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PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

May 13, 2019 Submitted electronically at www.regulations.gov

Norman E. Sharpless, MD
Acting 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RE: Docket No. FDA-2019-D-0358, "Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients; Draft Guidance for Industry" (84 *Federal Register* 9124)

Dear Acting Commissioner Sharpless:

Public Responsibility in Medicine and Research (PRIM&R) appreciates the opportunity to comment on the Food and Drug Administration (FDA)'s Draft Guidance for Industry, "Cancer Clinical Trial Eligibility Criteria: Minimum Age for Pediatric Patients," published in the *Federal Register* March 13, 2019.

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, including members and staff of human research protection programs and institutional review boards (IRBs), investigators, and their institutions. 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.

We applaud the FDA for their ongoing work to enhance clinical trial access for younger patients. As we previously noted in our comments on the FDA's draft guidance document "Considerations for Inclusion of Adolescents in Adult Clinical Trials," we agree with the need to design cancer clinical trials, where possible, to include pediatric patients, in the interest of learning sooner than we do currently about the dosing, safety, efficacy, and long-term effects of potential cancer treatments in these populations.

With respect to this guidance, specifically, **we especially appreciate the level of detail provided on lines 119-147 regarding the types of evidence, including from prior pediatric trials, preclinical trials, and adults trials, that could support including pediatric patients in adult clinical trials**. As far as we are aware, this is the first time the FDA has provided such details, which will be invaluable to sponsors, investigators, and IRBs as they make the required determination whether enrollment in the study provides the prospect of direct clinical benefit to a pediatric subject. We note that this language regarding what data the FDA believes can be used to support the prospect of direct benefit is consistent with recommendations made by the Secretary's Advisory Committee on Human Research Protections in July 2005.

However, we suggest that the FDA clarify what is meant in lines 62 to 63 by the sentence, "In some cases, separate pediatric trials may have been infeasible because the disease occurs so rarely in pediatric patients." There are at least two, and possibly more, ways to interpret "infeasible" in this sentence, which can lead to drastically different lines of discussion. First, it may be interpreted as meaning "operationally and/or logistically infeasible," in which case inclusion of a small group of pediatric patients in an adult trial could address the infeasibility, thereby allowing pediatric patients who may have no other treatment options to receive the experimental therapy and enabling the collection of data that may inform pediatric labeling. Alternatively, "infeasible" might be interpreted as meaning "scientifically infeasible." If the pediatric population with the disease in question is too small to support a scientifically sound pediatric trial, it raises the question of whether and when including a cohort of that very small pediatric population in an adult trial will allow for the collection of adequate data to draw conclusions about dosing, safety, and efficacy in that population.

In the first instance, inclusion of pediatric patients in an adult oncology clinical trial might be justified, so long as their inclusion resulted in pediatric data that could, by itself or in combination with other data, either from the same trial or other trials, support pediatric labeling regarding dosing, safety, and/or efficacy. In the second circumstance, inclusion of pediatric patients in an adult oncology clinical trial would likely not be justified, as it appears it would be inconsistent with arguments the FDA has provided in lines 63 through 68 regarding how design of adult trials to include pediatric patients can provide information for labeling that promotes safe and effective use of products in pediatric populations. While it appears the FDA means "operationally and/or logistically infeasible" in lines 62 to 63, this is not entirely clear from the text of the guidance. PRIM&R encourages the FDA to clarify which of these two senses of "infeasible" (or another) it means.

PRIM&R also recommends that the FDA encourage sponsors pursuing adult oncology clinical trials that include pediatric patients to describe in protocols how the pediatric data obtained will be used to support pediatric labeling, whether by itself or in combination with other data (including, if appropriate, data from other clinical trials and from adults). While the FDA may be privy to such methods of using pediatric data based on their discussions with sponsors of pediatric study plans (PSPs) and/or proposed pediatric study requests (PPSRs), IRBs are dependent on the protocol, the investigator's

brochure, proposed informed consent and sometimes assent forms, and whatever other materials the sponsor provides. These materials often do not include information on modeling and simulation of pharmacokinetics and dosing, extrapolation of efficacy from one population to another (including adults to children), and other analyses that often involve data from more than one trial and/or from pediatric and adult patients. This puts IRBs in the awkward and challenging position of trying to review and approve a protocol involving adults and pediatric patients without having the necessary information to do so. The FDA would provide both sponsors and IRBs a substantial benefit by addressing this situation in this guidance.

Thank you again for the opportunity to comment on this important issue. My PRIM&R colleagues and I are available to discuss our comments further, 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