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Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen

Draft Guidance for Industry

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance document provides you, blood establishments that collect blood and blood components, including Source Plasma, with FDA's recommendations for testing blood and blood components for hepatitis B surface antigen (HBsAg) to reduce the risk of transfusion-transmitted hepatitis B virus (HBV). The recommendations contained in this guidance apply to the collection of Whole Blood and blood components, including Source Plasma.

Under 21 CFR 610.40(a), an establishment that collects blood and blood components must test each donation of human blood or blood components for transfusion or for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device, for evidence of infection due to certain relevant transfusion-transmitted infections (RTTIs), including HBV. In addition, under 21 CFR 610.40(b), establishments must perform one or more screening tests that FDA has licensed, approved or cleared as necessary to reduce adequately and appropriately the risk of transmission of RTTIs.

This guidance recommends that when donations, other than for Source Plasma, are tested for HBV DNA by nucleic acid tests (NAT) and for antibody to hepatitis B core antigen (anti-HBc) using screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions, testing for HBsAg is not necessary to reduce adequately and appropriately the risk of transmission of HBV. We have not changed our recommendations with respect to HBsAg testing for Source Plasma; our thinking continues to be that testing of Source Plasma donations for HBsAg and HBV DNA by NAT is necessary to reduce adequately and appropriately the risk of transmission of HBV.

This guidance, when finalized, will supersede the recommendation to test all blood donations for HBsAg in the guidance document entitled: "Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples From Donors of Whole Blood and Blood Components,

Including Source Plasma, to Reduce the Risk of Transmission of Hepatitis B Virus," dated October 2012 (Ref. 1).[1]

With finalization of the new recommendations set forth in this guidance, we intend to consolidate all FDA recommendations for testing blood and blood components for HBV and issue one guidance that includes finalized recommendations for testing donations to reduce the risk of transfusion transmission of HBV. Except for conforming changes needed to reflect the new recommendations set forth in this guidance, we do not intend to revise existing recommendations for HBV donation testing, quarantine and disposition of reactive units, donor deferral and requalification.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HBV is an RTTI (21 CFR 630.3(h)(1)(ii)). Blood establishments that collect blood and blood components intended for transfusion or for use in manufacturing a product must test each donation for evidence of HBV (21 CFR 610.40(a)(1)). To perform this testing, blood establishments must use screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions. Blood establishments must perform one or more such tests as necessary to reduce adequately and appropriately the risk of HBV (21 CFR 610.40(b)).

To meet the requirement under 21 CFR 610.40(b), FDA currently recommends testing each donation for the following markers of HBV: HBsAg, anti-HBc (except Source Plasma), and HBV DNA (Refs. 1-3). This combination of tests[2] detects acute (i.e., HBsAg, HBV DNA by NAT), chronic (i.e., HBsAg, HBV DNA by NAT, and anti-HBc), and occult (i.e., anti-HBc, HBV DNA by NAT) HBV infections. The residual risk of HBV transmission by blood transfusion has decreased since implementation of FDA's testing recommendations for HBV DNA by NAT by U.S. blood establishments in 2012. Currently, the estimated residual risk of potential HBV transmission by a blood transfusion is 1:1,193,146 or 1:842,864 depending on the calculation method and assumptions, using data from the Transfusion-Transmissible Infections Monitoring System (TTIMS) from October 1, 2019, to September 30, 2021 (Ref. 4).

FDA does not recommend that establishments test Source Plasma donations for anti-HBc (Ref. 1). Anti-HBc reactive units are included in Source Plasma pools used for the manufacture of

[1] See also "Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg), Memorandum," dated, December 1987 (Ref. 2).

[2] See FDA's website for additional information on licensed donor screening tests for HBV, accessible at https://www.fda.gov/vaccines-blood-biologics/complete-list-donor-screening-assays-infectious-agents-and-hiv-diagnostic-assays.

plasma derivatives because hepatitis B surface antibody, which occurs with anti-HBc and neutralizes HBV, is believed to contribute to the safety of certain plasma products. 21 CFR 610.40(h)(2)(v) permits the use of anti-HBc reactive donations for further manufacturing into plasma derivatives and 21 CFR 610.41(a)(4) permits a donor deferred for a reactive anti-HBc test to serve as a donor for Source Plasma in accordance with the terms of the regulation. Furthermore, manufacturing pools of Source Plasma are subjected to multiple viral removal and inactivation steps. The resultant plasma derivatives are not known to have transmitted HBV in many decades in the U.S.

There are no available data on HBV screening test results among presenting Source Plasma donors to evaluate the effect of discontinuing HBsAg testing for Source Plasma. 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.

III. DISCUSSION

FDA's recommendation about the lack of need for HBsAg testing when donations are tested for HBV DNA by NAT and for anti-HBc is based on epidemiologic trends in the incidence and prevalence of HBV in the U.S., and the extensive experience in screening blood donations with the three-test algorithm for many years. Acute HBV cases in the general U.S. population have consistently decreased with the introduction in 1991 of universal HBV vaccination of newborns and other prevention efforts (Ref. 7). Concomitantly, the incidence and prevalence of HBV among blood donors in the U.S. also decreased, and the risk for transfusion-transmission of HBV may continue to decrease over time as donors who were immunized against HBV in childhood represent an increasing proportion of donors in the U.S. over time (Ref. 8).

Direct evidence to support the lack of need for HBsAg testing when anti-HBc and HBV NAT screening tests are performed comes from four publications that report on the extensive experience of three large blood establishments in screening millions of donations for HBsAg, HBV DNA, and anti-HBc in the U.S., Germany, and the Netherlands (Refs. 5-6 and 9-10). The totality of data show that HBsAg testing does not identify HBV infections that are missed (nonreactive) by both HBV NAT and anti-HBc screening tests.

Specifically, two publications from authors at the American Red Cross compared the yield of each of the tests in the 3-test screening algorithm (HBsAg, anti-HBc and HBV DNA by mini-pool NAT (MP-NAT)) (Refs. 5-6). HBsAg yield donations are those donations detected only by HBsAg (confirmed reactive) and missed (nonreactive) by anti-HBc testing and HBV NAT. The HBsAg yield donations identified by screening in the studies were extensively investigated and tested by individual donation HBV NAT (ID-NAT) in multiple replicates to increase the sensitivity of NAT. Of the approximately 12.8 million donations screened between July 1, 2009, and June 30, 2011, only 2 donations were identified as reactive for HBsAg and ID-NAT but were

nonreactive for both anti-HBc and MP-NAT. Further testing suggested that the results on these 2 donations were false positives (Ref. 5). Repeating the study over a second time period, the authors reported that of the approximately 22.4 million donations screened by the American Red Cross between July 1, 2011, and June 30, 2015, only 6 donations were identified as reactive for HBsAg and nonreactive for both anti-HBc and MP-NAT. Further investigation of the 6 HBsAg yield donations suggested that they likely contained extremely low or negligible levels of HBV DNA. In contrast, the yield of HBV NAT was higher than the yield of HBsAg. MP NAT detected 34 donations that were missed by HBsAg and anti-HBc screening (Ref. 6). In total, from both publications, the contribution of the HBsAg test in the 3-test screening algorithm over 6 years was 8 HBsAg reactive donations of questionable significance, in approximately 35.1 million donations (or 1 in 4.4 million donations).

In contrast, a consideration to eliminate HBsAg testing in the absence of anti-HBc test results, when HBV NAT is performed, is not supported by these data (Refs. 5-6). For example, in one study of volunteer blood donors, 13% of HBV infected donations were detected by HBsAg but were missed by HBV NAT screening (i.e., donations were reactive for HBsAg and nonreactive for HBV DNA by minipool testing) (Ref. 6).

Two international studies, from Germany and the Netherlands, provide additional data supporting the discontinuation of HBsAg when anti-HBc tests and HBV NAT are performed (Refs 9 and 10). These countries use a similar HBV testing algorithm to the one recommended by FDA in the U.S. The general population in Germany has an estimated HBV prevalence rate of 0.7%, which is higher than the estimated prevalence in the U.S.; in contrast, in the Netherlands, the HBV prevalence is low, about 0.3% based on HBsAg testing. Regardless, the countries' experiences with the HBV screening algorithm are informative.

In Germany, approximately 45 million blood donations were screened between 2008 and 2015 and only one donation was identified that was HBsAg positive with low-level HBV DNA detectable by ID-NAT on further investigation, but negative by MP-NAT and anti-HBc screening tests (Ref. 9). Thus, the individual contribution of the HBsAg screening test for yield donations in this study was 1 in 45 million. In contrast, NAT identified 29 cases of HBV infection that were nonreactive for HBsAg or anti-HBc.

In the Netherlands, approximately 5.6 million blood donations were screened between July 2011 to July 2018, and there were no donors that were HBsAg positive only who were infected with HBV (Ref. 10). In comparison, there were 5 HBV-infected donations that were detected by MP-NAT only.

In summary, these studies demonstrate that screening blood donations by HBV NAT is effective in detecting early (acute) and ongoing infection, and screening for anti-HBc is effective in detecting chronic or occult (HBsAg nonreactive) HBV infection. Anti-HBc typically persists for life (Ref. 11) and is detected even when HBV DNA may be suppressed below detectable levels or only intermittently detected by screening tests (Ref. 12). The combination of HBV NAT in detecting acute cases and the contribution of anti-HBc testing, especially in the detection of chronic infections, is effective in detecting HBV infection throughout the entire clinical course of HBV infection. Therefore, we conclude that the available information supports the safety of

discontinuing HBsAg screening when donations are tested for both HBV DNA by NAT and anti-HBc.

IV. RECOMMENDATIONS

Based on the available scientific evidence described in section III of this guidance, testing donations for HBV DNA by NAT and anti-HBc using FDA-licensed donor screening tests reduces adequately and appropriately the risk of HBV transmission by blood and blood components (21 CFR 610.40(b)). Therefore, when donations of blood and blood components are tested for HBV DNA and anti-HBc using screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions, FDA believes that testing of the donations for HBsAg is not necessary to comply with 21 CFR 610.40(b). Blood establishments that discontinue testing donations for HBsAg should revise their Circular of Information to remove the statement that donations are nonreactive for hepatitis B surface antigen (HBsAg).

Blood establishments must comply with all applicable requirements related to the management of reactive screening test results, including restrictions on shipment and use (21 CFR 610.40(h)), donor deferral and requalification (21 CFR 610.41), donor notification (21 CFR 630.40), and donation suitability (21 CFR 630.30). Blood establishments that continue testing blood and blood component donations for HBsAg must comply with the regulatory requirements above and should refer to FDA guidance for recommendations addressing donations that test reactive for HBsAg.

The recommendation that testing blood donations for HBV DNA by NAT and anti-HBc is sufficient to reduce adequately and appropriately the risk of transmission of HBV does not apply to the collection of Source Plasma. The scientific evidence continues to support that testing donations of Source Plasma for HBsAg and HBV DNA by NAT is necessary to reduce adequately and appropriately the risk of transmission of HBV (see 21 CFR 610.40(a)(1) and (b)).

You must continue to follow your standard operating procedures for testing Source Plasma for HBV (21 CFR 606.100(b)) and comply with all applicable requirements, including for donation testing (21 CFR 610.40), donor deferral and requalification (21 CFR 610.41), donor notification (21 CFR 630.40), and donation suitability (21 CFR 630.30). We continue to recommend that blood establishments follow recommendations in FDA guidance[3] for donation testing, quarantine and disposition of reactive units, donor deferral and requalification for donations of Source Plasma.

[3] As mentioned in section I of this guidance, we intend to consolidate all FDA recommendations for testing blood and blood components for HBV into one guidance that finalizes recommendations for testing donations to reduce the risk of transfusion transmission of HBV.

V. IMPLEMENTATION OF RECOMMENDATIONS

The guidance is for comment purposes only. Once the guidance is finalized, licensed blood establishments must report changes to their approved application in accordance with 21 CFR 601.12: For licensed blood establishments that implement the recommendations in section IV of this guidance, when finalized, we consider the implementation be a minor change. Licensed blood establishments that discontinue testing donations for HBsAg and revise their Circular of Information consistent with the recommendations in section IV of this guidance, must report the change in an annual report under 21 CFR 601.12(d), noting the date of implementation (see 21 CFR 601.12(a)(3)).

For licensed blood establishments that intend to implement a new HBV testing strategy other than as recommended in section IV of this guidance, we consider that to be a major change and a prior approval supplement would be required under 601.12(b).

Unlicensed blood establishments do not need to report changes to FDA.

VI. REFERENCES

1. Guidance for Industry: Use of Nucleic Acid Tests on Pooled and Individual Samples From Donors of Whole Blood and Blood Components, Including Source Plasma, to Reduce the Risk of Transmission of Hepatitis B Virus, October 2012 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-nucleic-acid-tests-pooled-and-individual-samples-donors-whole-blood-and-blood-components.

2. Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg), Memorandum, dated, December 1987 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommendations-management-donor-and-units-are-initially-reactive-hepatitis-b-surface-antigen-hbsag.

3. FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc), Memorandum, September 10, 1991 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-recommendations-concerning-testing-antibody-hepatitis-b-core-antigen-anti-hbc.

4. Notari E, et al., Prevalence, incidence, and residual risk of HIV, HBV, and HCV in the US blood supply 2015-2021, on behalf of the US Transfusion-Transmissible Infections Monitoring System (TTIMS) Program (abstract) Vox Sang; 2023;118(Suppl. 1), 70.

5. Stramer, SL, et al., Hepatitis B virus testing by minipool nucleic acid testing: does it improve blood safety? Transfusion; 2013. 53(10): p. 2449-58.

6. Dodd, RY, et al., Blood donor testing for hepatitis B virus in the United States: is there a case for continuation of hepatitis B surface antigen detection? Transfusion; 2018. 58(9): p. 2166-70.

7. Ramachandran, S, et al., Recent and occult hepatitis B virus infections among blood donors in the United States. Transfusion; 2019. 59(2): p. 601-11.

8. Zou, S, et al., Current incidence and residual risk of hepatitis B infection among blood donors in the United States. Transfusion; 2009. 49(8): p. 1609-20.

9. Scheiblauer, H, et al., Detection of hepatitis B virus infection in German blood donors 2008-2015. Vox Sang; 2020. 115(3): p. 152-61.

10. van de Laar, T, et al., Blood donor screening in the Netherlands: Universal anti-HBc screening in combination with HBV nucleic acid amplification testing may allow discontinuation of hepatitis B virus antigen testing. Transfusion; 2021. 61(7): p. 2116-24.

11. Conners, EE, et al., Screening and Testing for Hepatitis B Virus Infection: CDC Recommendations – United States, 2023. MMWR Recomm Rep; 2023. 72(1): p. 1-25.

12. Jeng, W-J, et al., Hepatitis B. Lancet; 2023. 401(10381): p. 1039-52.