Society for Women's Health Research

July 8, 2019

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

Amy Abernethy, MD, PhD
Principal Deputy Commissioner
U.S. Food and Drug Administration

Re: Docket No. FDA-2018-4693 for "Postapproval Pregnancy Safety Studies Guidance for Industry"

Dear Dr. Abernethy:

The Society for Women's Health Research (SWHR) commends the Food and Drug Administration (FDA) for issuing draft guidance with recommendations to sponsors and investigators on the design of pregnancy safety studies.

SWHR, an education and advocacy nonprofit dedicated to promoting research on biological differences in disease and improving women's health through science, policy, and education, is pleased to provide these comments. SWHR strongly supports well-designed clinical research that is inclusive of pregnant women, including studies to evaluate safety data on drugs and biological products in pregnant women, where significant gaps persist.

The lack of evidence for clinical decision-making concerning medication use during pregnancy is an important public health issue that must be addressed.

Each year, more than 6 million pregnancies occur[1] and nearly 4 million women give birth.[2] Women get sick during pregnancy, and sick women get pregnant.[3] Nearly 94% of pregnant women take at least one prescription or over-the-counter medication during pregnancy;[4] more than 50% of pregnant women take four or more prescription or over-the-counter medications during pregnancy.[5]

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Despite these profound statistics, there is a paucity of human data on drug safety and efficacy in pregnant women.

Limited animal studies of drug interactions in pregnancy are often all the information medical professionals have prior to prescribing an FDA-approved drug for pregnant women. When a pregnant woman needs a therapeutic because of chronic disease, diagnosis of a new disease, or an accident, both she and her health care provider are largely blind as to the effect therapeutics could have on the fetus or the pregnancy. Because drug labeling information for pregnant women is limited, if it exists at all, women and their health care providers are often reluctant to continue to treat disease. This is especially troubling given the increasing global prevalence of chronic disease and the increasing number of women who are entering pregnancy with pre-diagnosed illnesses associated with medication usage.[6]

Exclusion of pregnant women in research has led to significant gaps in scientific information, and as a result, health care providers are uncertain about whether to prescribe needed medications.

In many instances, this uncertainty has resulted in ill-informed decisions and suboptimal care for pregnant patients with an illness.[7] Further, without the availability of reliable information, women who are pregnant may decide to stop taking drugs, even though this may not be the best health option for the woman or fetus.

SWHR urges FDA to reiterate the importance of consideration of all possible study designs to determine the best approach to answer the research question of interest.

SWHR agrees that "pregnancy registries remain an important tool for safety data collection in the postmarketing setting because of the prospective design and the ability to collect detailed patient level data. However, because of the recurring challenges of achieving sufficient enrollment, pregnancy registries are *not sufficient by themselves* to assess the safety of products during pregnancy" (lines 83-87).

SWHR is supportive of the three general approaches that FDA recommends and discusses in the draft guidance: pharmacovigilance, pregnancy registries, and complementary data sources. Further, we agree that "each approach may uniquely contribute to the overall safety assessment of a product during pregnancy" (lines 97-98). However, despite this contextual framing, FDA's draft guidance focuses predominantly on pregnancy registries.

Toward that end, SWHR supports the use of complementary approaches that can provide sponsors and researchers with other options to study a given research question. With any specific study design, there are inherent limitations. Use of complementary approaches present opportunities to address study design limitations as well as provide greater confidence in study conclusions (lines 90-91). A broad array of approaches that seek to capture real-world evidence derived from data collected during routine health care practice (such as electronic health records, claims and billing activities, and disease registries) should be considered and used when appropriate.

FDA guidance should expand upon how FDA, sponsors, clinical research organizations, and study sites can overcome study recruitment and retention barriers.

Representation of pregnant women in clinical research cannot occur without successful recruitment and retention strategies. SWHR appreciates FDA addressing this important issue in the draft guidance (IV. Pregnancy Registries, B. Registry Design Considerations, 13. Recruitment and Retention Plans). However, the concepts and considerations discussed in the draft guidance are not unique to pregnancy registries and apply to other types of clinical research and surveillance programs studying pregnant populations. SWHR encourages FDA to clarify this point in the final guidance.

Lines 495-528 of the guidance outline three recruitment strategies: facility-based, health care provider-initiated, and patient-initiated. Multiple medical disciplines, including the field of obstetrics, have acknowledged challenges in the recruitment of pregnant women in clinical trials, and researchers are capitalizing on their real-world experiences to examine unsuccessful and successful recruitment approaches to improve their recruitment efforts. For example, researchers from the Pennington Biomedical Research at Louisiana State University examined their "failure to recruit a healthy population of overweight and obese pregnant women in their first trimester."[8] With guidance from a survey they disseminated to improve their understanding of women's feelings about participating in research while pregnant, they uncovered "lessons learned" that taught them that *active recruitment within its population* (i.e., direct, face-to-face discussions at obstetric appointments) versus *passive recruitment* (i.e. indirect flyers and general emails) is vital to an individual's willingness to participate.

Another recent publication identifies critical barriers and facilitators to recruitment and retention of pregnant women in clinical research trials and proposes sampling and recruitment methods that make broader use of prenatal providers and general practitioners, who are the first point of contact into the health care system for most pregnant women, and therefore can be strong allies and advocates for study enrollment.[9]

SWHR encourages FDA to include in the final guidance more detailed discussion about novel approaches and best practices to overcome challenges to recruitment and retention of pregnant women.

GENERAL COMMENTS

Real-World Evidence Sources about Pregnancy

Data collection can take many forms. Innovative research projects, like PregSource, launched by the National Institutes of Health (NIH), are creating new opportunities and platforms for women to share information about their pregnancy and overall health. For example, pregnant women can use the PregSource website to:

- Track their weight, mood, sleep, diet and physical activity.
- Share health updates with their health care providers.

- Compare their experiences with other pregnant women across the nation.
- Get expert health information from trusted sources.

While this research project is not evaluating any medical treatments, it is fostering the collection of RWE about pregnancy (including medications taken during pregnancy) directly from pregnant women. ***As discussed above, SWHR strongly supports RWE sources like PregSource that have the potential to generate valuable information for a range of applications, including informing clinical trial and observational study design, monitoring post-market safety, and substantiating coverage decisions.***

HHS Inter-Agency Initiatives on Research in Pregnant Women

The 21st Century Cures Act sought to help address the significant gap in research on safe and effective therapies in pregnant women and lactating women by requiring NIH to establish a Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC), which provided recommendations in September 2018 report to the secretary of the Department of Health and Human Services (HHS) and Congress. In March 2019, HHS extended the term of the PRGLAC Task Force for two additional years to provide guidance to HHS on the implementation of the report's recommendations. Task Force membership consists of the heads of NIH and other national research agencies and institutes, the Office of the FDA Commissioner, and representatives from medical societies, industry, nonprofit organizations, and others with expertise on pregnant women, lactating women, or children. ***SWHR strongly supports HHS interagency collaboration to advance concurrent work to address gaps in research on medication use by pregnant women.***

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Thank you for providing SWHR this opportunity to comment on FDA-2018-4693 and for consideration of the above comments. We look forward to serving as a resource on this and other topics affecting women's health. If you have questions, please contact me or Sarah Wells Kocsis, Vice President of Public Policy, at 202.496.5003 or swellskocsis@swhr.org.

Sincerely,

Amy M. Miller

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

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[2] Martin et al. National Vital Statistics Report. 2017 Jan 5;66(1).
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[6] Clemow et al. *Therapeutic Innovation & Regulatory Science* 2015. doi 10.1177/216847901552373.
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[9] Frew, P et al. Recruitment and Retention of Pregnant Women into Clinical Research Trials: An Overview of Challenges, Facilitators, and Best Practices. *Clinical Infectious Diseases*. 2014 Dec15; 59(Suppl 7): S400-S407. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4303058/