September 26, 2025

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted via http://www.regulations.gov

Re: **Docket No. FDA-2024-D-5942**, Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen; Draft Guidance for Industry

Dear Dockets Manager:

The Association for the Advancement of Blood and Biotherapies (AABB), America's Blood Centers (ABC), and the American Red Cross (ARC) are pleased to submit joint comments to the U. S. Food and Drug Administration (FDA) in response to the July 2025, draft guidance, Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen; Draft Guidance for Industry.

Our organizations appreciate the opportunity to comment on the Draft Guidance and applaud FDA's ongoing commitment to enhancing the safety of the nation's blood supply. We commend the Center for Biologics Evaluation and Research for its dedication to updating testing requirements based on evidence-based decision making. We have long advocated for the removal of the hepatitis B surface antigen (HBsAg) testing requirement, and the Draft Guidance reflects the key requests outlined in our 2022 Joint Letter to FDA on Hepatitis B Surface Antigen Testing Requirements. We thank FDA for its responsiveness and thoughtful consideration of these requests.

Comment:

We gratefully acknowledge FDA's recommendation that HBsAg testing of donations of blood and blood components intended for transfusion (and by inference, plasma for further

manufacture not labeled as Source Plasma [i.e., Recovered Plasma]) is not necessary when testing for HBV DNA by NAT and anti-HBc using FDA-licensed donor screening tests. However, FDA's perspective that scientific evidence continues to support the required testing of Source Plasma donations for both HBsAg and HBV DNA by NAT significantly limits the application of this Draft Guidance. A large proportion of whole blood-derived plasma is labeled as Recovered Plasma and sent for further manufacture. Not treating all plasma-derived medicinal products (PDMPs) source materials equally creates a regulatory inconsistency for blood collectors and fractionators and contributes to fractionators' unwillingness to accept recovered plasma that has not been tested for HBsAg. Many jurisdictions mandate HBsAg testing of starting materials for PDMPs, while in the U.S., only HBV NAT and anti-HBc testing will be required for Recovered Plasma. Indeed, the CFR permits the use of anti-HBc-reactive / HBV NAT-negative Recovered Plasma in the manufacture of PDMPs, effectively requiring a negative HBV NAT as the sole requirement for Recovered Plasma in the U.S.

Based upon HBV NAT testing of plasma intended for fractionation and the extensively validated virus reduction steps via inactivation and removal embedded into the manufacturing processes of PDMPs, HBsAg testing should no longer be required for either Source Plasma or Recovered Plasma in the U.S. as well as internationally. Nor as FDA notes in its Draft Guidance is there a need for Source Plasma to undergo anti-HBc testing. However, for transfusable blood products not undergoing viral inactivation, requiring anti-HBc testing in addition to HBV NAT is necessary to reduce adequately and appropriately HBV transmission risk.

The presence of HBsAg in the absence of HBV DNA in an HBV-infected individual is not inherently different between donors of Source Plasma and transfusable whole blood used to produce Recovered Plasma; this is a function of the virus and not the individual. High levels of HBsAg are produced during the later stages of HBV infection when little infectious virus is produced and the ratio of free HBsAg to infectious particles is extremely high. In the absence of anti-HBc testing, some Source Plasma candidates chronically infected with HBV who would have HBsAg / anti-HBc reactivity may have HBV DNA levels below the lower limit of pooled sample detection. Any residual virus will, however, be readily removed by robust PDMP pathogen inactivation and reduction steps.

An approach consistent with this concept is described in the Guideline on Plasma-Derived Medicinal Products, Chapter 9, page 25 on Assessing the Risk for Virus Transmission (former guideline CPMP/BWP/5180/03), that describes how:

> "*The estimated number of virus particles per vial can be calculated from the product of the worst case virus concentration in the starting material and the plasma required to produce one vial, divided by the virus reduction factor obtained from validation studies*, where *… a sensitive NAT testing of the manufacturing pool defines a well-controlled upper limit for a potential virus contamination*."

FDA's Draft Guidance, II Background, page 4, states:

> *"Moreover, the available data on blood donations for transfusion do not support discontinuing HBsAg testing when HBV NAT is performed in the absence of anti-HBc testing (Refs. 5-6). Because Source Plasma donations are not tested for anti-HBc, we have determined that both HBsAg and HBV NAT testing for Source Plasma donations are necessary to reduce adequately and appropriately the risk of HBV transmission and we are not recommending discontinuing HBsAg testing for Source Plasma."*

This considers HBsAg plus HBV NAT without anti-HBc as not adequate in the absence of pathogen inactivation (PI). These are data from whole blood studies where PI was not performed (Refs. 5-6). While the need for anti-HBc is clear for blood components not undergoing PI, this is not true for Source Plasma (or any plasma derivative) where robust levels of PI have been validated. In the future, when PI for all blood components becomes available, we then should also be able to eliminate the requirement for anti-HBc.

Request:

We respectfully request FDA's consideration of a recognition that HBV NAT, combined with robust PI, is sufficient to reduce adequately and appropriately the risk of transmission of HBV from all PDMP source materials, not just Recovered Plasma. While FDA does not have regulatory authority over PDMP manufacturing in other countries, alignment on this point would be highly valuable. Supporting efforts to eliminate unnecessary HBsAg testing of all whole blood donations – especially when Recovered Plasma production cannot be predicted when testing is ordered – will help advance the spirit and intent of the Guidance within the U.S.

Héma-Québec, a member of AABB and ABC, has shared their response, a conservative mathematical risk model supporting the elimination of HBsAg testing for Source Plasma. We thoroughly agree with their conclusions and, as noted above, share their virological viewpoint. We appreciate your thoughtful consideration of both our comments and those submitted by Héma-Québec.

AABB (Association for the Advancement of Blood & Biotherapies) is an international, not-for-profit organization representing individuals and institutions involved in the fields of transfusion medicine and biotherapies. The Association works collaboratively to advance the field through the development and delivery of standards, accreditation and education programs. AABB is dedicated to its mission of improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide.

Founded in 1962, America's Blood Centers is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the U.S., and a quarter of the Canadian blood supply. These blood centers

serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The American Red Cross shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. 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.

Thank you for the opportunity to offer these comments.

Sincerely,

[*signatures on file*]

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