June 8, 2018

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

Scott Gottlieb, MD
Commissioner
U.S. Food and Drug Administration

Re: Docket No. FDA-2018-D-1201 for "Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials; Draft Guidance; Availability"

Dear Dr. Gottlieb:

The Society for Women's Health Research (SWHR®) commends the Food and Drug Administration (FDA) for issuing draft guidance that represents the agency's recommendations and current thinking regarding the inclusion of pregnant women in clinical trials for drugs and therapeutic biological products.

SWHR is a nonprofit organization based in Washington, DC, that is widely recognized as a national thought leader in promoting research on biological differences in disease and eliminating imbalances in care for women through science, policy, and education. SWHR strongly supports the inclusion of pregnant and breastfeeding women in research. The lack of evidence-based decision-making concerning medication use and pregnancy is an important public health issue, and SWHR is pleased to provide comments on this topic.

RATIONALE FOR INCLUSION OF PREGNANT AND LACTATING WOMEN IN CLINICAL TRIALS

Each year, nearly 4 million women give birth and more than 3 million breastfeed.[1,2] Pregnant and lactating women get sick, and sick women get pregnant.[3] Nearly 94% of pregnant women take at least one prescription or over-the-counter medication during pregnancy.[4] Over 50% of pregnant women take four or more prescriptions 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 and lactating 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 or lactating woman needs a therapeutic because of chronic disease, diagnosis of a new disease, or an accident, both she and her physician are largely blind as to the effect therapeutics could have on the fetus, the pregnancy, or the breast milk. Because drug labeling information for pregnant and breastfeeding women is limited, if it exists at all, women and their physicians 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 morbidities associated with medication usage.[6]

Exclusion of pregnant women in research has led to significant gaps in scientific information, which have made health care providers uncertain about whether to prescribe needed medications. In many instances, this uncertainty has resulted in ill-informed decisions and suboptimal care for pregnant or breastfeeding patients with an illness.[7] Further, without the availability of reliable information, women who are pregnant or nursing may decide to stop taking drugs or stop breastfeeding, even though this may not be the best health option for the woman, fetus, or baby.

In 1979, FDA established five letter risk categories — A, B, C, D, or X — to indicate the potential of a drug to cause birth defects if used during pregnancy. The categories did not take into account risks from pharmaceutical agents or their metabolites in breast milk.[8] In 2015, FDA took the important step of replacing the risk letter categories with narrative sections and subsections to include pregnancy, lactation, and females and males of reproductive potential to allow for informed decision-making for women seeking medical therapies.[9]

Because the timeline for implementing this new information on drug labels has been variable, some package inserts (PIs) still include the former pregnancy categories. For example, PIs for certain migraine therapies have Category B or C designations, meaning there is a lack of human research regarding whether these treatments are safe during pregnancy and lactation.[10,11,12,13] Triptans, the most common pharmacological treatment for migraine, are currently not recommended during pregnancy, although preliminary research has indicated they are safe.[14,15]

Due to widespread use of opioids for pain treatment, a large amount of data exists regarding opioid use during pregnancy.[16,17] The availability of this data, however, could influence health care providers to recommend opioids over triptans for migraine treatment for women who are pregnant or lactating even though this may not be the best option. Instead, transitioning from prescribing opioids to triptans, as well as incorporating other available treatment options, may be safer and more effective for pregnant or lactating women with migraine.

Similarly, data is limited on pregnant and lactating women and narcolepsy, which can affect decisions on family planning. Studies show that most clinicians have advised women with narcolepsy to discontinue their medications while pregnant and breastfeeding.[18,19] Pregnant

women with narcolepsy (the majority of whom are not on medication) are more likely to be older when they get pregnant and more likely to have pregnancy-related complications such as anemia, impaired glucose metabolism, and excess weight gain during pregnancy.[20] Further, symptoms of narcolepsy can adversely affect neonatal care. More research on the safety and efficacy of narcolepsy drugs used by women during pregnancy and while breastfeeding may provide better guidance for clinicians and patients on management of the disease during this time. In addition to addressing research gaps in pregnant and lactating women as the examples above demonstrate, there is a need for dissemination of known research findings.

SWHR seeks clarification from the FDA as to whether this draft guidance applies to breastfeeding women. The rationale for considering the inclusion of breastfeeding women is similar to the reasons stated in the draft guidance for considering the inclusion of pregnant women in clinical trials (lines 97-106), all of which SWHR supports:

- *Women need safe and effective treatment during pregnancy.*
- *Failure to establish the dose/dosing regimen, safety, and efficacy of treatments during pregnancy may compromise the health of women and their fetuses.*
- *In some settings, enrollment of pregnant women in clinical trials may offer the possibility of direct benefit to the woman and/or fetus that is unavailable outside the research setting.*
- *Development of accessible treatment options for the pregnant population is a significant public health issue.*

If the draft guidance does not apply to breastfeeding women, we ask the agency to clarify its intent and plans to issue separate guidance addressing this population.

ETHICAL CONSIDERATIONS FOR INCLUSION OF PREGNANT WOMEN IN CLINICAL TRIALS

The ethical (and corresponding legal) considerations involved in designing clinical trials that include pregnant (and breastfeeding) women are complex and we applaud FDA for making them a central issue in this draft guidance.

If implemented, FDA regulatory recommendations would place a significant burden on the inclusion of pregnant women in research. FDA recommends that the same requirements under 45 CFR part 46, subpart B be satisfied for FDA-regulated clinical research, even though current FDA regulations do not contain a section similar to subpart B (lines 137-146). The recommendation that pregnant women or fetuses be involved in research only if all of the following 10 conditions (lines 148-181) are met places too high of a threshold on the inclusion of pregnant women in research:

1. Where scientifically appropriate, nonclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses;
2. The risk to a fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or if there is no such prospect of

benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;
3. Any risk is the least possible for achieving the objectives of the research;
4. The pregnant woman's consent is obtained in accord with the informed provisions of 45 CFR part 46, subpart A;
5. If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of 45 CFR part 46, subpart A, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest;
6. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate;
7. For children defined in § 46.402(a) who are pregnant, assent and permission are obtained in accord with the provisions of 45 CFR part 46, subpart D.
8. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;
9. Individuals engaged in the research will have no part in any decision as to the timing, method, or procedures used to terminate a pregnancy; and
10. Individuals engaged in the research will have no part in determining the viability of a neonate.

Further review of the above 10 conditions and the feasibility of <u>all of them</u> satisfying FDA-regulated clinical research requirements is necessary. The above 10 conditions are "subject to much interpretation, difference of opinion, and are typically determined very conservatively by institutional review boards … and are inconsistently applied across the states within the U.S."[21] Examples of FDA-regulated clinical trials in pregnant women that have met all of the 10 conditions provide valuable information to research stakeholders, and ***we encourage FDA to include these examples in the final guidance.***

SWHR has particular concerns about the parental consent condition (Condition 5 above; lines 163-167). Parental consent from the father [or domestic partner] should not be required. In pediatric studies where there is a prospect of direct benefit for the child, only one parent is required to give consent, and this HHS requirement should be consistent for FDA-regulated clinical studies in pregnant women.

Here is relevant excerpted text from HHS Regulatory Requirements for Research Involving Children[22]:

> *Permission from parent(s) or guardian(s) must be obtained prior to enrolling a child in research. This permission must meet the requirements for informed consent found in 46.116.*
> - *The permission of one parent may be sufficient for research to be conducted under 46.404 or 46.405.*
> - *Where research is covered by 46.406 and 46.407 and permission is to be obtained by parents, both parents must give their permission unless:*

- *One parent is deceased, unknown, incompetent, or not reasonably available; or*
- *Only one parent has legal responsibility for the care and custody of the child. (46.408(b))*

We encourage FDA to consider revising Condition 5 so that it is consistent with the above HHS regulatory requirements for research involving children.

SWHR agrees with institutional review board (IRB) professional competency requirements (lines 183-195). Those knowledgeable about research involving pregnant and breastfeeding women and experienced in working with them as research subjects should sit on IRB committees that regularly review this kind of research.

SWHR agrees with FDA's guidance surrounding women who become pregnant while enrolled in a clinical trial (lines 293-307). Should a woman become pregnant while enrolled in a clinical study, she should have the opportunity to meet with appropriate researchers responsible for her care and have access to counseling to discuss implications for her and the fetus. SWHR agrees that pregnant women who choose to continue in the clinical study should undergo a second informed consent process that reflects the additional risk-benefit considerations.

The collection and reporting of clinical information is paramount, and SWHR supports collection and reporting of the pregnancy outcome, regardless of whether the woman continues in the trial, as well as the efficacy outcome of the therapeutic under evaluation. This information may be the only clinical information available to women and physicians and therefore is incredibly valuable to address information gaps and reduce uncertainty for health care providers when making clinical care decisions for pregnant and breastfeeding patients.

ADDITIONAL CONSIDERATIONS

Data collection can take many forms. Innovative research projects, like PregSource,[23] recently launched by the National Institutes of Health, 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 real-world evidence (RWE) about pregnancy (including medications taken during pregnancy) directly from pregnant women. SWHR 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.

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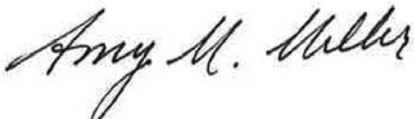
Thank you for providing SWHR this opportunity to comment on Docket No. FDA-2018-D-1201 and for your consideration of the above comments. We look forward to serving as a resource on this important women's health issue. If you have questions, please contact Sarah Wells Kocsis, Vice President of Public Policy, at 202.496.5003 or swellskocsis@swhr.org.

Sincerely,



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

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[1] Martin et al. National Vital Statistics Report. 2017 Jan 5;66(1).
[2] CDC Press Release. August 22, 2016. https://www.cdc.gov/media/releases/2016/p0822-breastfeeding-rates.html
[3] Partnership to Fight Chronic Disease. 2009 Almanac of Chronic Disease. http://www.fightchronicdisease.org/sites/default/files/docs/2009AlmanacofChronicDisease_updated81009.pdf
[4] Mitchell et al. *Am J Obstet Gynecol.* 2011 Jul;205(1):51.e1-8. doi: 10.1016/j.ajog.2011.02.029.
[5] Ibid.
[6] Clemow et al. *Therapeutic Innovation & Regulatory Science* 2015. doi 10.1177/216847901552373.
[7] Ibid.
[8] FDA Pregnancy Categories. Drugs.com. https://www.drugs.com/pregnancy-categories.html
[9] FDA Pregnancy and Lactation Labeling (Drugs) Final Rule https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm
[10] Nezvalová-Henriksen et al. *Eur J Epidemiol.* 2013;28:759-769.
[11] Morgan et al. *J Neurol Neurosurg Psychiatry*. 2006;77:117-119.
[12] Blumenfeld et al. *Headache.* 2013;53:437-446.
[13] Govindappagari et al. *Obstet Gynecol.* 2014;124:1169-1174.
[14] Spielmann et al. *Cephalalgia*. 2017 Jul 31;38(6):1081-1092. doi: 10.1177/0333102417724152.
[15] Loder. *CNS Drugs*. 2003;17:1-7.
[16] Marcus Expert Opin *Pharmacother.* 2002;3:389-393.
[17] Buse et al. *Headache.* 2012;52:18-36.
[18] Maurovich-Horvat et al. *Journal of Sleep Research*. 2013; 22 (5): 496-512.
[19] Thorny et al. *Sleep Medicine.* 2013; 14 (4): 367-376.
[20] Maurovich-Horvat et al. *Journal of Sleep Research*. 2013; 22 (5): 496-512.
[21] Clemow et al. *Therapeutic Innovation & Regulatory Science* 2015. doi 10.1177/216847901552373.
[22] HHS Regulatory Requirements for Research Involving Children Described in Subpart D. https://humansubjects.nih.gov/children1
[23] https://pregsource.nih.gov/