



AMERICAN SOCIETY OF HEMATOLOGY

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March 28, 2018

Peter Marks, MD, PhD
Director
Center for Biologics Education and Research
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Docket No. 2017-P-0867 (<https://www.regulations.gov/docket?D=FDA-2017-P-0867>)

Dear Dr. Marks,

The American Society of Hematology (ASH) appreciates the opportunity to comment on docket number 2017-P-0857, regarding requests that the U.S. Food and Drug Administration (FDA) immediately require the removal of hydroxyethyl starch (HES) intravenous (IV) solutions from the U.S. market. Requests for removal of this product from the market are based on a complaint from Public Citizen which is referenced in the docket. The American Society of Hematology opposes this proposed action, as the removal would have a major impact on patients with hematologic conditions.

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 anemia, thalassemia, bone marrow failure, venous thromboembolism, and hemophilia. In addition, hematologists were pioneers in demonstrating the potential of treating various hematologic diseases through bone marrow transplantation, and continue to be innovators in the fields of gene and cellular therapy, regenerative medicine, and transfusion medicine. ASH membership is comprised of basic, translational, and clinical scientists, as well as physicians who provide care to patients in diverse settings including teaching and community hospitals, as well as private practice.

HES solutions met the extant regulatory requirements for approval when originally submitted; however, following approval, extensive literature regarding the lack of efficacy for resuscitation indications, and the association with adverse clinical outcomes resulted in “black box” warnings in the prescribing information. This makes the Agency’s continuing review of the use HES solutions in those particular indications necessary and appropriate. The broad case made for removal of the product from the market, however, does not recognize other uses for HES, where available data do not suggest problems.

In hematology, HES solutions are used for hematopoietic cell transplants (HCT), a procedure that is commonly done for patients who have major blood cancers such as leukemias, lymphomas, and myeloma as well as non-malignant mood disorders such as sickle cell disease, thalassemias and aplastic anemia. Outside of its use as a fluid for resuscitating patients with a life-threatening drop in their blood pressure (that provoked the concerns voiced to the FDA), HES plays an important role in supporting the care of patients with life-threatening diseases who require bone marrow and cord blood cell

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transplants. These types of HCT are frequently performed using donors who are red cell (ABO) incompatible with their recipients. As part of the transplant procedure, donor bone marrow or cord blood cells (the 'graft') are infused intravenously into the recipient. Without red blood cell depletion of the HCT, infusion of the HCT graft would be associated with life-threatening and/or potentially lethal complications in patient care. The use of HES is essential in depleting these products of red blood cells, thus ensuring that the life-saving transplant procedure can be performed safely, effectively, and without unnecessary risks. As such, the Society recommends FDA provide a special consideration for the use of HES for HTC. ASH also agrees with the special considerations noted in the [comment letter](#) submitted by America's Blood Centers, American Red Cross, AABB, and American Society for Apheresis. Those considerations include:

1. The use of HES preparations as sedimenting agents in therapeutic and donor apheresis. These include primarily therapeutic white cell reductions for the treatment of hyperleukocytosis complicating the leukemias and donor granulocyte collections for the treatment and prophylaxis of severe infections complicating granulocytopenia; and,
2. The use of HES for umbilical cord blood, bone marrow and peripheral blood hematopoietic stem cell processing, storage and transplantation.

At this time, ASH opposes a complete rescission of the FDA approvals for HES preparations. ASH encourages the FDA to work with the blood and cellular therapy communities to develop a transition plan that will provide ample time to identify acceptable alternatives and study their use, since the clinical applications can be potentially lifesaving. Additionally, the effectiveness of the current "black box" warnings for preventing its inappropriate use during resuscitation needs to be evaluated.

Thank you for the opportunity to provide these comments. We welcome any discussion on this docket, and other related issues. If you have any questions or require further clarification, please contact Stephanie Kaplan, ASH Senior Manager, Government Relations and Public Health at skaplan@hematology.org or 202-292-0263.

Sincerely,

A handwritten signature in black ink that reads "Alexis Thompson" followed by a long horizontal flourish.

Alexis Thompson, MD, MPH
President