Contains Nonbinding Recommendations

Recommendations for Reducing the Risk of Transfusion-Transmitted Hepatitis B Virus

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Guidance for Industry

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Recommendations for Reducing the Risk of Transfusion-Transmitted Hepatitis B Virus

Guidance for Industry

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I. INTRODUCTION

We, FDA, are providing you, blood establishments that collect blood and blood components, including Source Plasma, with recommendations for testing blood and blood components for hepatitis B virus (HBV) to reduce the risk of transfusion-transmitted HBV. The recommendations contained in this guidance apply to the collection of Whole Blood and blood components, including Source Plasma.

HBV is a relevant transfusion-transmitted infection (RTTI) (Title 21 of the Code of Federal Regulations (CFR) 630.3(h)(1)(ii)) and, therefore, subject to the testing requirements in 21 CFR 610.40, the donor deferral requirements in 21 CFR 610.41 and the donor notification requirements in 21 CFR 630.40.

Under 21 CFR 610.40(a)(1), 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 HBV. In addition, under 21 CFR 610.40(b), establishments must use, in accordance with the manufacturer's instructions, one or more screening tests that FDA has licensed, approved or cleared as necessary to meet the testing requirement and to reduce adequately and appropriately the risk of transmission of RTTIs. This guidance provides recommendations for testing blood donations to reduce adequately and appropriately the risk of HBV transmission under these regulations.

FDA previously issued recommendations to blood establishments on HBV in the following documents:

- Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg), Memorandum, December 2, 1987 (December 1987 Memorandum)

- FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc), Memorandum, September 10, 1991 (September 1991 Memorandum)

- Recommendations for the Quarantine and Disposition of Units from Prior Collections from Donors with Repeatedly Reactive Screening Tests for Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and Human T- Lymphotropic Virus Type I (HTLV-I), Memorandum, July 19, 1996 (July 1996 Memorandum)

- Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes, November 2007 (November 2007 Final Guidance)

- Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc); Guidance for Industry, May 2010 (May 2010 Final Guidance)

- Requalification Method for Reentry of Donors Who Test Hepatitis B Surface Antigen (HBsAg) Positive Following a Recent Vaccination against Hepatitis B Virus Infection; Guidance for Industry, November 2011 (November 2011 Final Guidance)

- 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; Guidance for Industry, October 2012 (October 2012 Final Guidance)

- Recommendations for Testing Blood Donations for Hepatitis B Surface Antigen; Draft Guidance for Industry, July 2025 (July 2025 Draft Guidance)

This guidance consolidates FDA's current recommendations on HBV, as follows:

- Finalizes the July 2025 Draft Guidance.

- Supersedes the recommendations specific to HBV contained in the July 1996 Memorandum.

- Supersedes the December 1987 and September 1991 Memoranda, and the November 2007, May 2010, November 2011 and October 2012 Final Guidance documents.

The new recommendations introduced in this guidance relate to the finalization of the recommendations in the July 2025 Draft Guidance, specifically the recommendation for the discontinuation of testing certain donations for hepatitis B surface antigen (HBsAg) and conforming changes for donor requalification and labeling, found in section III of this guidance. Namely, we recommend that when donations of blood and blood components, excluding 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. For Source Plasma donations, we continue to recommend that testing for HBsAg and HBV DNA by NAT is necessary to reduce adequately and appropriately the risk of transmission of HBV.

Additionally, we have revised some recommendations because of advances in the tests used to screen blood donations for HBV. We removed recommendations that blood establishments use HBsAg and HBV NAT tests with specific sensitivity levels, as described in the November 2007 and October 2012 Final Guidance documents. These recommendations are no longer relevant because all currently available FDA-licensed tests for HBsAg and HBV DNA meet the detection levels previously recommended and blood establishments must use FDA-licensed, approved or cleared screening tests in accordance with the manufacturer's instructions (see 21 CFR 610.40(b)). Further, we have made minor changes in recommendations for donor requalification and product management for consistency and alignment with current practice.

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

A. HBV and Blood Safety

HBV is a human pathogen of global significance that can cause acute and chronic hepatitis. HBV infection is a blood borne infection and is transmitted from HBV-positive mothers to infants (perinatal route), through sexual contact, close person-to-person contact (e.g., contact with open cuts or sores) and through sharing of contaminated syringes and needles among people who inject drugs (Refs. 1-2).

Worldwide, approximately 254 million people have chronic HBV infection, with the highest prevalence observed in sub-Saharan Africa, the Western Pacific, and South-East Asia (Ref. 3). In the U.S., based on the January 2017- March 2020 National Health and Nutrition Examination Survey, an estimated 660,000 persons aged 6 years and older had HBV infection (Ref. 4). In immunocompetent adults, most infections with HBV are acute and resolve spontaneously. Many cases of acute HBV infection are subclinical. Adults with acute HBV infection only develop icteric hepatitis in approximately 30-50% of cases and severe disease such as fulminant hepatitis is rare (Ref. 5). Most chronic HBV infections in the United States are caused by infection acquired before or at birth (perinatal transmission) and acute HBV infection in newborn infants and children is often without symptoms. Following exposure, the risk of progressing from acute to chronic infection is estimated to be 90% among infants born to HBV-infected mothers, 20% in children under 6 years, and <5% in older children and adults (Ref. 1). Those infections that progress to chronic HBV infection can remain asymptomatic for decades. As a result, HBV-positive individuals may be unaware of their infection status. Chronic HBV infection can lead to

progressive liver disease including fibrosis, cirrhosis, and hepatocellular carcinoma, resulting in significant morbidity and mortality. There is no treatment that completely eliminates the virus from the body. However, there are effective prophylactic vaccines that can protect against HBV infection and antiviral therapies for management of chronic infection (Ref. 6).

The risk of posttransfusion hepatitis was recognized in the 1940s, but the etiology was unknown for many years. In the 1960s, posttransfusion hepatitis was reported in up to 1.5% of transfusion recipients (Ref. 7). HBsAg was identified to be associated with HBV infection in 1970, and HBsAg assays became the first to screen blood donations for a viral infection. Subsequent improvements in blood donor screening assays resulted in detection of early or acute viral markers (HBsAg, HBV DNA) and chronic infection (anti-HBc) in plasma and serum. On average, HBsAg becomes detectable 30 days after exposure (with a range of 6-60 days), while HBV DNA can be detected 10-20 days earlier (Ref. 8). Anti-HBc appears after HBV DNA and HBsAg and persists for life in most infected individuals (Ref. 9). With currently available sensitive tests for markers of HBV infection, the risk of transfusion-transmission per donation in the U.S. is currently estimated to be less than 1 in 2 million (Ref. 10).

B. FDA Regulatory History

FDA first recommended testing for HBV in December 1987. In a memorandum addressed to all registered blood establishments, FDA recommended testing each donation for HBsAg using an FDA-licensed test and that an HBsAg-reactive unit should not be used for transfusion or further manufacturing use. The December 1987 memo also recommended using an FDA-licensed confirmatory (neutralization) test for HBsAg to evaluate donors whose donation tested repeatedly reactive. FDA provided recommendations for evaluating the status of the donor, including that the donor should be permanently deferred when the HBsAg confirmatory test is positive by neutralization. If the HBsAg reactivity in the donor's sample is not neutralizable (i.e., not confirmed positive), the memo recommended testing for anti-HBc with an FDA-approved test. If repeatedly reactive for anti-HBc, the donor is permanently deferred; if not reactive, then the donor should be deferred for 8 weeks, and the subsequent donation should be tested for HBsAg and anti-HBc to determine donor eligibility and donation suitability.

On February 20, 1990, FDA announced in the Federal Register that, effective March 31, 1991, total anti-HBc test kits used for the purpose of screening blood donations would be regulated as licensed biological products. In September 1991, in a memorandum to all registered blood establishments, FDA recommended that all donations of blood and blood components intended for transfusion be screened by an FDA-licensed anti-HBc test in accordance with the manufacturer's instructions. The memo recommended that a repeatedly reactive donation should not be used for transfusion and that donors who tested repeatedly reactive for anti-HBc on more than one occasion should be deferred. The memo provided recommendations for labeling and quarantine and disposition of repeatedly reactive donations.

The September 1991 recommendations to test donations for anti-HBc did not apply to Source Plasma because of the possibility that excluding plasma containing anti-HBc from pools for further manufacturing into plasma derivatives might result in decreased safety of plasma derivatives, because it would also reduce the content of antibody to hepatitis B surface antigen

(anti-HBs), which is protective against HBV infection in plasma therapeutics. The memo clarified that recovered plasma donations may be shipped for further manufacture under a valid short supply agreement regardless of the anti-HBc test results.

In a July 1996 memo to blood establishments, FDA provided recommendations for the quarantine and disposition of blood, blood components, and Source Plasma from prior collections from donors with repeatedly reactive screening tests for HBV. The July 1996 memo recommended that blood and plasma establishments should identify and quarantine such donations in their inventory within one week and notify consignees to quarantine components that had been distributed. The memo provided recommendations for the disposition of units placed in quarantine based on the result of further testing of the initially reactive donation.

FDA issued guidance in November 2007 that recommended minimum sensitivity standards for HBsAg tests for the purpose of blood donation screening. The guidance recommended that blood establishments use HBsAg assays that have a lower limit of detection capability of 0.5 nanograms (ng) HBsAg/mL or less. The guidance also provided test kit manufacturers with a recommended performance standard when testing the CBER HBsAg Lot-Release Panel #12 under 21 CFR 610.44.

In May 2010, with the availability of FDA-licensed NAT for HBV DNA and improved sensitivity of licensed total anti-HBc tests, FDA provided recommendations for a requalification method for donors deferred because of falsely positive repeatedly reactive test results for anti-HBc on more than one occasion. The guidance recommended that after an eight-week period, a follow-up pre-donation sample from the donor should be tested for HBsAg, anti-HBc and HBV DNA by NAT (with a sensitivity of <2 IU/mL at 95 % detection rate) using FDA-licensed tests. Negative results on all three tests in the follow-up sample qualified the donor for reentry. The May 2010 guidance also recommended continued indefinite deferral of the donor if the follow-up sample tested repeatedly reactive on the HBsAg or anti-HBc test or reactive on the HBV NAT.

FDA provided recommendations in the November 2011 guidance for the requalification of certain deferred donors following a recent vaccination against HBV. Specifically, based on the transient detection of HBsAg following HBV vaccination, the guidance recommended a requalification method for reentry of donors with repeatedly reactive screening tests for HBsAg, confirmed positive by neutralization, when the donor received vaccination against HBV within 28 days prior to collection of the donation that was confirmed positive for HBsAg and the donor is not infected by HBV. The recommended requalification method varied depending on whether the donor received the vaccination for protection from possible future exposure or if the vaccination was given for the purpose of HBV prophylaxis following a specific incident of potential exposure (e.g., needlestick, risk behavior).

In October 2012, FDA notified blood establishments in guidance that we consider the use of an FDA-licensed NAT for HBV DNA to be necessary to reduce adequately and appropriately the risk of transmission of HBV under 21 CFR 610.40(b). The October 2012 guidance recommended that when testing for HBV DNA by NAT is implemented, blood establishments should continue testing blood and blood components for transfusion for HBsAg and anti-HBc,

and Source Plasma for HBsAg. The guidance provided recommendations for testing and product disposition, donor deferral and methods for donor requalification, and labeling in the context of testing for HBV DNA by NAT.

For donation screening, the October 2012 guidance recommended use of an FDA-licensed NAT for HBV DNA with a lower limit of detection of < 100 IU/mL HBV DNA for HBV DNA detection in an individual donation of blood and blood components for transfusion, and <500 IU/mL HBV DNA for HBV DNA detection in an individual donation of Source Plasma. The guidance clarified that screening with a licensed NAT for HBV DNA could be in minipool donation-sample testing format or an individual donation testing format and may include multiplex NAT with testing of other agents, such as HIV and HCV. The guidance also recommended further testing of donations reactive for HBsAg with an FDA-licensed NAT for HBV DNA with a supplemental testing indication or HBsAg neutralization to meet the requirement of 21 CFR 610.40(e). The guidance recommended, as part of the requalification method for donor reentry, use of an FDA-licensed NAT for HBV DNA with a sensitivity of $\leq$ 2 IU/mL at 95% detection rate at least 6 months after the positive test results that led to donor deferral.

In May 2015, FDA issued a final rule titled, "Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use" (the "Donor Eligibility" rule, 80 FR 29841). Among other things, the rulemaking defined RTTI as including HBV in 21 CFR 630.3(h)(1)(ii)) and codified that each donation of blood and blood components for transfusion or for use in manufacturing a product must be tested for evidence of HBV (21 CFR 610.40(a)(1)). The 2015 final rule clarified that when a donation tests reactive on a screening test for an RTTI, including HBV, you must perform further testing as described in 21 CFR 610.40(e); the donation is not suitable for release unless an exception applies (21 CFR 630.30(b)); and, the donor must be deferred (21 CFR 610.41) and notified of the reason for deferral (21 CFR 630.40).

In July 2025, FDA issued draft guidance recommending that testing for HBsAg is not necessary to reduce adequately and appropriately the risk of transmission of HBV under 21 CFR 610.40(b) when donations of blood and blood components are tested for HBV DNA by NAT and for anti-HBc using screening tests that FDA has licensed for such use, in accordance with the manufacturer's instructions. The guidance explained that FDA's recommendation was based on epidemiologic trends in the incidence and prevalence of HBV in the U.S., and the extensive experience over many years in screening blood donations with the three-test algorithm. Acute HBV infection cases in the general U.S. population have consistently decreased with the introduction in 1991 of universal hepatitis B vaccination of newborns and other prevention efforts (Ref. 11). Concomitantly, the incidence and prevalence of HBV infection among blood donors in the U.S. also decreased, and the risk for transfusion-transmission of HBV may continue to decrease as donors who were immunized against HBV infection in childhood represent an increasing proportion of donors in the U.S. (Ref. 12).

The recommendations in the 2025 draft guidance were supported by data from four publications that reported 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. 13-16). The totality of data showed that HBsAg testing does not identify HBV infections that are missed by both HBV NAT and anti-HBc screening test.

The draft guidance did not change our recommendations with respect to HBsAg testing for Source Plasma donations because there are no available data on HBV screening test results to evaluate the effect of discontinuing HBsAg testing. Although data on blood donations is not directly comparable to Source Plasma because the latter is collected from paid donors, extrapolating from the available blood donation data does not support discontinuing HBsAg testing when HBV NAT is performed in the absence of anti-HBc testing (Refs. 13-14). Because Source Plasma donations are not tested for anti-HBc, the draft guidance continued to recommend that both HBsAg and HBV NAT testing for Source Plasma donations are necessary to reduce adequately and appropriately the risk of HBV transmission under 21 CFR 610.40(b).

FDA considered public comments on the July 2025 draft guidance and the available scientific evidence and decided to finalize the recommendations without changes. Therefore, this guidance finalizes the July 2025 draft guidance and recommends that blood establishments may discontinue testing blood donations (other than Source Plasma) when donations are tested for HBV DNA by NAT and for anti-HBc. Conforming changes to FDA's recommendations for donor requalification and labeling are also made in this guidance. Consistent with Good Guidance Practices, FDA may modify this guidance, including recommendations for testing Source Plasma donations, in the future based on scientific evidence as it becomes available.

C. Terminology

For the purpose of this guidance and for consistency with the regulations in part 21 CFR Part 610, we use the terms "reactive" and "nonreactive" for results of screening tests (HBsAg, anti-HBc, and HBV NAT) performed under 21 CFR 610.40(a) and use the terms "positive" and "negative" for results of further testing (HBsAg neutralization and HBV NAT) performed under 21 CFR 610.40(e). The term "reactive" includes "repeatedly reactive" when the test requires initial and repeat testing as part of a single screening procedure (i.e., for HBsAg and anti-HBC tests). Blood establishments must perform HBV testing in accordance with the manufacturer's instructions (21 CFR 610.40(b) and 21 CFR 606.65(e)).

III. RECOMMENDATIONS

These recommendations apply to the collection of Whole blood and blood components for transfusion or for further manufacturing use, including Source Plasma.

A. Donation Testing, Donor Deferral and Notification

As a general matter, you must test each donation for evidence of HBV infection (21 CFR 610.40(a)(1)). You must use screening tests that FDA has licensed, approved or cleared for

such use, in accordance with the manufacturer's instructions[1] and you must perform one or more such tests as necessary to reduce adequately and appropriately the risk of HBV transmission by blood and blood components (21 CFR 610.40(b)).

Subject to certain limited exceptions outlined in 21 CFR 610.40(e), you must further test each donation found reactive on a licensed screening test for HBV using a licensed, approved or cleared supplemental test, when available, or perform a licensed, approved or cleared test as adequate and appropriate to provide additional information concerning the donor's infection status (21 CFR 610.40(e)).

You must not ship or use donations that have a reactive screening test for HBV, unless an exception applies (see 21 CFR 610.40(h)).

You must defer a donor that tests reactive for HBV (see 21 CFR 610.41(a)) and notify the donor of the deferral (see 21 CFR 630.40).

1. Donations of Whole Blood and Blood Components, Except Source Plasma

    a. You must test each donation for evidence of HBV infection (21 CFR 610.40(a)(1)). You must test each donation for anti-HBc and HBV DNA by NAT to adequately and appropriately reduce the risk of HBV transmission (21 CFR 610.40(b)).

        Testing such donations for HBsAg is not necessary to comply with 21 CFR 610.40(b)[2].

    b. You must use FDA-licensed donor screening tests in accordance with the manufacturer's instructions (21 CFR 610.40(b) and 606.65(e)). Accordingly, when testing for anti-HBc, you must use an individual donation testing format. You may use an FDA-licensed HBV NAT that uses a minipool or an individual donation testing format, and it may be a multiplex NAT with testing of other agents, such as HIV and HCV, or single virus NAT for HBV.

    c. You may release donations that are nonreactive for anti-HBc and HBV DNA by NAT using licensed donor screening tests, provided all other donation suitability requirements are met (21 CFR 630.30).

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[1] 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.

[2] We recognize that some blood establishments may continue testing for HBsAg when donations are tested for anti-HBc and HBV DNA by NAT. In this case, and as described further in section IV.A of this guidance, you must continue to comply with all applicable RTTI requirements, including requirements related to the management of HBsAg reactive screening test results, including further testing and restrictions on shipment and use (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). For example, you must not ship or use a donation that tests reactive for HBsAg (21 CFR 610.40(h)) and you must defer the donor, unless an exception applies (21 CFR 610.41).

d. You must not ship or use donations that have a reactive screening test for HBV (i.e., HBV DNA by NAT, anti-HBc, or HBsAg), unless an exception for shipment or use is applicable (21 CFR 610.40(h)). Note that 21 CFR 610.40(h)(2)(v) permits the use of anti-HBc reactive donations for further manufacturing into plasma derivatives.

e. You must defer donors with a reactive screening test result for HBV (21 CFR 610.41(a)) and you must notify the donor of the reason for their deferral (21 CFR 630.40). Deferred donors must be counseled about the possible medical significance of the results (21 CFR 630.40(b)(4)). Note the following for donors that test reactive for anti-HBc:

   i. Consistent with 21 CFR 610.41(a)(1), you are not required to defer a donor who tests reactive for anti-HBc on only one occasion. However, you must defer the donor if:

      - further testing for HBV has been performed under 21 CFR 610.40(e) and the donor is found to be positive, or
      - a second, licensed, cleared, or approved screening test for HBV has been performed on the same donation under 21 CFR 610.40(a) and is reactive, or
      - the donor tests reactive for anti-HBc on more than one occasion.

   ii. A donor deferred for a reactive anti-HBc test may serve as a donor for Source Plasma, provided all other eligibility criteria are met (21 CFR 610.41(a)(4)).

   See section III.B. of this guidance for recommendations on requalification of deferred donors.

2. Donations of Source Plasma

   a. You must test each donation of Source Plasma for evidence of HBV infection (21 CFR 610.40(a)(1)). You must test each donation of Source Plasma for HBsAg and HBV DNA by NAT to adequately and appropriately reduce the risk of HBV transmission (21 CFR 640.10(b)).

      FDA does not recommend testing Source Plasma donations for anti-HBc. Anti-HBc reactive units are included in Source Plasma pools used for the manufacture of 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.

   b. You must use FDA-licensed donor screening tests in accordance with the manufacturer's instructions (21 CFR 610.40(b) and 606.65(e)). Accordingly, when

testing Source Plasma for HBsAg, you must use an individual donation testing format. You may use an FDA-licensed HBV NAT that uses a minipool or an individual donation testing format, and it may be a multiplex NAT with testing of other agents, such as HIV and HCV, or single virus NAT for HBV.

c. You may release donations of Source Plasma that are nonreactive for HBsAg and HBV DNA by NAT using licensed donor screening tests, provided all other donation suitability requirements are met (21 CFR 630.30).

d. You must not ship or use donations of Source Plasma that have a reactive screening test for HBV (i.e., HBsAg or HBV DNA by NAT) unless an exception for shipment or use is applicable (see 21 CFR 610.40(h)).

e. You must further test donations of Source Plasma that are reactive for HBsAg using a licensed supplemental test to provide additional information concerning the reactive donor's infection status (21 CFR 610.40(e)).

   i. You may use a licensed HBsAg neutralization test for further testing; or,

   ii. When a donation is reactive on a licensed donor screening test for HBsAg, you may use a licensed HBV NAT intended for both donor screening and use as a supplemental test to confirm HBV infection. In this case, a reactive HBV NAT result on a donation that is reactive for HBsAg confirms HBV infection and fulfills the further testing requirement in 21 CFR 610.40(e) and no additional testing is necessary. However, if a licensed HBV NAT with a supplemental indication is nonreactive, you must perform further testing using a licensed HBsAg neutralization test.

f. You must defer donors with a reactive screening test result for HBV (21 CFR 610.41(a)) and you must notify the donor of the reason for their deferral (21 CFR 630.40). Deferred donors must be counseled about the possible medical significance of the results (21 CFR 630.40(b)(4)). Notification must include the result of further testing, when applicable (21 CFR 630.40(b)(3)).

   Note that a deferred donor who showed evidence of infection due to hepatitis B surface antigen (HBsAg) when previously tested under 21 CFR 610.40 subsequently may donate Source Plasma for use in the preparation of Hepatitis B Immune Globulin (Human) provided the current donation tests nonreactive for HBsAg and the donor is otherwise determined to be eligible. (21 CFR 610.41(a)(3)).

B. Requalification of Donors Deferred Because of Reactive HBV Test Results

A deferred donor may subsequently be found eligible as a donor by a requalification method or process found acceptable for such purpose by FDA (21 CFR 610.41(b)). The recommendations in this section provide an acceptable requalification method for reentry of

deferred donors because of falsely reactive screening test results for HBV. See also Tables 1 and 2.

1. Donors of Whole Blood and Blood Components, Except Source Plasma (See also Table 1)

   a. Not eligible for reentry: FDA has not found a requalification method or process acceptable for donors with the following test results and you should permanently defer such donors :

      - HBV NAT reactive and anti-HBc reactive on the same donation.
      - HBV NAT reactive and HBsAg reactive and confirmed positive either by neutralization or HBV NAT with supplemental indication (historical results or current donation, if tested)

   b. May be eligible for reentry: Deferred donors with the following test results may be eligible for reentry, using the requalification methods described below:

      - anti-HBc reactive on second occasion and HBV NAT nonreactive.
      - HBV NAT reactive and anti-HBc nonreactive.

      i. To requalify a deferred donor with an anti-HBc reactive test result on a second occasion and a HBV NAT nonreactive test result, we recommend the following:

         a. At least 8 weeks following the last reactive anti-HBc test result, obtain a follow up sample from the donor (no donation is made at this time) and test the sample using a licensed donor screening test for anti-HBc and HBV DNA by NAT.
         b. If the sample tests nonreactive on both the anti-HBc test and HBV NAT test, the donor may be eligible for reentry, provided the donor meets all eligibility criteria when presenting to donate.
         c. If the sample tests reactive on one or both tests, the donor should be deferred permanently.
         d. Note that nonreactive test results obtained earlier than the 8-week waiting period may be useful in donor notification and counseling but should not be used to requalify the donor. Only nonreactive test results obtained at least 8 weeks following the last reactive anti-HBc test result would qualify the donor for reentry. If during the 8-week waiting period, a reactive HBV NAT or anti-HBc test result is obtained, the donor is not eligible for reentry and should be deferred permanently.
         e. A donor who has been requalified as described above may subsequently be deferred solely for anti-HBc reactive test results. The deferred donor may be eligible for reentry by using the requalification method described in this section.

ii. To requalify a deferred donor with HBV NAT reactive and anti-HBc nonreactive test results, we recommend the following:

a. At least 6 months following the reactive HBV NAT, obtain a follow up sample from the donor (no donation is made at this time) and test the sample using a licensed donor screening test for anti-HBc and HBV DNA by NAT.
b. If the sample tests nonreactive on both the anti-HBc test and HBV NAT, the donor may be eligible for reentry, provided the donor meets all eligibility criteria when presenting to donate.
c. If the sample tests reactive on the HBV NAT, the donor should be deferred permanently.
d. If the sample tests nonreactive on the HBV NAT and reactive on the anti-HBc test, the donor may be further evaluated using the requalification method described in section III.B.1.b.i of this guidance.
e. Note that nonreactive test results obtained earlier than the 6-month waiting period may be useful in donor notification and counseling but may not be used to requalify the donor. Only nonreactive test results obtained at least 6 months following the last reactive HBV NAT result would qualify the donor for reentry. If during the 6-month waiting period, a reactive HBV NAT or anti-HBc test result is obtained, the donor is not eligible for reentry and should be deferred permanently.
f. A donor who has been requalified as described above may subsequently be deferred for HBV NAT reactive results. The deferred donor may be eligible for reentry by using the requalification method described in this section.

Note: Blood establishments that have historical test results for a deferred donor that include HBsAg may consider whether a donor is eligible for reentry based only on test results for HBV NAT and anti-HBc, using the requalification method described above. However, the requalification method or process found acceptable by FDA does not provide for reentering a donor that tested reactive for HBsAg and confirmed positive (by NAT supplemental or neutralized). Therefore, such a donor is permanently deferred, unless the donor has received a vaccination against HBV in the 28 days prior to the confirmed positive HBsAg test. To requalify a recently vaccinated donor, you may use the requalification process described in section III.B.2.b.i. of this guidance.

Table 1. Donor Eligibility and Requalification: Donors of Whole Blood and Blood Components

Screening test results (index donation)		Donor eligibility	Minimum interval for reentry testing	Acceptable test results for requalification
HBV NAT	Anti-HBc			
Reactive	Reactive	Defer permanently	N/A[b]	N/A
Nonreactive	Reactive on only one occasion	Not a cause for deferral[a]	N/A	N/A
Nonreactive	Reactive on second occasion	Eligible for reentry	8 weeks	HBV NAT - NR[c] Anti-HBc - NR
Reactive	Nonreactive	Eligible for reentry	6 months	HBV NAT - NR Anti-HBc - NR

[a] See 21 CFR 610.41(a)(1).

[b] N/A means not applicable.

[c] NR means nonreactive.

2. Donors of Source Plasma (See also Table 2)

   a. Not eligible for reentry: FDA has not found a requalification method or process acceptable for donors with the following test results and you should permanently defer such donors:

      - HBV NAT reactive and HBsAg reactive and confirmed positive (neutralized or by HBV NAT with supplemental indication).
      - HBsAg reactive and confirmed positive (neutralized) and HBV NAT nonreactive, if donor has not received vaccination against HBV within 28 days of collection.

   b. May be eligible for reentry: Deferred donors with the following test results may be eligible for reentry, using the requalification methods described below:
      - HBsAg reactive and confirmed positive by neutralization and HBV NAT nonreactive[3], if donor has received vaccination against HBV within 28 days of collection.
      - HBsAg reactive and not confirmed positive (i.e., non-neutralized) and HBV NAT nonreactive.

[3] If a donor tests reactive for HBsAg and reactive for HBV DNA using an HBV NAT with a supplemental indication, the HBsAg test result should be considered positive without performing HBsAg neutralization test. These results are indicative of HBV infection and are not caused by vaccination against HBV. Therefore, such a donor should be deferred permanently.

- HBV NAT reactive and HBsAg nonreactive.
- HBV NAT reactive and HBsAg reactive and not confirmed positive.

i. The requalification process for a deferred donor with HBsAg reactive and confirmed positive by neutralization and HBV NAT nonreactive test results who has received vaccination against HBV within 28 days of collection depends on the indication for vaccination. We recommend the following:

   a. If you determine that the donor received vaccination against HBV within 28 days prior to the donation that tested confirmed positive for HBsAg, and the vaccination was given solely to protect the donor from future exposure to HBV or as part of an approved HBV immunization program for Source Plasma donors, the donor may be eligible for reentry 8 weeks after the donation that tested reactive and confirmed positive for HBsAg, provided all donor eligibility criteria are met. Testing of a follow-up sample) for the purpose of reentry prior to the donation is not necessary under this requalification method or process.

   b. If you determine that the donor received vaccination against HBV within 28 days prior to the donation that tested confirmed positive for HBsAg, and the vaccination was given as a prophylaxis following a specific incident of potential HBV exposure, obtain a follow up sample from the donor at least 6 months after the potential exposure (no donation is made at this time) and test the sample using a licensed donor screening test for HBsAg and HBV DNA by NAT. If both tests are nonreactive, the donor may be eligible for reentry, provided all donor eligibility criteria are met.

ii. To requalify a deferred donor with HBsAg reactive and not confirmed positive (non-neutralized) results (i.e., negative) and HBV NAT nonreactive test results, we recommend the following:

   a. At least 8 weeks after the reactive HBsAg, the donor may present for donation. Testing of a follow-up sample for the purpose of reentry prior to the donation is not necessary.
   b. The donation should be tested using a licensed donor screening test for HBsAg and HBV DNA by NAT.
   c. If the donation tests nonreactive on both the HBsAg test and HBV NAT, the donation is suitable, provided all other suitability criteria are met.
   d. If the donation tests reactive on the HBV NAT or reactive on the HBsAg test and not confirmed positive (non-neutralized), you should continue to defer the donor. The donor may be eligible for future requalification using the methods described in this section, as appropriate.
   e. If the donation tests reactive on the HBsAg and is confirmed positive by neutralization or by a HBV NAT with supplemental indication, the donor should be deferred permanently.

iii. To requalify a deferred donor with HBV NAT reactive and HBsAg nonreactive test results or HBV NAT reactive and HBsAg reactive and not confirmed positive (non-neutralized) (i.e., negative) test results, we recommend the following:

a. At least 6 months after the reactive HBV NAT, obtain a follow up sample from the donor (no donation is made at this time) and test the sample using a licensed donor screening test for HBsAg and HBV DNA by NAT.
b. If the sample tests nonreactive on both the HBsAg test and HBV NAT, the donor may be eligible for reentry, provided the donor meets all eligibility criteria when presenting to donate.
c. If the sample tests reactive on the HBV NAT test, the donor should be deferred permanently.
d. If the sample tests nonreactive on the HBV NAT and reactive on the HBsAg test and not confirmed positive (non-neutralized), the donor may be further evaluated using the requalification method described in section III.B.2.b.ii of this guidance.
e. Note that nonreactive test results obtained earlier than the 6-month waiting period may be useful for donor notification and counseling but may not be used to requalify the donor. Only nonreactive test results obtained at least 6 months following the last reactive HBV NAT result would qualify the donor for reentry. If during the 6-month waiting period, a reactive HBV NAT or reactive HBsAg test that is confirmed positive (neutralized or by HBV NAT with supplemental indication) is obtained, the donor is not eligible for reentry and should be deferred permanently.
f. A donor who has been requalified as described above may subsequently be deferred for HBV NAT reactive results. The deferred donor may be eligible for reentry by using the requalification method described in this section.

Table 2. Donor Eligibility and Requalification: Donors of Source Plasma

Screening test results (index donation)			HBV vaccination 28 days of index donation	Donor eligibility	Minimum interval for reentry testing	Acceptable test results for requalification
HBV NAT	HBsAg	HBsAg Confirmatory				
Reactive	Reactive	Positive	N/A[a]	Defer permanently	N/A	N/A
Nonreactive	Reactive	Positive	No	Defer permanently	N/A	N/A
Nonreactive	Reactive	Positive	Yes Immunization program[b]	Defer for 8 weeks[c]	N/A	N/A
Nonreactive	Reactive	Positive	Yes Possible HBV exposure	Eligible for reentry	6 months	HBV NAT - NR[d] HBsAg - NR
Nonreactive	Reactive	Negative	N/A	Defer for 8 weeks[c]	N/A	N/A
Reactive	Reactive or Nonreactive	Negative	N/A	Eligible for reentry	6 months	HBV NAT - NR HBsAg - NR

[a] N/A means not applicable.

[b] Vaccination was given solely to protect the donor from future exposure to HBV or as part of an approved HBV immunization program for Source Plasma donors.

[c] Additional testing for the purpose of reentry is not necessary.

[d] NR means nonreactive.

C. Product Management, Retrieval and Quarantine, Notification of Consignees

1. You may release donations that are nonreactive for HBV when tested in accordance with 21 CFR 610.40 provided all other donation suitability requirements are met (21 CFR 630.30).

2. You must not ship or use a donation that is reactive for HBV, unless an exception for shipment or use is applicable (21 CFR 610.40(h) and 21 CFR 630.30(b)(1)).

3. We recommend that you destroy or relabel blood and blood components that test reactive for HBV. The blood and blood components may be released for research or for further manufacture into non-injectable products or in vitro diagnostic reagents when no other suitable sources are available, when written approval by FDA is obtained and the blood and blood components are labeled appropriately as described below (see 21 CFR 610.40(h)(2)(ii).

   You must label the reactive unit as required under 21 CFR 606.121 and with the "BIOHAZARD" legend (21 CFR 610.40(h)(2)(ii)(B)). You must use the following caution statements to prominently relabel the blood components (21 CFR 606.121(c)(12), 606.121(f), and 610.40(h)(2)(ii)), as applicable:

   a. "NOT FOR TRANSFUSION: Collected from a Donor Determined to be Reactive for [HBV DNA, Anti-HBc, and/or HBsAg]"

   AND

   b. "Caution: For Laboratory Research Only"

   OR

   "Caution: For Further Manufacturing into In Vitro Diagnostic Reagents for Which There Are No Alternative Sources"

   OR

   "Caution: For Further Manufacturing Use as a Component of a Medical Device for Which There Are No Alternative Sources"

4. We recommend that you take the following actions on previous collections from the donor when a current donation tests reactive for HBV by a licensed donor screening test.

   a. Within 1 week of the reactive screening test(s) for HBV, identify all blood and blood components previously collected from the donor in the 12 months prior to the date of the reactive index donation.

b. Quarantine the identified in-date blood components held at your establishment.

c. Notify consignees to quarantine all identified blood components collected from the donor in the 12 months prior to the date of the reactive index donation that have been distributed.

   The recommendations for quarantine, consignee notification and retrieval do not apply to plasma components that have been pooled for further manufacture or plasma derivatives manufactured from the plasma of such a donor or to Source Plasma subject to 21 CFR 640.69(f).[4]

d. You should release from quarantine, destroy or relabel the quarantined blood and blood components consistent with the results of further testing under 21 CFR 610.40(e) of the currently reactive unit, or the results of the reactive screening tests when further testing using a licensed, approved or cleared supplemental test is not available.

   i. You may release blood components from quarantine when further testing under 21 CFR 610.40(e) is performed and negative (i.e., the index donation tests reactive for HBsAg only and is not confirmed positive (non-neutralized)).

   ii. You should not release blood components from quarantine when further testing is performed under 21 CFR 610.40(e) and is positive (i.e., the index donation tests reactive for HBsAg and is confirmed positive by neutralization or supplemental HBV NAT), or if the index donation is reactive for HBV DNA by NAT or anti-HBc and further testing is not available. You should take the actions described in Section III.C.3 of this guidance.

D. Labeling

1. Circular of Information for Blood and Blood Components Intended for Transfusion

   The circular of information must include the names and results of all tests performed when necessary for safe and effective use (21 CFR 606.122(h)). We recommend the following statements:

   "A licensed test for antibodies to hepatitis B core antigen (anti-HBc) has been performed and found to be nonreactive."

[4] Per 21 CFR 640.69(f), Source Plasma donated by paid donors determined to be suitable for further manufacturing into injectable products must be held in quarantine for a minimum of 60 calendar days before it is released for further manufacturing. If, after placing a donation in quarantine under 21 CFR 640.69(f), the donor is subsequently deferred under 21 CFR 610.41 of this chapter or subsequently determined by the blood establishment to be ineligible under 21 CFR 630.10 due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection, the prior donations under 60-day quarantine must not be distributed for further manufacturing use to make an injectable product.

"A licensed nucleic acid test (NAT) for HBV DNA has been performed and found to be nonreactive."

When testing for HBsAg is discontinued, you must update your circular of information (21 CFR 606.122(h)) to remove the statement referring to HBsAg testing results.

2. Blood Components Intended for Further Manufacture

   The container label of blood components intended for further manufacturing use must include a statement listing the results of all the tests for RTTI required under 21 CFR 610.40 for which the donation has been tested and found negative (see 21 CFR 606.121(c)(11). We recommend the following statements, as applicable:

   "Nonreactive for HBsAg"

   "Nonreactive for HBV DNA"

IV. REPORTING CHANGES TO AN APPROVED APPLICATION

Licensed blood establishments must report changes to their approved biologics license application in accordance with 21 CFR 601.12.

A. Licensed blood establishments that discontinue testing donations for HBsAg, make conforming changes to donor requalification, revise their circular of information, or make other changes to their standard operating procedures consistent with the recommendations in section III 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)). Unlicensed blood establishments do not need to report those changes to FDA.

   We recognize that some blood establishments may continue testing for HBsAg when donations are tested for anti-HBc and HBV DNA by NAT. In this case, you must continue to follow your current standard operating procedures for testing donations for HBV (21 CFR 606.100(b)) and comply with all applicable requirements, including requirements related to the management of reactive screening test results, including further testing and restriction on shipment and use (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). Because you are not making any changes to your approved application, you do not need to report to FDA under 21 CFR 601.12.

B. We consider implementation of an HBV testing strategy or other procedures other than as recommended in section III of this guidance to be a major change. Licensed blood establishments must submit a prior approval supplement under 21 CFR 601.12(b).

V. REFERENCES

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Appendix A

Guidance History[*]	**Date**	**Description**
Level 1 Final Guidance	November 2026	See Notice of Availability for more information.**
Level 1 Draft Guidance	July 2025	See Notice of Availability for more information.**

*This table was implemented, beginning February 2025 and previous guidance history may not be captured in totality.
** The Notice of Availability is accessible via the Search for FDA Guidance Documents webpage.