AMERICAN SOCIETY OF HEMATOLOGY
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June 22, 2018

John Leighton, PhD
Haleh Saber, PhD
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: Docket No. FDA-2018-D-1328: *Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals; Draft Guidance for Industry; Availability*

Dear Drs. Leighton and Saber,

The American Society of Hematology (ASH) appreciates the opportunity to submit comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's Draft Guidance for Industry: *Severely Debilitating or Life-Threatening Hematologic Disorders (SDLTHDs): Nonclinical Development of Pharmaceuticals* as published in the Federal Register (FDA-2018-D-1328) on April 24, 2018.

ASH represents over 17,000 clinicians and scientists worldwide who are committed to the study and treatment of blood and blood-related diseases. These disorders encompass malignant hematologic disorders such as leukemia, lymphoma, and multiple myeloma, as well as non-malignant conditions such as sickle cell disease (SCD), thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists are pioneers in demonstrating the potential of treating various hematologic diseases through the transplantation of bone marrow stem cells and continue to be innovators in the fields of stem cell biology, regenerative medicine, transfusion medicine, and gene therapy. ASH members include clinicians who regularly render services to patients with SDLTHDs, as well as scientists who conduct research aimed at understanding these diseases.

ASH commends the FDA for releasing a draft guidance that will help facilitate the use of pre-clinical data to inform the development of pharmaceutical products used to treat non-oncology patients with SDLTHDs. ASH supports the overall provisions outlined in the draft guidance and recommends that the Agency consider additional guidance on preclinical studies focused on understanding combination therapies in the pediatric population, as well as preclinical models aimed at enhancing the safety and efficacy profiles of immune-based therapies in humans. The Society also encourages the FDA to consider making the following changes to help strengthen the guidance document.

Recommendation 1:
ASH urges the addition of "sickle cell disease" or "hemoglobinopathies" to the list of diseases on page 2, beginning on line 53. The Society recognizes that the list cannot be comprehensive, but SCD and other hemoglobinopathies are quite common relative to some of the diseases outlined. ASH believes that the high incidence of chronic pain, end organ damage, and early mortality for individuals with SCD, make the disease qualify as a "severely debilitating" disease. Additionally, individuals with beta thalassemia, another type of hemoglobinopathy, experience complications that also make this disease qualify as "severely debilitating." These complications include fatigue, splenomegaly, gallstones, heart failure, hepatic cirrhosis, diabetes, osteoporosis, and pulmonary hypertension, plus early mortality.

Recommendation 2:
ASH encourages the FDA to modify the *First-in-Human Dose and Dose Escalation* section to base trial eligibility criteria on known pharmacokinetic and toxicology data, which could help expand the patient population eligible for these studies. As currently written, the guidance may allow trials to only enroll a small patient population. A number of studies, including those referenced below, show that eligibility criteria are often arbitrary and have little connection to known drug toxicities.

- *Comparable Outcomes of Patients Eligible versus Ineligible for SWOG Leukemia Studies.* Statler A, Othus M, Erba HP, Chauncey TR, Radich JP, Coutre S, Advani A, Nand S, Ravandi F, Mukherjee S, Sekeres MA. Blood. 2018 Apr 4.

- *The relationship between eligibility criteria and adverse events in randomized controlled trials of hematologic malignancies.* Statler A, Radivoyevitch T, Siebenaller C, Gerds AT, Kalaycio M, Kodish E, Mukherjee S, Cheng C, Sekeres MA. Leukemia. 2017 Aug;31(8):1808-1815. doi: 10.1038/leu.2016.374. Epub 2016 Dec 7.

Thank you for your consideration of ASH's comments and recommendations. The Society looks forward to continuing to work with you to ensure patient access to safe and effective treatments for hematologic diseases. Please contact ASH Senior Manager, Government Relations and Public Health, Stephanie Kaplan (*skaplan@hematology.org* or 202-776-0544), if we can provide additional information or expertise.

Sincerely,

Alexis Thompson, MD, MPH
President