



# AMERICAN SOCIETY OF HEMATOLOGY

2021 L Street, NW, Suite 900, Washington, DC 20036 **ph** 202.776.0544 **fax** 202.776.0545 **e-mail** ASH@hematology.org

## 2018

### President

Alexis Thompson, MD, MPH  
Ann & Robert H. Lurie Children's Hospital of Chicago  
225 E. Chicago Avenue  
Box #30  
Chicago, IL 60611  
phone 312-227-4834  
a-thompson@northwestern.edu

### President-Elect

Roy L. Silverstein, MD  
Medical College of Wisconsin  
Clinical Cancer Center  
9200 W. Wascosin Avenue  
Milwaukee, WI 53226  
phone 414-805-0518  
rsilverstein@mcw.edu

### Vice President

Stephanie Lee, MD, MPH  
Fred Hutchinson Cancer Research Center  
1100 Fairview Avenue N, D5-290  
PO Box 19024  
Seattle, WA 98109  
phone 206-667-5160  
sjlee@fhcrc.org

### Secretary

Robert A. Brodsky, MD  
Johns Hopkins University  
Ross Building, Room 1025  
720 Rutland Avenue  
Baltimore, MD 21205  
phone 410-502-2546  
brodsro@jhmi.edu

### Treasurer

Susan Shurin, MD  
222 Quince Street  
Unit 2C  
San Diego, CA 92103  
phone 240-328-8542  
shurinsb@mail.nih.gov

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### Executive Director

Martha Liggett, Esq.  
mliggett@hematology.org

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*Severely Debilitating or Life-Threatening Hematologic Disorders: Nonclinical Development of Pharmaceuticals; Draft Guidance for Industry; Availability*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the opportunity to submit comments to the U.S. Food and Drug Administration (FDA) in response to the Agency's Draft Guidance for Industry: *Severely Debilitating or Life-Threatening Hematologic Disorders (SDLTHDs): Nonclinical Development of Pharmaceuticals* as published in the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](mailto:skaplan@hematology.org) or 202-776-0544), if we can provide additional information or expertise.

Sincerely,



Alexis Thompson, MD, MPH  
President