June 21, 2022

Nicole Verdun, M.D., Director
Office of Blood Research and Review
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Verdun,

AABB (Association for the Advancement of Blood & Biotherapies), America's Blood Centers (ABC), and the American Red Cross (ARC) are submitting this joint letter to request an update on the current testing recommendations for hepatitis B virus (HBV). We respectfully request that you consider discontinuation of the testing requirement for hepatitis B surface antigen (HBsAg) in blood donations of Whole Blood and blood components intended for transfusion.

Our organizations support the Center for Biologics Evaluation and Research's (CBER) continued efforts to make evidence-based changes to regulatory requirements and recommendations, as seen in the recent updates to donor eligibility requirements. We welcome the agency's May 2022 Guidance, Recommendations to Reduce the Risk of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jacob Disease, eliminating the unnecessary indefinite deferral of blood donors for geographic risk of variant Creutzfeldt-Jakob disease. We also wish to acknowledge CBER's efforts to update draft guidance on compliance policies for donor blood pressure and pulse and on donation suitability, donor eligibility and source plasma quarantine hold requirements and welcome the opportunity to submit comments.

Consistent with CBER's evidence-based updates to donor eligibility, we believe the HBsAg testing requirement for Whole Blood and blood components intended for transfusion should be removed because HBsAg testing, is one of three tests currently required for HBV, and (1) does not increase transfusion safety; (2) is outdated, and (3) is overly burdensome because other required testing methods have proven to be highly effective in identifying HBV risk in donors for years.

We request the agency consider the following information supporting the removal of the current HBsAg testing requirement. Currently, in the United States (U.S.) the risk of HBV transfusion transmission is reduced by testing all blood donations for three FDA-required markers: HBsAg (since 1971), antibody to hepatitis B core antigen (anti-HBc, since 1986), and HBV DNA by

minipool nucleic acid testing (NAT, since 2006-2009). As judged by the absence of reported confirmed cases of HBV transfusion transmission, the policy has been successful. However, it is reasonable to ask if the use of three separate tests to detect HBV infection in blood donors is redundant, particularly since two of three are direct markers of infection. Thus, our question is whether the continued use of serologic testing for HBsAg is justified.

As a point of reference, recently published data providing long-term trends over time for HBV markers in U.S. blood donors demonstrate an HBV-positive donation frequency of approximately 6 per 100,000 (ranging from 50 in first-time donors to 2 in repeat donors) with residual risk calculations for all donations of 1 per 1.5 million; these rates have been consistent since the implementation of HBV NAT (Dodd et al., 2020; TMR). Similarly, for 6.7 million donations from 2018-2019, the Transfusion-Transmissible Infections Monitoring System published prevalence of 6 per 100,000 with residual risks for all donations of 1 per million, ranging from 1 per 1.73 million in donations from repeat versus 1 per 370,000 in first-time donors (Steele et al, 2020 and 2021; Transfusion). These low rates are due to extensive detection by both anti-HBc and direct marker(s) of HBV infection. Early detection of infection is achieved by NAT in seronegative donations (referred to as the serologic window period), where such donations would certainly be infectious. Detection of occult HBV infection, with variable reports worldwide of infectivity, is identified by reactive anti-HBc, while HBsAg is non-reactive but low levels of HBV DNA are present. Thus, for the two extremes of HBV infection, HBsAg is not present. Between these two phases of infection (window phase and occult HBV infection [OBI]), either or both HBV DNA and anti-HBc are present and detected in donated blood. Another important consideration is that since 1986 a highly effective HBV vaccine has been available including the recommendation for vaccination since 1996-1997 of all children aged 0-18 years and all at-risk adults; prevalence of vaccination in adults as reported by NHANES for the last reporting period (2015-2018) is 25.2%, thus an increasing proportion of the population is HBV immune.

Studies by the American Red Cross regarding the feasibility of eliminating HBsAg, reported HBV testing data from 12.8 million donations and 1368 HBV-infected donors (2009-2011). HBsAg-reactive donations that were minipool-NAT and anti-HBc non-reactive were retested by individual donation NAT. In this study, no donation was identified as truly positive for HBsAg that would not be detected by routine anti-HBc and/or HBV NAT, even in minipools (Stramer et al., 2013; Transfusion). Two anti-HBc non-reactive donations having HBsAg low-signal strengths were identified containing low-level HBV DNA, but when retested by HBsAg and HBV NAT in replicate, both were non-reactive and thus deemed as false-positive likely due to contamination. Using the same methods, additional data were reviewed, and further testing was performed, as needed, for an additional 22.4 million donations, collected over the next four years (Dodd et al., 2018; Transfusion). Similarly, of 2035 HBV-infected donors, all were detectable by HBV minipool NAT and/or anti-HBc except six that had isolated HBsAg low-signal strengths and some degree of low-level NAT reactivity (from 10-replicate individual donation NAT). Most NAT reactivity could not be repeated. As speculated by Dodd et al., it is reasonable to suggest that at least some of these samples might reflect false positivity, undisclosed recent HBV vaccine receipt, or contamination of the test sample from a source representing an infected donor containing HBsAg and HBV DNA. At face value, however, these six donors would be

interpreted as HBsAg confirmed positive with circulating HBV DNA at a level below that detected by routine minipool NAT. Of the total eight in both studies and 35.2 million donations, even if one assumes that these represent infected donors whose donations would be infectious, this equates to an added risk of one potentially infected donor per 4.4 million donations. However, it is unclear whether the finding of such donations represents a risk of infection, undisclosed recent HBV vaccination or simply sample contamination. These findings should not preclude the consideration of elimination of a test that appears to be redundant in the face of sensitive HBV NAT. The level of additional risk, assuming infectivity, is less than that which has been accepted as tolerable for other agents (using a threshold of 1 per million). However, HBsAg testing would still be of utility for donor confirmatory algorithms as part of donor counseling.

Studies in Europe (the Netherlands and Germany) confirm the redundancy of ongoing HBsAg when MP-NAT and anti-HBc are simultaneously performed, with Germany reporting a residual risk for confirmed infectious HBsAg-only donations of < 1 per 45 million (Scheiblauer et al., 2020; Vox Sanguinis). Since implementation of anti-HBc in the Netherlands in 2011 and among 5.5 million screened donations, 89 HBV-infected donors were identified of which none confirmed solely based on HBsAg. The authors conclude, "HBV donor screening could be limited to MP-NAT and anti-HBc screening. MP-NAT and anti-HBc improved blood safety by intercepting infectious donations from donors with recent infection or OBI, while HBsAg did not. Unnecessary donor loss related to anti-HBc screening is substantial but does not endanger the continuity of the blood supply." (Laar et al., 2021; Transfusion).

In contrast, in countries considered HBV endemic, anti-HBc testing of blood donations cannot be performed due to unacceptable donor loss; in these settings, HBsAg testing likely warrants retention, optimally with parallel sensitive NAT, to interdict window phase and occult HBV infections that otherwise may not be detected due to mutated or low levels of HBV DNA.

Lastly, another consideration is the growing use of FDA-licensed pathogen reduction technology (PRT) of platelets in the U.S.; platelets are most often transfused to immunosuppressed patients in whom low levels of HBV infectivity if such exists following screening, would be the most at risk, where PRT adds an additional layer of safety.

Weighing the established evidence demonstrating the sensitivity of HBV NAT and anti-HBc testing of blood we respectfully request the discontinuation of HBsAg testing of Whole Blood and blood components intended for transfusion in the U.S. We believe that the elimination of HBsAg testing is a first step in an ongoing dialogue of how to streamline the qualification of blood donations that maintains safety while eliminating unnecessary testing.

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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Vice President Science and Practice	Chief Executive Officer	President, Biomedical Services
AABB	America’s Blood Centers	American Red Cross