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PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

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Scott Gottlieb, MD
FDA Commissioner
C/o Dockets Management Staff (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

RE: Docket No. FDA-2018-D-1201-0001, *Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials; Draft Guidance; Availability*. (83 Federal Register 15161)

Dear Commissioner Gottlieb:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s draft guidance on Pregnant Women: Scientific and Ethical Considerations for Inclusion in Clinical Trials, published in the *Federal Register* on April 9, 2018.

PRIM&R is a nonprofit organization dedicated to advancing the highest ethical standards in the conduct of research. Since 1974, PRIM&R has served as a professional home and trusted thought leader for the research protections community, in particular, members and staff of human research protection programs and institutional review boards (IRBs). Through educational programming, professional development opportunities, and public policy initiatives, PRIM&R seeks to ensure that all stakeholders in the research enterprise understand the central importance of ethics to the advancement of science.

PRIM&R applauds the FDA for taking this important step to fill current regulatory gaps around the inclusion of pregnant women in FDA-regulated research. Ethical considerations of justice, respect, and beneficence demand that pregnant women who are or may become sick, or sick women who may become pregnant, share in the benefits of clinical trials, namely, access to safe and effective medications. The guidance's support of "judicious inclusion" of pregnant women in clinical trials is a significant step forward.

It is now widely recognized that "informed and balanced" inclusion of pregnant women in research of the sort the guidance supports

provides invaluable opportunities for the collection of data about how investigational drugs and biological products may affect both pregnant women and fetuses, data that will help fill existing knowledge gaps regarding safe and effective treatments for pregnant women. (Below, we follow the guidance in referring primarily to "investigational drugs," though just as the guidance covers both drugs and biologics (per footnote 2), we intend this to serve as shorthand for both types of investigational products.) We therefore welcome the guidance's focus on the collection of such data and appropriate ways to do so. At the same time, we appreciate that the guidance thoughtfully acknowledges and considers the tension between the need for more information about how to appropriately treat pregnant women and the ethical and scientific complexity involved in including women who are pregnant in clinical trials.

The guidance also appropriately focuses on the risk-benefit considerations involved in enrolling pregnant women in clinical trials, making clear that in some cases, it may be riskier for a pregnant woman not to enroll in a trial than to enroll, for instance, when there are no currently available treatment options for her condition. This is a welcome sign of progress beyond the view that pregnant women are particularly vulnerable to, and must first and foremost be protected from, the risks of research.

We also have a few suggestions for the FDA to consider. First, we recommend amending the title of the guidance document to make clear that this guidance is not only for industry but also for the IRBs who review and ethically oversee such research.

Second, in section III.C of the guidance, titled "General Guidelines for Including Pregnant Women in Clinical Trials," we note there are listed only two conditions under which it is ethically justifiable to include pregnant women with a disease or medical condition in premarketing studies of investigational drugs: (1) when adequate nonclinical studies have been completed, and (2) when "the clinical trial holds out the prospect of direct benefit to the pregnant woman and/or fetus that is not otherwise available outside the research setting or cannot be obtained by any other means." This language seems more restrictive than the corresponding language of 45 CFR 46 Subpart B that the current guidance recommends for FDA-regulated clinical research. For instance, Subpart B includes the following as one of 10 conditions that must be met for acceptable inclusion of pregnant women in research: "The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit to 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*" (emphasis added). If someone were to look only at section III.C of this guidance for the FDA's view about the inclusion of women, he or she would think it was unacceptable to conduct minimal risk research that holds out no prospect of direct benefit to the pregnant woman or her fetus but could lead to important biomedical knowledge for other pregnant women with the disease or condition in question in the future. We urge the FDA to revisit Section III.C to ensure it is not inadvertently limiting the inclusion of pregnant women in investigational drug studies in ways that are at odds with the spirit or letter of the rest of the guidance.

Third, and in this same section, we recommend the FDA add or acknowledge a third clinical trial "setting" that sits somewhere between pre- and postmarketing settings and may include pregnant women but be subject to different considerations: the testing of new indications for drugs that are already on the market, where there may be data from prior indications that could be used to inform the current study.

Fourth, we think the guidance could provide more detail about what ought to happen when women become pregnant during the course of a clinical trial. We endorse the general recommendation that women who become pregnant while enrolled in clinical trials should not automatically be unenrolled, but rather that decisions about continuing on the trial should wait until the risks and the benefits of leaving or staying in the trial are appropriately assessed. With respect to blinded trials, the guidance suggests that whenever a woman becomes pregnant during a clinical trial, unblinding should occur. While unblinding may typically be the best course of action, especially if continuing in the trial entails new or different risk-benefit considerations, the guidance document should clarify that decisions to unblind—and what those decisions entail regarding remaining in the trial versus continuing to receive the investigational treatment outside of the trial—will be complex. The guidance should furthermore make clear that such decisions will typically involve ethics oversight bodies (e.g., IRBs, DSMBs), the pregnant woman, and some combination of the sponsor and/or the investigator(s), and will necessarily take into account a host of considerations about the drug or biological product in question, the disease, the research subject, the status of the pregnancy, and the like.

We endorse the guidance's recommendation that one outcome of such decisions might be to allow a pregnant woman to continue on the investigational drug outside of the trial, but urge the FDA to clarify that, as in the case of continuing on the trial unblinded, here, too, the woman should undergo a separate informed consent process, which should make clear that researchers will continue to collect data and follow pregnancy outcomes related to the investigational drug. Lastly on this point, we suggest the guidance note that whether or not unblinding will occur if a subject becomes pregnant is a matter that should be discussed before the trial begins and be included in the protocol and the initial consent process.

Finally, we point out that the requirement under 21 CFR 56.111 that IRBs determine whether "additional safeguards" to protect the rights and welfare of pregnant women have been included in the trial protocol, which is referenced in the draft guidance, may soon disappear. The pending revisions to the Common Rule remove pregnant women from the list of vulnerable populations requiring such additional protections. Given the 21st Century Cures Act requirement that FDA harmonize its regulations with the revised Common Rule, reference to this requirement in the guidance will, we presume, soon be obsolete.

Ultimately, we believe this new guidance document will be of great benefit to industry, oversight bodies, and research subjects, and we encourage the FDA to issue additional,

similar guidance on two related topics: research with lactating women and device research in pregnant women.

Thank you again for the opportunity to comment on this important guidance. My PRIM&R colleagues and I are available to discuss our recommendations, should that be of interest. Please feel free to contact me at 617.303.1872 or ehurley@primr.org.

Respectfully submitted,

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Executive Director

cc: PRIM&R Public Policy Committee, PRIM&R Board of Directors