Working collaboratively with FDA is part of SWHR's legacy. SWHR championed the framework for the scientific discipline of sex-based biology, which encourages the inclusion of female subjects in clinical trials and analyzes the differences between women and men in relation to disease. Through the systematic collection and reporting of more accurate, sex-specific drug and device information and labeling, FDA has been able to better serve female and male patients and ensure that sex-specific data analysis of post-market surveillance is available to physicians and patients.[5]

SWHR has conceived a set of principles to inform topics addressed in FDA PFDD draft and final guidance documents that have implications for women and their health.

About SWHR

SWHR is an education and advocacy thought leader dedicated to promoting research on biological differences in disease and improving women's health through science, policy, and education. Founded in 1990 by a group of physicians, medical researchers and health advocates, SWHR aims to bring attention to a variety of diseases and conditions that disproportionately, differently, or exclusively affect women. Today, SWHR continues to lead the way in correcting imbalances in health care for women by addressing unmet needs and research gaps in women's health.

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SWHR PFDD Principles

Principle 1: Patients in the clinical research study sample should *represent* the *target population* to the greatest extent possible.

To the greatest extent possible, people from *all relevant* demographics within the target population and subgroups of interest (*e.g.,* age, sex, gender, race/ethnicity, level of education, and socioeconomic status) should be considered for inclusion in the clinical research study sample to enhance generalizability of the results.[6]

- Greater diversity in the patient population increases the potential of learning more about how different subgroups might respond to a medical product.[7]
- When subgroup data are analyzed, more information can then be communicated to the public, resulting in greater assurance in the safety and effectiveness of medical products.[8]

Populations who may be considered special — for example, pregnant and lactating women who often are excluded from clinical research[9, 10] — should be considered to the greatest extent possible.

- Exclusion of pregnant and lactating women in clinical research has resulted in a lack of data on drug safety and efficacy in these women, making health care providers uncertain about whether to prescribe needed medications.
- The collection of patient experience information in pregnant and breastfeeding women may be impacted by their pregnancy and breastfeeding status. To elicit patient experience information fully and accurately, additional questions may need to be considered.

FDA, sponsors, clinical research organizations and study sites should aim to address barriers that affect the recruitment of diverse and special patient populations to the greatest extent possible. For example:

- The location of study sites may present access issues for certain patient populations (*e.g.,* elderly patients with limited mobility and those in underserved communities).
- Some patient populations may not have access to information (*e.g.,* the internet) or access to coverage/reimbursement for clinical research studies.

FDA PFDD guidance and glossary of terms should more clearly define *target population* in the context of *patient experience data and representativeness*.

- The definition of *target population* in PFDD Draft Guidance 1 Glossary is too general and simplistic: "the group of individuals (patients) about whom one wishes to make an inference."[11]
- Draft Guidance 1 and Guidance 2 and 3 public workshop discussion documents do not sufficiently discuss what the agency considers a *"target population."*
- However, the definition of *representativeness* in PFDD Draft Guidance 1 Glossary addresses *intended population* in the context of patient experience data.
    - "Confidence that a sample from which evidence is generated is sufficiently similar to the intended population. In the context of patient experience data, representativeness includes the extent to which the elicited experiences,

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perspectives, needs, and priorities of the sample are sufficiently similar to those of the intended patient population."[12]

- Examples of possible *"target population"* definitions include:
    - a population similar to the disease subpopulation that would be included in the pivotal trial;
    - the population with the target disease, composed of subpopulations with different attributes (*e.g.,* severe vs. mild disease, advanced vs. early disease, patients with comorbidities vs. patients without comorbidities); or
    - patients who have prior experience participating in clinical studies vs. those who do not.[13]

Principle 2: Patient experience information should reflect physical and psychosocial impacts of a disease/condition, related therapy, or clinical investigation, to the extent possible.[14]

Sex and *gender* play critical roles in the risk, pathophysiology, presentation, diagnosis, treatment, and management of disease. As defined by the Institute of Medicine:

- *Sex* refers to the classification of living things according to reproductive organs and functions assigned by chromosomal complement.[15]
- *Gender* refers to the social, cultural, and environmental influences on the biological factors of women or men. Gender is rooted in biology and shaped by environment and experience.[16]

The study of *sex and gender differences* is leading to important discoveries of how women and men differ in fundamental ways and how these differences affect disease risk, symptoms, diagnostic sensitivity and specificity, and response to therapy.

- Migraine is one example of a chronic condition that affects women differently than men.[17]
    - Migraine is three times more common in women than men, and the pathophysiology, presentation, and management of the disease is different in women and men.
    - Women are more likely than men to experience longer and more intense migraine attacks, report more migraine-associated symptoms such as nausea and visual aura, and have higher levels of migraine-related disability.[18,19]
    - FDA drug trial snapshots for three approved drugs for migraine report that 85% or greater of the participants enrolled in the clinical trials to evaluate safety were women.[20] This percentage is consistent with the population affected by the disease.
- Biological and physiological differences and hormonal fluctuations have been shown to play a role in the rate of drug absorption, distribution, metabolism, and elimination, resulting in drug response differences in women vs men.[21]

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Research demonstrates that psychosocial factors affect women differently than men.

- Psychosocial factors such as depression, anxiety, inadequate social and economic resources, caregiver stress, marital stress, and adversities early in life are highly prevalent in women, and have been linked to adverse cardiovascular outcomes. While marriage largely reduces cardiovascular risk in men, the stress of marriage increases cardiovascular risk for women.[22]

Sex differences information can provide a deeper understanding of a patient's history and disease risk factors.

- Women develop clinical manifestations of coronary heart disease (CHD) about 10 years later than men. At all ages the prevalence of CHD is lower among women than men. Despite this, women have higher rates of morbidity and mortality from CHD than men.[23]

Principle 3: The FDA PFDD Program should encourage stakeholders to use all potential acceptable methods for patient experience collection, reporting, and analysis.

PFDD Draft Guidance 1 and Glossary provides an overview of the three most commonly used research approaches:

- *Qualitative research* is "a method of inquiry used to gain insight into the patient experience and to better understand the meaning of research concepts."[24]
- *Quantitative research* methods are "characterized by the collection of quantifiable data and the application of statistical methods to summarize the collected data."[25]
- *Mixed methods* is "where both qualitative and quantitative methods are used" [26] and can complement each other.

The choice and use of methods to collect patient experience information may differ depending on the intended objective.

- There may be circumstances for which a range of different methods might be applicable, some of which may require less prescriptive approaches.
    - For example, in instances where sampling approaches are well-understood, a more prescriptive approach may be warranted.[27]

Because the level of rigor needed for generating patient-provided input can vary, FDA PFDD guidance should clearly describe and explain how evidentiary standards may vary depending on intended use.

- Applying the same evidentiary standard to all types of patient experience data could be unnecessarily burdensome to certain stakeholders.[28]

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FDA PFDD guidance should encourage innovative research approaches (*e.g.,* use of digital health tools) and provide sufficient clarity regarding their use for research and regulatory decision-making.

- For example, FDA has released MyStudies Application, a new open-source computer code technology to foster collection of real-world evidence via patients' mobile devices.
    - The release follows the completion of a pilot study that FDA and Kaiser Permanente conducted of 64 pregnant women who used the app to report on health outcomes.[29]

Principle 4: FDA PFDD guidance should include hypothetical case examples that identify and explain different circumstances for collecting and using patient experience information.

FDA PFDD guidance should provide a detailed explanation of instances when certain acceptable research methods may be preferred for specific stages of the medical product development lifecycle.

- Preferred research methods for clinical trials and the evidentiary standards needed for each objective often differ from those for FDA regulatory review/approval and for FDA post-market surveillance.
    - For example, the data collection method to inform a clinical study *endpoint* may differ from the data collection method to develop a *clinical outcome assessment (COA) tool*.[30]
- PFDD Guidance October 2018 public workshop discussion documents identify four types of COAs all stakeholders must understand and differentiate:
    - *"Clinician-reported outcome (ClinRO)* — a measurement based on the report that comes from a trained health care professional after observation of a patient's health condition
    - *Patient-reported outcome (PRO)* — a measurement based on a report that comes directly from the patient about the status of the patient's health condition without interpretation of the patient's response by a clinician or anyone else
    - *Observer-reported outcome (ObsRO)* — a measurement based on a report of observable signs, events, or behaviors related to a patient's health condition by someone other than the patient or a health care professional
    - *Performance outcome (PerfO)* — a measurement based on a standardized task(s) performed by a patient that is administrated and evaluated by an appropriately trained individual or is independently completed."[31]

Stakeholder awareness and understanding of these COA tools and how they will be used in the PFDD program is especially important given that FDA intends to replace 2009 *Guidance for Industry: Patient-Reported Outcomes Measures: Use in Medical Product Development to Support Label Claims* with forthcoming PFDD *Guidance 3 (Select, Develop, or Modify Fit-for-Purpose COAs)*.

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Principle 5: FDA should implement a standardized glossary of PFDD terms that applies across all PFDD guidance.

Consistent use of terms is vital to shared understanding of the concepts that underlie the science of patient engagement and collection of patient-provided information.

FDA's PFDD glossary should be comprehensive, relevant, and applicable to all FDA PFDD guidance and updated periodically to address identified omissions and modifications.

- The current FDA PFDD Glossary[32] does not include the terms, *sex* and *gender,* defined on Page 3 of this document.
- SWHR recommended these terms be added to the PFDD glossary in our February 16, 2018 comment letter to Docket No. FDA-2017-N-5896.
- SWHR restated these recommendations in our December 14, 2018 comment letter to Docket No. FDA-2018-N-2455-0001.

Definitions presented in the FDA PFDD Glossary should be easy for all relevant stakeholders (*i.e.,* patients, advocates, physicians, innovators, and researchers) to comprehend.

Principle 6: There should be a clear and predictable process for all stakeholders to engage with FDA on PFDD-related issues.

FDA has suggested that stakeholders (*i.e.,* patients, researchers, sponsors/medical product developers and others) come to the agency "early and often" to ensure the best results in planning for PFDD.

- FDA has announced the availability of new draft guidance for industry titled, "Developing and Submitting Proposed Draft Guidance Relating to Patient Experience Data."[33]

Industry sponsors should have a clear understanding of when and how they can consult with FDA regarding the conduct of studies and the incorporation of patients' experience in regulatory decisions.

- FDA should identify a timely and flexible communication process for sponsors to meet with the agency to seek feedback and clarifying input on various types of PFDD plans that address investigational new drug applications, non-investigational new drug applications, and post-marketing surveillance programs.[34]

PFDD guidance should also outline a predictable, streamlined process whereby patients, patient advocacy organizations, and other relevant stakeholders may also meet with FDA.

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