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December 23, 2019

Submitted electronically to: <https://www.regulations.gov>

Jeffrey Shuren, MD, JD

Director, Center for Devices and Radiological Health
U.S. Food and Drug Administration

Terri L. Cornelison, MD, PhD

Director, Health of Women Program
Center for Devices and Radiological Health
U.S. Food and Drug Administration

Re: FDA-2019-N-3804: Center for Devices and Radiological
Health (CDRH) Health of Women Strategic Plan

Dear Dr. Shuren and Dr. Cornelison,

The Society for Women's Health Research (SWHR) commends the U.S. Food and Drug Administration (FDA) for releasing its initial strategic plan for the Center for Devices and Radiological Health (CDRH) Health of Women Program.

SWHR is a nearly 30-year-old national education and advocacy nonprofit dedicated to promoting research on biological sex differences in disease and improving women's health through science, policy, and education. SWHR strongly supports FDA in recognizing and addressing sex and gender issues related to the performance of medical devices.

Sex and gender disparities within the realm of medical devices, as well as within the areas of device outcomes and side effects, are pressing issues for the health of women. These disparities must be addressed.

Women – 51% of the total population – constitute a significant part of the overall market for health care products. However, technology designed to improve and monitor women's health specifically has historically lagged far behind technology designed for men or without recognition of biological differences between women and men.

Research suggests women experience illness in different ways and suffer from certain diseases at different prevalence rates as compared to men. Women's bodies function differently than men's bodies do, yet technology has traditionally used male-oriented disease models to investigate efficacy. Further, researchers often fail to carefully examine

sex and gender differences within clinical trial outcomes. Health care innovation must take these issues into account.

The past several years have seen improvements in this trend, but much of the investment in women's health remains centered around reproductive health. This is true despite the fact that women do not reach menarche until adolescence and later begin experiencing symptoms of menopause in their 40s or 50s. Therefore, women are within the reproductive age range for only about half of their lives. Technology aimed at improving women's health need not demonstrate a singular focus on fertility — although there are certainly new devices that implement creative ways of addressing reproductive concerns, such as wearable fertility monitors and forms of digital birth control.¹

Innovation outside of the reproductive sphere has led to creativity that benefits women in a variety of ways. For example, acknowledging sex disparities in orthopedic function led to a prosthetic knee designed to cater to anatomical differences between women and men. Understanding differences in metabolism has helped us to better tailor drug dosage to women's metabolic rates.² Unfortunately, these examples are part of a small sample size of women's health-specific innovation. We are hopeful that CDRH's Health of Women Program will advance device innovation for women.

Moving forward, SWHR is encouraged to see a strategic plan as the basis for ongoing work within the CDRH Health of Women Program. The three priorities within the strategic plan — sex- and gender-specific analysis and reporting, integrated approaches for current and emerging issues related to the health of women, and a research roadmap — represent promising target areas through which FDA can strengthen the health of women in the device ecosystem. However, to truly foster ongoing improvement, SWHR recommends FDA strengthen certain areas of the plan with additional details on how improvements will be implemented.

SWHR appreciates this opportunity to provide recommendations and feedback in response to CDRH's proposed Health of Women Strategic Plan.

Priority 1: Sex- and Gender-Specific Analysis & Reporting

SWHR Recommendation 1: CDRH should go further in highlighting gaps in women's health in the device space and identifying ways in which CDRH can lead the scientific community in addressing these disparities.

Within Priority 1, Goal 1.B. states that CDRH hopes to ensure policies “evolve with current science.” SWHR supports the intent of this goal, given that the changing nature of technological innovation demands rapid updates to regulation and oversight. Page 11 of the strategic plan suggests that “[t]he science has advanced” across both basic and clinical trials.

However, the research remains outdated in several significant areas. While federal agencies are now mandated to better represent women within federally-funded research trials, data suggest

¹ The Medical Futurist (2019). 10 outstanding companies for women's health. *The Medical Futurist*. <https://medicalfuturist.com/10-outstanding-companies-for-womens-health/> Accessed on November 21, 2019.

² Das, Reenita (2018). Women's healthcare comes out of the shadows: Femtech shows the way to billion-dollar opportunities. <https://www.forbes.com/sites/reenitadas/2018/04/12/womens-healthcare-comes-out-of-the-shadows-femtech-shows-the-way-to-billion-dollar-opportunities/#2ea04e766159> Accessed on November 21, 2019.

women are still underrepresented, and racial and ethnic minorities remain severely underrepresented.^{3,4} Clinical trials also often limit enrollment to adults ages 18-64 years, so elderly patients are often not well-represented despite the fact that our population is aging overall.⁵

Perhaps most importantly — while representation of women and minorities is increasing, analyses by age, race, ethnicity, and gender and sex still occur only in a select subsection of clinical trials,⁶ despite the 2014 FDA Action Plan calling for these analyses specifically. Per research in *JAMA Internal Medicine*, only 17% of 77 studies examined performed comparative effectiveness analyses by sex and only 4% of 82 studies performed analyses by race. In the studies that did examine sex differences, two found safety to be significantly different by sex, while one study found results suggesting the device was less effective in women.

Analyzing for sex-based differences is not just important to address safety concerns — although this has certainly been a focus within the device ecosystem. There are some areas in which women may show greater benefit than men. For example, while women experience more adverse effects following cardiac catheterization, research suggests they may benefit more from cardiac resynchronization therapy. In regards to orthopedic function, women tend to show worse knee function and higher rates of pain following total knee arthroplasty, but they also have lower rates of surgical revisions as compared to men.⁷ However, there is relatively little oversight in ensuring that all researchers perform the sorts of analyses that allow us to better understand these disparities. Pushing researchers to address sex differences is not only integral to improving safety, but to advancing our understanding of how sex affects all aspects of health.

We applaud CDRH for pursuing a commitment to evidence-based decision-making. CDRH should ensure that it keeps up with advances in areas where research is rapidly evolving. However, it is clear that the research community still has progress to make in ensuring device trials specifically address and investigate issues in women's health. We encourage FDA to not only follow innovative research, but also to lead in this field by continuing to advance the scientific community through its oversight, regulation, and approval processes. The strategic plan could go further in highlighting disparities in women's health and clarifying where CDRH will follow recent scientific developments, as well as areas where the Health of Women Program can act as a leader for the rest of the scientific community.

Priority 2: Integrated Approach for Current & Emerging Issues Related to the Health of Women

SWHR Recommendation 2a: CDRH should clarify the role of the steering committee as well as the core community of practice and outline its plan for inclusion of diverse stakeholders — including patients and caregivers — within decision-making bodies.

³ Chen, A. et al. (2018). Clinical trials for new molecular entities and original therapeutic biologics approved by FDA CDER from 2013 to 2015. *Journal of Women's Health*, 27(4). doi: <http://doi.org/10.1089/jwh.2016.6272>

⁴ Scott P.E., et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *Journal of the American College of Cardiology*, 71(18):1960-1969. doi: 10.1016/j.jacc.2018.02.070.

⁵ Shenoy, P. & Harugeri A. (2015). Elderly patients' participation in clinical trials. *Perspectives in Clinical Research*, 6(4), 184-189. doi: 10.4103/2229-3485.167099

⁶ Dhruva, S.S., et al. (2017). Inclusion of demographic-specific information in studies supporting US Food & Drug Administration Approval of High-Risk Medical Devices. *JAMA Internal Medicine*, 177(9), 1390-1391. doi: 10.1001/jamainternmed.2017.3148.

⁷ Pinnow, E., Herz, M., Loyo-Berrios, M., & Tarver, M. (2014). Enrollment and monitoring of post-approval studies for medical devices mandated by the Food and Drug Administration. *Journal of Women's Health*, 23(3), 218-233. doi: 10.1089/jwh.2013.4343.

Within Priority 2, Goal 2.A., CDRH suggests the use of an internal steering committee to provide recommendations to the center and a core community of practice for coordinating subject-matter expertise within the center. We would recommend more specifically defining the role of both of these committees.

SWHR has gone on record repeatedly to encourage representation of diverse stakeholders within decision-making committees — including patient, caregiver, clinician, and researcher perspectives.^{8,9} We recommend CDRH outline a plan for stakeholder inclusion within each group. We suggest input from these key stakeholders:

- Medical device makers and innovators
- Researchers and scientists who work to develop or refine major medical devices
- Health care professionals who routinely prescribe the use of medical devices
- Patients who rely on medical devices
- Caregivers who assist patients dependent on a medical device

Additionally, we recommend CDRH take into account barriers that may make it difficult for patients and other key stakeholders to become involved in these decision-making groups. Partnering with patients has improved health care in a variety of ways. In the 1980s, HIV patient advocates led the push for advancing research and drug approvals in this area. More recently, the Parkinson's Foundation Parkinson's Advocates in Research (PAIR) program has shown the benefits of patient involvement with both researchers as well as FDA. PAIR advocates interact directly with FDA, help to design studies for new treatments, and serve on Data Safety Monitoring Boards and Institutional Review Boards for these projects.¹⁰ SWHR would be supportive of the Health of Women Program partnering with women's health advocacy groups in a similar way to the work of the Parkinson's Foundation program in order to better connect CDRH to the lived experiences of patients.

SWHR is supportive of recent FDA efforts¹¹ to improve patient interaction with the device community. We encourage continued efforts to improve recruitment and retention of women within medical device trials — including a focus on telecommunication with patients and participants as is feasible within the bounds of a clinical trial, as well as appropriate reimbursement for patient time and transportation. As women frequently assume caregiver roles within their families, SWHR recommends that researchers make every effort to provide supportive mechanisms such as on-site child care during participation as well as efforts to minimize the time commitment and travel as appropriate. SWHR is hopeful that CDRH will be thoughtful in considering factors that may act as barriers to patient participation in its work as well as how it may ease this process.

⁸ SWHR (2019). SWHR recommendations on ICER's 2020 value assessment framework. https://swhr.org/swhr_resource/swhr-recommendations-on-icers-2020-value-assessment-framework/ Accessed November 19, 2019.

⁹ SWHR (2019). SWHR's health care value assessment principles. https://swhr.org/swhr_resource/swhrs-health-care-value-assessment-principles/ Accessed November 19, 2019.

¹⁰ Hoos, A. et al. (2015). Partnering with patients in the development and lifecycle of medicines: A call for action. *Therapeutic Innovation & Regulatory Science*, 49(6), 929-939. doi: 10.1177/2168479015580384

¹¹ U.S. Food & Drug Administration. (2019). Patient engagement in the design and conduct of medical device clinical investigations: draft guidance for industry, food and drug administration staff, and other stakeholders. <https://www.fda.gov/media/130917/download> Accessed on November 21, 2019.

SWHR Recommendation 2b: CDRH should clarify the types of strategic partnerships it intends to engage in for the Health of Women Program and outline the goals for these partnerships in a way that allows for stakeholder feedback.

Goal 2.B., and specifically Strategy 2.B.1., calls to expand upon current strategic alliances as well as to build new alliances in order to maximize innovation for women's health within the device ecosystem. We support this recommendation of new alliances but would encourage further clarity on what goals underlie the intent of this strategy. We also recommend CDRH include more specificity on what types of new alliances it will pursue within the Health of Women Program and allow time for stakeholder comment and feedback on these initiatives.

Public-private partnerships (PPP) have shown success in the device world before. For example, the Medical Device Innovation Consortium (MDIC) created in 2012 has focused on improving patient safety as well as device effectiveness and quality. Given that MDIC already targets some of the strategies mentioned in Strategy 2.B.1., SWHR encourages CDRH to provide more information on how MDIC might be used to pursue specific women's health goals. For example:

- How will existing infrastructure and grant money be used to support the agenda of improving women's health within the medical device space?
- How will existing PPPs interact with new alliances designed to focus on these goals?

SWHR also suggests that CDRH provide additional information on where women's health-specific alliances might be housed and what specific goals they will aim to achieve.

SWHR Recommendation 2c: CDRH should explore topics related to marketing, physician training, and patient education around medical devices, as these are key elements in promoting uptake of new devices or device redesigns.

Strategy 2.B.3. encourages CDRH to explore potential recommendations for improving innovation for sex- and gender-specific issues. SWHR believes CDRH can and should be a leader in stimulating scientific innovation within the field of women's health. Despite advances in technology, women's health devices have, in many ways, remained stagnant for decades. Devices such as hip implants have been slow to be updated to accommodate the needs of women, despite evidence suggesting they are more likely to fail in women than in men.¹²

Updating devices or creating new devices to better address the needs of women is difficult — it requires significant investment not only in research, but in dissemination, marketing, and clinician training. New devices must appeal to patients as well as physicians, who are often in the position to recommend innovative devices. Devices must also be covered by insurance companies to make them worthwhile for patients and physicians. These barriers to innovation go above and beyond simply researching and developing new methods of treatment.¹³

Innovators suggest it is not simply the lack of new devices that hinders advancement in women's health. Marketing new devices, training physicians to use them properly, and long-

¹² Haughom, B.D., Erickson, B. J., Hellman, M.D., & Jacobs, J.J. (2015). Do complication rates differ by gender after metal-on-metal hip resurfacing arthroplasty? A systemic review. *Clinical Orthopaedics and Related Research*, 473(8), 2521-2529.

¹³ Herzlinger, R.E. (2006). Why innovation in health care is so hard. *Harvard Business Review*. <https://hbr.org/2006/05/why-innovation-in-health-care-is-so-hard> Accessed November 21, 2019.

term implementation require significant time and financial investment.¹⁴ SWHR is hopeful that in advancing continued innovation, CDRH takes the time to consider not only device design and efficacy, but these other important issues as well.

Priority 3: Research Roadmap

SWHR Recommendation 3a: CDRH should clarify details about its plans for a portfolio of women-specific device efforts and a registry for women's health devices, including how these projects will be created, where they will be housed, and who will be able to access them. Existing infrastructure should be updated to address these needs before creating new registries.

Within Priority 3, Strategy 3.B.1. recommends the establishment of a portfolio of women-specific device efforts. We commend CDRH for this strategy to highlight the significant work being done in this area, but would recommend more detail in what this portfolio might look like and how it will be made available. Specifically, we recommend that a portfolio be available online for broad public access and that clinician-specific communications efforts are conducted to ensure providers are well-informed as to what updated technologies are available to their patients.

Similarly, Strategy 3.B.4 calls for the creation of a registry for women's health devices, with one goal being to facilitate sex and gender analyses across this registry. SWHR encourages CDRH to provide further details on where the registry will be housed (ideally, online and easily accessible to the public) and whether it will be a new, stand-alone registry or be subsumed under current FDA device registries, such as the Manufacturer and User Facility Device Experience (MAUDE) database or the Medical Device Epidemiology Network's Women's Health Technologies Coordinated Registry Network (WHT-CRN).

Importantly, SWHR does not believe that women's health-specific device information should be housed in a separate registry. First and foremost, separating women's health devices from the rest of the device world gives the impression that women's devices are out of the norm and reinforces current cultural stereotypes that "gender-neutral" devices are the standard of care. Women make up over half of the U.S. population. Separating men's and women's devices into different registries only serves to reinforce existing gender stereotypes.

Secondly, FDA already has been involved in the creation of both MAUDE and WHT-CRN, two separate medical device registries designed to assess safety issues. Establishing an additional database would increase the burden on employees responsible for creating and maintaining the database; on manufacturers and clinicians, who would potentially need to increase time spent reporting; and on patients, who may not understand differences in registries.

SWHR believes FDA could build upon a current database by requiring inclusion of sex- and gender-specific information about *all* devices. In addition, encouraging pilot analyses of already-existing registry data would go a long way in increasing our understanding of sex-based information. Continuing FDA's efforts to improve the MAUDE database¹⁵ — to address missing, duplicated, and non-standard entries, and making the database more user-friendly — would

¹⁴ Luk, Christine. (2018). Opening up about challenges in women's health innovation. *Rice Medical Innovation Blog Series*. <https://innovation.rice.edu/blog/opening-up-about-challenges-in-womens-health-innovation> Accessed November 18, 2019.

¹⁵ Lim, David. (2019). FDA ends alternative reporting program, pledges to make MAUDE user friendly. *MedTech Dive*. <https://www.medtechdive.com/news/fda-ends-alternative-reporting-program-pledges-to-make-maude-user-friendly/557465/> Accessed November 21, 2019.

have a positive impact on researchers and patients alike. SWHR supports efforts to use existing MAUDE data and improve the MAUDE system as a primary approach, or expanding an existing registry such as MDEpiNet's WHT-CRN, before creating additional databases that would increase burden for many.

SWHR Recommendation 3b: CDRH should clarify how it will incorporate patient input into the device innovation process, including the types of patients who will be included, and whether it will include other stakeholders such as clinicians with critical knowledge of patient needs.

Strategies 3.B.3. and 3.B.4. involve strategic partnership with customers and the use of patient input. We are pleased to see CDRH's understanding of the need for patient input into the device innovation process, as it is often the patients who are best suited to critique issues with device use and quality of life impact. Similar to our recommendation 2a, SWHR encourages CDRH to specify details about what types of patients will be included (ideally, a broad array of patients with experiences across the device field) and urges CDRH to consider inclusion of science, clinician, and industry stakeholders who are best suited to discuss the broad needs of patients within their respective fields.

SWHR General Comments

SWHR is largely encouraged by the priorities outlined by CDRH in the Health of Women Strategic Plan. Improving research and reporting guidelines to better delineate health disparities as well as sex and gender differences is one of SWHR's core values, and CDRH's efforts to further these goals are commendable. The strategies detailed above will be improved by the inclusion of further detail, which we hope will be included at subsequent steps of the revision and dissemination process. SWHR is hopeful we will be able to further contribute as these strategies are refined and finalized.

Thank you for providing this opportunity to comment on the CDRH Health of Women Strategic Plan. We look forward to serving as a resource on sex and gender differences in device health as well as women's health more broadly. If you have questions, please contact Melissa Laitner, Director of Science Policy, at 202.496.5002 or melissa@swhr.org.

Sincerely,



Amy M. Miller, PhD
President and Chief Executive Officer
Society for Women's Health Research