ENDOCRINE SOCIETY
Hormone Science to Health

September 2, 2020

Lowell Schiller, JD
Principal Associate Commissioner for Policy
Food and Drug Administration
Room 4300, White Oak Building One
10903 New Hampshire Avenue
Silver Spring, MD 20993

Kaveeta Vasisht, MD
Associate Commmissioner for the Office of Women's Health
Food and Drug Administration
Room 2322, White Oak Building 32
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: FDA-2020-N-1391: Office of Women's Health Strategic Priorities; Establishment of a Public Docket; Request for Comments

The Endocrine Society appreciates the opportunity to comment on the strategic priorities of the Food and Drug Administration's Office of Women's Health (OWH). Founded in 1916, the Endocrine Society is the world's oldest, largest, and most active organization devoted to research on hormones and the clinical practice of endocrinology. The Society's membership of over 18,000 includes experts in all research and clinical aspects of hormone health, including women's health and reproductive health.

We offer the recommendations below, which highlight areas of particular relevance to endocrine research and clinical practice. These recommendations are also shared by the Society for Women's Health Research.

Lead inter- and intra-agency conversations on how best to advance sex as a biological variable (SABV) and the inclusion of women within clinical trials.

Until about 25 years ago, almost all health research was conducted on men due to the persistent idea that female hormonal cycles were too difficult to manage in experiments — including the fear of harming potential pregnancies — and that using only one sex would reduce variation in results. This exclusion of females in health research extended to research on female animals, cells, and tissue. Researchers assumed that they could simply extrapolate their male-only study results to females, which created a dangerous precedent that overlooked fundamental biological differences between women and men.

While women are increasingly included in clinical research (accounting for 72% of all clinical trial participants for FDA-approved new drugs in 2019), there also remains insufficient ethnic diversity in female study populations.[1]

[1] Ortman, E. (2020). Women make up 72% of study participants for FDA-approved new drugs in 2019. Accessed from: https://swhr.org/women-make-up-72-of-study-participants-for-fda-approved-new-drugs-in-2019/

2055 L Street NW
Suite 600
Washington, DC
20036

T. 202.971.3636
F. 202.736.9705

endocrine.org

Within preclinical research, the dominance of male subjects and ignorance of SABV persists. Even though significantly more preclinical articles published in 2019 included both sexes in the sample population compared to 2009,[2] little progress has been made in analyzing study results by sex. Specifically, among studies that included both sexes as subjects, only 42% included sex-disaggregated analyses, actually down from 50% of articles in 2009.[3]

Endocrine Society journals, such as the *Journal of the Endocrine Society*, and the *Journal of Clinical Endocrinology and Metabolism*, require that submitting authors report the sex of research subjects or justify why only one sex was used in their study. The FDA OWH should champion similar reporting measures in all clinical trials to further advance our understanding of sex differences in therapeutic responses.

We urge the FDA OWH to act as a leader in advancing conversations around SABV and the inclusion of diverse populations of women within therapeutic and device research and the approval process. In addition, it is important to not only include both women and men in research, but to analyze outcomes for potential sex and gender differences. The OWH should promote policies encouraging those seeking approvals to ensure appropriate inclusion as well as robust analyses to understand sex and gender differences.

Improve the inclusion of pregnant and lactating women within clinical trials for vaccines, therapeutics, and devices, and encourage further research on already-approved products that have yet to be studied within the pregnant and lactating population.

We acknowledge that clinical research involving women in general remains an urgent need and pregnant and lactating women are an understudied population that stands to benefit greatly from improved access to clinical research. Exclusion of pregnant and lactating women in research has led to significant, unacceptable gaps in women's health and therefore must be an OWH priority when considering sex and gender differences in safety and efficacy of FDA-regulated products.

The Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC),
established in the 21st Century Cures Act, released a report in 2018 recommending improvements to increase inclusion of pregnant and lactating women in clinical research. We encourage the OWH to consider how best to improve the inclusion of pregnant and lactating women in the development and approval process. We recommend coordination

[2] Beery, A, Zucker, I. Sex bias in neuroscience and biomedical research. Neurosci Biobehav Rev. 2010;35(3):565-572.
[3] Woitowich, NC, Beery, A, Woodruff, T. Meta-research: A 10-year follow-up study of sex inclusion in the biological sciences. *eLife.* 2020;9:e56344. doi: 10.7554/eLife.56344

with PRGLAC and implementation of its recommendations to remove regulatory barriers to research in pregnant and lactating women.

Achieving both maternal and paternal consent for trials during pregnancy is not only challenging but can be especially difficult for some people who do not live in traditional family units. While regulatory changes have created potential opportunities for inclusion of pregnant and lactating women in clinical research – there remain barriers that the FDA OWH should study and address in collaboration with National Institutes of Health's Office of Research on Women's Health and other agency partners.

In line with PRGLAC's 2018 recommendations,[4] we encourage the FDA OWH to lead both inter- and intra-agency conversations that highlight the importance of research in pregnant women and lactating women, including the impact of not taking medication during pregnancy and lactation as well as the impact of not breastfeeding on both mother and child. We look forward to PRGLAC's upcoming report that will detail implementation recommendations and are hopeful the FDA will take the full body of PRGLAC's important work into consideration.

Generate research and programming topics, interests, and areas of focus that predominantly affect women and/or would benefit from sex- and gender-related analyses.

Across areas of women's health, there exist an array of endocrine disorders that would benefit from improved screening and diagnostic technology as well as improved treatment options. For example, for women confronting the possibility of an ovarian cancer diagnosis, certain diagnostic tests have not been modernized since the 1980s, leading to diagnostic ovarectomy and resultant iatrogenic infertility in women who are then determined to not have cancer.[5] Many other endocrine cancers would similarly benefit from validated biomarkers to confirm the presence of disease and aid in risk stratification for men and women.[6] Some disorders, like polycystic ovary syndrome (PCOS), have no official diagnostic tests, despite affecting 6-12% of US women of reproductive age.[7]

We encourage the FDA OWH to identify and prioritize health conditions where there may be a need for innovation with regard to diagnosis and/or treatment of women's health-specific conditions as well as conditions that predominantly affect women. Encouraging

[4] PRGLAC report to the HHS Secretary and Congress (2018). Accessed from: https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations

[5] Laitner, M. (2020). New screening and diagnostic technologies could pave the way for improvements in women's health. Accessed from: https://swhr.org/new-screening-and-diagnostic-technologies-could-pave-the-way-for-improvements-in-womens-health/

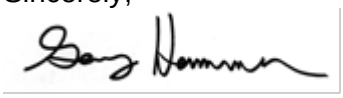
[6] Luo, Y, Zhu, H, Tan, T, He, J. (2018) Current Standards and Recent Advances in Biomarkers of Major Endocrine Tumors. Accessed from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6139354/

[7] CDC - PCOS (Polycystic Ovary Syndrome) and Diabetes. Accessed from: https://www.cdc.gov/diabetes/basics/pcos.html.

research and development in these areas and bringing public attention both the health conditions as well as the potential innovations will benefit the health of women.

In conclusion, we thank the FDA's Office of Women's Health for its continued work on women's health and for integrating SABV into the FDA's research design, analysis, and reporting. Thank you for considering the Endocrine Society's comments. If we can be of further assistance, please contact Grace Kranstover, Manager of Government Relegations & Grassroots Advocacy, at gkranstover@endocrine.org.

Sincerely,



Gary D. Hammer, MD, PhD
President
Endocrine Society