February 6, 2018

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research
US Food and Drug Administration

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

Dear Dr. Marks,

The complaint from Public Citizen referenced in this docket requests removal of hydroxyethyl starch (HES) from the U.S. market. America's Blood Centers, the American Red Cross, AABB and the American Society for Apheresis oppose this. These solutions met the extant regulatory requirements for approval when originally submitted, but the extensive literature on their lack of efficacy for ***resuscitation indications***, and their association with adverse clinical outcomes resulted in "black box" warnings in the prescribing information. This makes the agency's continuing review of their use in those indications appropriate. However, the broad case made for removal of the product from the market ignores, and in fact does not even recognize, other uses for HES, where available data do not suggest problems like those seen associated with resuscitation (see accompanying references).

The following indications require separate consideration:

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;
2. The use of HES for umbilical cord blood, bone marrow and peripheral blood hematopoietic stem cell processing, storage and transplantation.

Apheresis collection of granulocytes for transfusion exposes donors to a relatively small volumes (<500 ml) of HES with few adverse events outside of allergic reactions. The granulocyte products and cellular therapies actually infused contain little HES and are unlikely to have renal effects on the recipient. There are, indeed, insufficient long-term data in such donors, but we are aware that investigators at the Department of Transfusion Medicine of the Clinical Center of the NIH are reviewing their accumulated experience with long-term granulocyte and platelet donors for evidence of adverse effects (particularly renal) from HES (personal communication, Harvey Klein MD, 24 Jan. 2018).

While the evidence base regarding transfusion and cellular therapy uses is not as rigorous as we would like, the observational data are substantial and clinical experience extends over many years. We believe it is likely that the apparent safety of HES seen by the transfusion medicine and cellular therapies communities relates to the use of lower doses than in resuscitation and perhaps the presence of fewer severe contributory comorbidities in most of the donors and patients we expose to HES, compared to the resuscitation population.

HES may accumulate in tissues and chronic and cumulative effects are poorly characterized. Hence, we support developing evidence for clearer guidelines on disclosure of risks from HES to donors as well as on maximum exposure of HES over time. For example, American Red Cross guidelines allow 12 granulocyte donations with HES exposure per year. Since there do not appear to restrictions on the time frame over which those donations occur, is there a need to develop guidelines for a minimum interval?

In the absence of an alternative effective macromolecular RBC-sedimenting agent, our niche uses of HES should be considered when FDA deliberates any changes to its production and marketing in the U.S. Critically, alternative solutions are materially less efficient for donor indications, associated with lower recoveries of the therapeutically targeted cells. We believe that the complete removal of HES from the marketplace is unwarranted.

In conclusion, we oppose a blanket rescission of the FDA approvals for HES preparations at this time. Rather, sufficient time and resources must be allotted to understand data needs to support or refute the (admittedly largely observational) literature and experience responsible for our impression of its safety and efficacy in our "niche" indications. If generating more data is mandatory, time and resources will be required to design and execute further studies. If FDA intends to revoke the approval of HES preparations, the blood and cellular therapies communities will require ample time to identify acceptable alternatives and study their use, since our clinical applications can be potentially lifesaving.

Finally, the effectiveness of the current "black box" warnings for preventing its inappropriate use during resuscitation needs to be evaluated, and if they have effectively curtailed use in resuscitation, much in the Public Citizen petition becomes moot regarding the continued availability of HES in the US.

Thank you for your attention to these issues.

Louis M. Katz MD
Chief Medical Officer
America's Blood Centers
lkatz@americasblood.org

Pampee Young MD, PhD
Chief Medical Officer
American Red Cross
Biomedical Services
Pampee.young@redcross.org

Mary Beth Bassett
President
AABB
president@aabb.org

Laura Collins RN, BSN, HP(ASCP)
President
ASFA
laura-collins@uiowa.edu

ABC is the association of independent, FDA-licensed, not-for-profit community-based blood centers who supply over half of the U.S. blood supply. Many of our centers perform donor and therapeutic apheresis and are involved with the recruitment of stem cell donors, their evaluation and collection of their life saving cells.

The American Red Cross supplies about 40 percent of the nation's blood. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

AABB is an international, not-for-profit association representing individuals and institutions involved in the fields of transfusion medicine and cellular therapies. The association is committed to improving health through the development and delivery of standards, accreditation and educational programs that focus on optimizing patient and donor care and safety. AABB membership includes physicians, nurses, scientists, researchers, administrators, medical technologists and other health care providers. AABB members are located in more than 80 countries and AABB accredits institutions in over 50 countries.

ASFA is an organization of physicians, scientists, and allied health professionals whose mission is to advance apheresis medicine for patients, donors and practitioners through education, evidence-based practice, research and advocacy. ASFA represents a broad range of professionals involved in: donor apheresis, apheresis in transplantation, and therapeutic apheresis.