Recommendations to Reduce the Risk of Transmission of Hepatitis B Virus (HBV) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Draft Guidance for Industry

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Table of Contents

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I. INTRODUCTION

We, FDA or Agency, are issuing this guidance to assist you, establishments making donor eligibility determinations,[1] in understanding the requirements in Title 21 Code of Federal Regulations, part 1271, subpart C (21 CFR part 1271, subpart C). The regulations under 21 CFR part 1271, subpart C set out requirements for determining donor eligibility, including donor screening and testing, for donors of human cells, tissues, or cellular or tissue-based products (HCT/Ps).[2]

This guidance applies to human cells and tissues recovered on or after May 25, 2005, the effective date of the regulations contained in 21 CFR part 1271, subpart C, and provides recommendations to reduce the risk of transmission of hepatitis B virus (HBV) by HCT/Ps. This guidance updates information regarding HBV risk included in the guidance entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry," dated August 2007 (August 2007 HCT/P DE Guidance), by revising recommendations for: 1) donor screening that includes reducing certain time-based risk factors and conditions, and 2) assessing every HCT/P donor for HBV risk using the same individual risk-based questions regardless of sex. Additionally, this guidance incorporates information from the guidance entitled "Use of Nucleic Acid Tests to Reduce the Risk of Transmission of Hepatitis B Virus from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" dated August 2016 (August 2016 HBV NAT Guidance) and supersedes that guidance.

[1] See 21 CFR 1271.50.

[2] HCT/Ps are defined in 21 CFR 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."

When finalized, this guidance will provide specific recommendations for HCT/P donor testing and screening for risks associated with HBV infection and supersede information regarding HBV risk in the August 2007 HCT/P DE Guidance and the 2016 HBV NAT Guidance.

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA'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 FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

HBV infection is a major global public health problem (Refs. 1-4). According to the World Health Organization (WHO), there are 254 million people who are chronically infected with HBV, there are 1.2 million new infections each year, and an estimated 1.1. million deaths occurred worldwide in 2022 from HBV infections, mostly from cirrhosis and hepatocellular carcinoma (primary liver cancer) (Ref. 1). The burden of HBV infection varies in different parts of the world. The prevalence of chronic HBV infection ranges from less than 2% in low prevalence areas (e.g., Americas, Europe) to greater than or equal to 6% in high prevalence areas (e.g., Africa, Western Pacific) (Refs. 2-3).

HBV is a partially double-stranded DNA-containing enveloped virus in the family Hepadnaviridae. Important components of the viral particle include an outer lipoprotein envelope containing hepatitis B surface antigen (HBsAg) and an inner nucleocapsid consisting of hepatitis B core antigen (Ref. 4).

In 2022, the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) expanded previous risk factor-based vaccine recommendations. The ACIP recommends universal hepatitis B vaccination for all unvaccinated adults aged 19 to 59 years in addition to groups for whom vaccination was already recommended including infants at birth, unvaccinated children younger than 19 years of age, and adults with risk factors for Hepatitis B. Adults aged 60 and older without known risk factors may also be vaccinated. Still, HBV infection remains a public health issue in the U.S. Data collected from the National Health and Nutrition Examination Survey 2017-2020 report 640,000 non-institutionalized adults (20 years and older) living with chronic HBV infection in the U.S. (0.3% of the population) (Ref. 6). In 2022, a total of 2,126 cases of acute hepatitis B were reported to the CDC (Ref. 7). Cirrhosis and hepatocellular carcinoma are late complications caused by chronic HBV infection and, without intervention, are responsible for an estimated 14,000 deaths annually in the U.S. (Ref. 8).

The clinical course of HBV infection is determined by the balance between virus replication and the host's immune response. Most primary infections in adults are self-limited. Generally, the virus is cleared from blood and liver, and individuals develop a lasting immunity, however, HBV may persist in the body even after serological recovery from acute HBV infection. Chronic HBV infection after acute exposure can be serious; about 20% of chronically HBV-infected

individuals develop cirrhosis, and chronically HBV-infected subjects have 100 times higher risk of developing hepatocellular carcinoma than persons who test negative for HBsAg (Refs. 9-10).

There is a strong relationship between HBV genotype and geography worldwide. Additionally, different genotypes influence transmission patterns of infection (Refs. 11-12). There are different vaccines for HBV that vary in efficacy and cross protection against the different genotypes. These vaccines are very successful at preventing HBV globally. Although rare, Hepatitis vaccine efficacy is dependent on whether the vaccine matches the prevalent strain in a given population (Ref. 13). HBV infection can still occur in previously vaccinated individuals. Breakthrough infections caused by unexpected genotypic mutations can occur (Refs. 10, 13, -14).

III. DISCUSSION

In the Federal Register of May 25, 2004 (69 FR 29786), FDA issued a final rule entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products" (21 CFR part 1271, subpart C), which took effect on May 25, 2005. In this final rule, FDA identified HBV as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(1). Thus, for donors of HCT/Ps recovered on or after May 25, 2005, screening and testing for HBV is required (21 CFR 1271.75(a)(1)(ii) and 1271.85(a)(3)). Specific tests for HBV and donor screening for specific risk factors and conditions associated with HBV infection, have been recommended for HCT/P donors in order to adequately and appropriately reduce risk of transmission. Specific recommendations for donor testing and screening for risk associated with HBV were issued in the August 2007 HCT/P DE Guidance.

A. Risk of Transmission

There is a risk of transmission of HBV by HCT/Ps. This is supported by reported cases of HBV transmission via transfusion of blood products, by organ transplantation, and from the use of HCT/Ps.

HBV is transmitted through blood and body fluids (Ref. 4). Common modes of transmission include percutaneous and mucosal exposure to infectious body fluids, sharing or using non-sterilized needles or syringes, sexual contact with an infected person, living in the same household or institution, and perinatal exposure to an infected mother (Refs. 4, 15). Although in utero transmission accounts for less than 2% of all vertically transmitted HBV infections in most studies, perinatal transmission of HBV is highly efficient and usually occurs from blood exposures during labor and delivery (Refs. 4, 16).

HBV has also been transmitted through transplantation of infected organs (Refs. 17-19) and through use of contaminated human cells or tissues (Refs. 20-25). Although the prevalence rate of HBV in U.S. tissue donors has been estimated to be lower than in the

general population, the estimated probability of undetected viremia at the time of donation is higher among tissue donors than among first-time blood donors (Ref. 26).

1. Potential for Transmission of HBV by Blood Products and Solid Organs

In 2009, the American Red Cross implemented use of NAT for HBV when screening blood donations (Ref. 27).

Implementation of NAT donor screening tests has reduced the residual risk of HBV transmission via blood donation (Refs. 27-28). A recent study based on data from American Red Cross reported from 58 million donations from 2007 to 2016, estimated the residual risk of HBV transmission was 1 in 1.5 million, which was consistent with previously published data (Ref. 29).

Beginning in September 1985, FDA recommended that blood establishments indefinitely defer male donors who have had sex with another male, even one time, since 1977, because of the strong clustering of AIDS and the subsequent discovery of high rates of HIV infection among MSM (Ref. 15). FDA subsequently concluded that the available evidence supported a change from the indefinite deferral for MSM, and in December 2015, recommended a 12-month deferral for MSM.

While the studies used to support blood donor deferral recommendations (e.g., ADVANCE study, risk assessments) are not specific to HCT/Ps, they are nonetheless relevant beyond blood donation. These studies considered certain risk factors associated with blood donors acquiring HIV, which are also risk factors for acquiring HBV.

In 2014, FDA launched the Transfusion Transmissible Infections Monitoring System (TTIMS), a program implemented in the U.S. in order to facilitate monitoring blood safety, particularly in the context of changes in blood collection policy and practice. Following implementation of the 12-month blood donor deferral policy in December 2015, for men who have sex with men (MSM), four years of data from TTIMS indicated there had been no increase in risk to the blood supply from the policy change. Additionally, other countries, including the United Kingdom and Canada moved to a 3-month deferral period for MSM, after which, there were no reports from these countries suggesting safety concerns following the implementation of this change. Thereafter, FDA reduced the recommended blood donor deferral period to 3 months for MSM, through recommendations published in guidance in April 2020 (Ref. 30).

In addition to shortening the recommended deferral period for MSM in 2020, FDA concurrently evaluated the available scientific evidence that could support elevated risk for HIV. Based on the experience in the United Kingdom and Canada, along with the detection characteristics of the NAT noted above, in April

2020, FDA also revised the recommended deferrals for individuals who exchange sex for money or drugs or engage in non-prescription injection drug use from indefinite to 3-month deferrals. In addition, for similar reasons, the recommended 12-month deferral for other risk factors, including contact with another person's blood, receipt of a blood transfusion or a recent tattoo or piercing, was revised to 3 months.

FDA subsequently helped facilitate and fund the ADVANCE (Assessing Donor Variability and New Concepts in Eligibility) study, a pilot study intended to evaluate individual risk assessment strategies as an alternative to time-based deferrals for MSM (Ref. 31). The ADVANCE study examined a number of HIV risk factors, such as anal sex and rates of HIV infection among MSM study participants.

FDA also recognized that other countries with similar HIV epidemiology as the U.S. revised their donor eligibility criteria for MSM, based on risk assessments performed in these countries. Notably, the United Kingdom in 2021 and Canada in 2022 introduced a new approach for donor questioning based on individual risk factors (Refs. 32-36). The approach is based on surveillance, epidemiology, and risk assessments that demonstrate that new or multiple sexual partners, and for those with new or multiple partners, anal sex, are the most significant risk factors that increase the likelihood of HIV infection (Refs. 32-37). The United Kingdom and Canada have adopted an individual risk-based approach that asks all presenting blood donors (regardless of sex), if they have had a new sexual partner or more than one sexual partner in the last 3 months, and if so, they are asked if they had anal sex (Refs. 34, 38). Individuals who report having a new sexual partner and anal sex or having more than one sexual partner and anal sex in the last three months are deferred from blood donation. To date, the United Kingdom and Canada have not reported safety concerns following the implementation of this individual risk-based deferral policy.

Subsequently, FDA concluded that implementing an individual risk-based approach will maintain the safety of the blood supply and in May 2023, FDA issued guidance that recommends (1) eliminating the blood donor screening questions specific to MSM and women who have sex with MSM; and (2) assessing blood donor eligibility using the same individual risk-based questions relevant to HIV risk for every donor regardless of sex (Ref. 30).

Other federal agencies have also reconsidered the transmission risk of HBV through solid organs because transmission of HBV infection has been reported after solid organ transplantation (Ref. 39). Among solid organ transplant recipients, the risk of post-transplant HBV infection is seen primarily among seronegative liver recipients (Refs. 17-18); transmission is significantly lower in kidney transplant recipients and is essentially negligible in thoracic transplant recipients (Ref. 19). The absence of HBV DNA in donor serum does not preclude

transmission of HBV to liver recipients (Ref. 19). In addition, guidelines for assessing solid organ donors and monitoring transplant recipients for risk of HBV (as well as hepatitis C virus (HCV) and HIV) infection have evolved (Ref. 40). An evidence-based process was used to update guidelines that included developing key questions to evaluate behavioral and non-behavioral risk factors associated with transmission of these viruses, and an exhaustive literature review was undertaken where they were categorized according to strength and data quality, and evidence was graded. Organ donor screening guidelines were revised to identify donors at risk for acquiring a recent HIV, HBV, or HCV infection (Ref. 41).

2. Potential for Transmission of HBV by HCT/Ps

There is a risk for transmission of HBV by HCT/Ps (Refs. 20-21) and reports of suspected adverse reactions involving HBV after implantation, transplantation, infusion or transfer of human cells or tissues have been investigated (Ref. 42). Transmission of HBV infection has also been reported after use of an avascular tissue such as cornea (Ref. 22) and after implantation of a heart valve allograft (Ref. 23). Additionally, transmission of HBV infection has been reported after hematopoietic stem cell transplantation (Ref. 24) and from use of donated semen in assisted reproductive technology procedures (Ref. 25).

As noted above and elaborated further below, advances in HBV donor testing, when using HBsAg, total antibody to hepatitis B core antigen (total anti-HBc), and an HBV NAT, have reduced the "window period" when HBV infection may not be detectable by screening tests (Refs. 27, 29).

Formal studies and collection of data specific to HCT/P donors are lacking, however, many of the studies used to support blood donor deferral recommendations (e.g., ADVANCE study, risk assessments, etc.) are relevant beyond blood donation. These studies considered certain risk factors associated with donors acquiring HIV, and the same risk factors associated with acquiring HIV are relevant to screening not only blood donors but also donors of HCT/Ps. Further, many of the key risk factors for acquiring HIV are also risk factors for acquiring HBV. In addition, the evidence-based process used to update organ donor screening guidelines that evaluated behavioral and non-behavioral risk factors associated with transmission of HIV, HBV, or HCV, for which a number of risk factors overlap, provides substantial support to identify donors at risk for acquiring a recent infection. Having a recent infection is relevant to risk of transmission presented by HCT/P donors in addition to organ donors. Given these data, experience with a 3-month blood donor deferral in other countries, and the uniform use of HBV NAT for testing HCT/P donors (which can detect HBV well within a 3-month period following initial infection), the Agency concludes, at this time, that a change to a recommended 3-month risk period as detailed

below is scientifically supported for certain risk factors and conditions associated with HBV for donors of HCT/Ps (Refs. 40, 41).

Additionally, based on our review of the available science, adequacy of available test methods, studies used to evaluate risk behaviors, and experiences with updated blood donor screening questions, FDA also recommends eliminating the HCT/P donor screening questions specific to MSM and women who have sex with MSM and, instead, recommends assessing every HCT/P donor for HBV risk using the same individual risk-based questions relevant to HBV risk regardless of sex.

B. Severity of Effect

Among adults with acute HBV infection, approximately 5 to 10% will progress to chronic HBV infection. Most individuals with chronic HBV infection are asymptomatic, because only one-third of adults develop symptoms during an acute HBV infection which may include fever, fatigue, malaise, abdominal pain, and/or jaundice (Ref. 43).

Approximately 12% of patients with chronic HBV infection develop cirrhosis each year, and a smaller percentage develop hepatocellular carcinoma. As many as 20% of people with chronic HBV infection will die from complications of liver disease such as cirrhosis, and 1-2% will die of hepatocellular carcinoma (Refs. 43-44).

C. Availability of Appropriate Screening and/or Testing Measures

As described above, appropriate donor screening measures have been developed for HBV, and specific details are listed below for screening a donor for clinical and physical evidence, and risk factors and conditions to reduce the risk of transmission of HBV.

FDA-licensed donor screening tests to detect HBsAg, total anti-HBc, and HBV viral nucleic acid (using NAT) are available for screening cadaveric (non-heart-beating) and/or living donors of HCT/Ps.

The addition of NAT to screen HCT/P donors significantly reduces the risk of transmission of HBV (Refs. 26, 45-51). The probability of HBV viremia at the time of tissue donation has been estimated to be reduced from 1 in 34,000 to 1 in 100,000 when individual HBV NAT testing is used (Ref. 26). Depending on the relative sensitivities of HBsAg and HBV NAT assays used, HBV DNA can be detected 2 to 5 weeks after infection, and up to 40 days (mean 6 to 15 days) before HBsAg (Refs. 8, 48).

All HBsAg-positive persons are infectious. If HBsAg persists for greater than 6 months, spontaneous clearance is unlikely, and the infection is deemed chronic. In acute HBV infection, initially both Immunoglobulin M (IgM) and Immunoglobulin G (IgG) of anti-HBc appear 1–2 weeks after the appearance of HBsAg (Ref. 44). IgM anti-HBc often becomes undetectable within 6 months, and IgG anti-HBc predominates and remains

detectable for a lengthy period of time, often life-long (Refs. 52-53) and such results can be associated with infectivity (Refs. 54-60). In certain persons, anti-HBc is the only serologic marker detected (Refs. 54, 61). Some chronically infected persons with isolated anti-HBc-positivity have circulating HBsAg that is not detectable by a laboratory assay. HBV DNA has been detected in less than 10% of persons with isolated anti-HBc (Refs. 62-63), although the presence of detectable HBV DNA might fluctuate (Ref. 64).

In the August 2016 HBV NAT Guidance, FDA recommended the use of an FDA-licensed HBV NAT donor screening test, in addition to using FDA-licensed donor screening tests for HBsAg and total anti-HBc (IgG plus IgM), for testing donors of HCT/Ps for evidence of infection with HBV to adequately and appropriately reduce the risk of disease transmission (21 CFR 1271.85(a)(3)).

The FDA-licensed HBV NATs are intended to screen blood samples from donors of whole blood and blood components, other living donors (individual organ donors when specimens are obtained while the donor's heart is still beating), and blood specimens from cadaveric (non-heart-beating) donors. Some of these are multiplex assays that can simultaneously detect HBV, HIV, and HCV in a single blood specimen, thus improving the feasibility of routine NAT for HBV.

IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions of HBV Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records (21 CFR 1271.3(s)) and ask questions about the donor's medical history and relevant conditions and behavioral risks, including risk factors for RCDADs (21 CFR 1271.75(a)).

The list below provides risk factors and conditions for which we recommend screening in order to reduce the risk of transmission of HBV infection. Except as noted in this section, and in accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for HBV. The following conditions or behaviors should be considered risk factors for HBV:

1. Persons who have ever had a positive or reactive screening test for HBV (Refs. 20-25, 42).

2. Persons who have engaged in non-prescription injection drug use in the preceding 3 months, including intravenous, intramuscular, or subcutaneous injections (Refs. 4, 15, 30, 38, 65-67, 68).

3. Persons who have had sex[3] in exchange for money or drugs or other payment[4] in the preceding 3 months (Refs. 4, 15, 30, 38, 65-67, 69-73).

4. Persons who have had sexual contact in the preceding 3 months with any individual who has ever had a positive test for HBV infection (Refs. 67, 74).

5. Persons who have had sexual contact in the preceding 3 months with any individual who has exchanged sex for money, drugs or other payment. If there is any uncertainty about when their sexual partner exchanged sex for money, drugs or other payment, the person is ineligible for 3 months (Ref. 74).

6. Persons who have had sexual contact in the preceding 3 months with any individual who has engaged in non-prescription injection drug use. If there is any uncertainty about when their sexual partner engaged in non-prescription injection drug use, the person is ineligible for 3 months (Ref. 67).

7. Persons who have had a new sexual partner[5] in the preceding 3 months **and** have had anal sex in the preceding three months (Refs. 4, 15, 30, 44, 65-68, 75).

Note: An anonymous semen donor who reports this behavior may be eligible provided that the semen donation is kept in quarantine and the results from initial and requisite retesting of the donor are negative (or non-reactive) and no other risk factor for an RCDAD is identified.[6] If a directed semen donor exhibits this behavior, you may elect to perform the quarantine and retesting steps described for an anonymous semen donor. If such steps are taken, the directed semen donor may be eligible provided that the results from initial testing and retesting of the donor are negative (or non-reactive) and no other risk factor for any RCDAD is identified.

[3] Throughout this guidance, unless specified as "anal sex," the term "sex" or "sexual contact" refers to vaginal, anal, or oral sex, regardless of whether a condom or other protection is used.

[4] https://www.unaids.org/sites/default/files/media_asset/2024-terminology-guidelines_en.pdf

[5] For the purposes of this guidance, the following examples would be considered having sex with a new partner: having sex with someone for the first time; or having had sex with someone in a relationship that ended in the past and having sex again with that person.

[6] In accordance with 21 CFR 1271.60(a), you must quarantine semen from anonymous donors until the retesting required under § 1271.85(d) is complete. In accordance with 21 CFR 1271.85(d), at least 6 months after the date of donation of semen from anonymous donors, you must collect a new specimen from the donor and test it for evidence of infection due to the communicable disease agents for which testing is required under paragraphs (a), (b), and (c) of 1271.85(d).

8. Persons who have had more than one sexual partner[7] in the preceding 3 months **and** have had anal sex in the preceding three months (Refs. 4, 15, 30, 44, 65-68, 75).

   Note: An anonymous semen donor who reports this behavior may be eligible provided that the semen donation is kept in quarantine and the results from initial and requisite retesting of the donor are negative (or non-reactive) and no other risk factor for an RCDAD is identified.[8] If a directed semen donor exhibits this behavior, you may elect to perform the quarantine and retesting steps described for an anonymous semen donor. If such steps are taken, the directed semen donor may be eligible provided that the results from initial testing and retesting of the donor are negative (or non-reactive) and no other risk factor for any RCDAD is identified.

9. Persons who have been exposed in the preceding 3 months to known or suspected HBV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane (Refs. 4, 15, 30, 44, 65-68, 76).

10. Persons who have been in lock up, jail, prison, or a juvenile correctional facility for more than 72 consecutive hours in the preceding 3 months (Refs. 30, 66, 68, 78-80).

11. Persons who have lived with (resided in the same dwelling) another person who has HBV infection in the preceding 3 months (Refs. 4-5, 15, 30, 44).

12. Persons who have undergone tattooing, ear piercing or body piercing in the preceding 3 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used. A person may be eligible, for example, if a tattoo was applied by a state regulated entity with sterile needles and non-reused ink, or if ear or body piercing was done using single-use equipment (Refs. 1, 30, 77, 81-82).

13. Children 1 month of age or younger who were born to a mother with, or at risk for, an HBV infection; see risk factors above (Refs. 2, 4, 7, 16, 40, 44, 66, 68).

[7] See footnote 5.
[8] See footnote 6.

B. Screening a Donor for Clinical Evidence of HBV Infection

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records for clinical evidence of relevant communicable disease agents and diseases (21 CFR 1271.75). In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who exhibits clinical evidence of HBV (Refs. 4, 43, 83-84). Examples of clinical evidence of HBV may include:

- A prior positive or reactive screening test for HBV;
- Unexplained jaundice;
- Unexplained hepatomegaly;
- Generalized lymphadenopathy; and/or
- Unexplained generalized rash or fever.

Records of the following laboratory data might assist you in making the donor eligibility determination when there is an inconclusive history of hepatitis infection; however, these test results should not be used alone to determine donor eligibility:

- alanine aminotransferase (ALT);
- aspartate aminotransferase (AST);
- bilirubin; or
- prothrombin time.

C. Screening a Donor for Physical Evidence of HBV Infection

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric donor (21 CFR 1271.3(o)) or the physical examination of a living donor.

Some of the following observations are not physical evidence of HBV, but rather are indications of high-risk behavior associated with the disease and would increase the donor's relevant communicable disease risk. Unless an exception identified in 21 CFR 1271.90(a) applies, in accordance with 21 CFR 1271.75(d)(1), you must determine to be ineligible any potential donor who has risk factors for or clinical evidence of HBV. The following are examples of physical evidence of HBV or high-risk behavior associated with HBV:

1. Physical evidence for risk of sexually transmitted diseases and infections, such as perianal lesions, genital ulcerative disease, herpes simplex, or chancroid (when making a donor eligibility determination, you should consider these findings in light of other information obtained about the donor) (Refs. 4, 15, 30, 44, 65-68).

2. Physical evidence of nonmedical percutaneous drug use such as needle tracks; your examination should include examination of tattoos, which might be covering needle tracks (Refs. 4, 15, 30, 44, 65-68).

3. Physical evidence of recent tattooing, ear piercing, or body piercing. Persons who have undergone tattooing, ear piercing, or body piercing in the preceding 3 months, in which sterile procedures were not used (e.g., contaminated instruments and or/ink were used), or instruments that had not been sterilized between uses were used. A person may be eligible, for example, if a tattoo was applied by a state regulated entity with sterile needles and non-reused ink, or if ear or body piercing was done using single-use equipment (Refs. 1, 30, 77, 81-82).

4. Unexplained jaundice, hepatomegaly, or icterus (Refs. 43, 83). Hepatomegaly may not be apparent in a physical assessment unless an autopsy is performed.

5. Generalized lymphadenopathy (Ref. 84).

6. Unexplained generalized rash or fever (Ref. 84).

D. Testing a Donor for Evidence of HBV Infection

You must test all donors of HCT/Ps for HBV as required under 21 CFR 1271.85(a), unless an exception under 21 CFR 1271.90(a) applies, and as required in 21 CFR 1271.80(c), you must use appropriate FDA-licensed, approved, or cleared screening tests in accordance with the manufacturer's instructions.[9]

The following donor screening tests adequately and appropriately reduce the risk of transmission of HBV (Refs. 26-30, 44-64, 85-87). Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. FDA-licensed donor screening test for hepatitis B surface antigen (HBsAg); and

2. FDA-licensed donor screening test for total antibody to hepatitis B core antigen (total anti-HBc means IgG and IgM); and

3. FDA-licensed donor screening Nucleic Acid Test for HBV (HBV NAT); or a combination or multiplex NAT that includes HBV.

Any HCT/P donor whose specimen tests negative (or non-reactive) for all three assays (i.e., HBsAg, total anti-HBc (IgG and IgM), and HBV NAT) is considered to be negative (or non-reactive) when making a donor eligibility determination. Note that a negative (or

[9] The following CBER website includes a list of FDA-licensed, approved, or cleared donor screening tests (including manufacturers and tradenames): https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/testing-human-cells-tissues-and-cellular-and-tissue-based-product-hctp-donors-relevant-communicable.

non-reactive) test does not necessarily mean that a donor is eligible; donor screening also applies as described above.

Any HCT/P donor whose specimen tests positive (or reactive) using any of the assays (i.e., HBsAg, total anti-HBc (IgG and IgM), or HBV NAT) is considered ineligible (21 CFR 1271.80(d)(1)).

V. REFERENCES

1. World Health Organization, Hepatitis B, April 2024. https://www.who.int/en/news-room/fact-sheets/detail/hepatitis-b. Accessed June 10, 2024.
2. Ott JJ, et al. Global epidemiology of hepatitis B virus infection: new estimates of age-specific HBsAg seroprevalence and endemicity, Vaccine, 2012; 30(12): 2212-2219.
3. Web Annex 1. Key data at a glance. In: Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016–2021: actions for impact. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.
4. Red Book Online. Committee on Infectious Diseases; American Academy of Pediatrics, 2018, 401-428.
5. Weng MK, Doshani M, Khan MA, et al. Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022. MMWR Morb Mortal Wkly Rep 2022;71:477–483. DOI: http://dx.doi.org/10.15585/mmwr.mm7113a1
6. Bixler D, Barker L, et al. Prevalence and awareness of Hepatitis B virus infection in the United States: January 2017 - March 2020. Hepatol Commun. 2023 Mar 30;7(4).
7. Centers for Disease Control and Prevention. Clinical Overview of Hepatitis B. https://www.cdc.gov/hepatitis/statistics/2022surveillance/hepatitis.
8. Mitchell T, et al. The increasing burden of imported chronic hep–itis B--United States, 1974-2008, PLoS One, 2011; 6(12): e27717.
9. Alter MJ. Centers for Disease Control and Prevention, Epidemiology of HBV and Programs on Prevention. Presentation to the Advisory Committee on Blood Safety and Availability. Transcript. August 27, 2004. https://wayback.archive-it.org/3919/20140404142428/http://www.hhs.gov/ash/bloodsafety/advisorycommittee/pastmeetings/transcripts/acbsa08272004.pdf.
10. Ganem D, Prince AM. Hepatitis B Virus Infection–Natural History and Clinical Consequences. New England Journal of Medicine, 2004; 350: 1118-1129.
11. Lin CL, Kao JH. Hepatitis B virus genotypes and variants, Cold Spring Harb Perspect Med, 2015; 5: a021436.
12. MacLachlan JH, Cowie BC. Hepatitis B Virus Epidemiology, Cold Spring Harb Perspect Med, 2015; 5: a021410.
13. Inoue T, Tanaka Y. Cross-Protection of Hepatitis B Vaccination among Different Genotypes. Vaccines (Basel). 2020;8(3):456. Published 2020 Aug 16. doi:10.3390/vaccines8030456
14. Kleinman SH, et al. Infectivity of Human Immunodeficiency Virus-1, Hepatitis C Virus, and Hepatitis B Virus and Risk of Transmission by Transfusion. Transfusion 2009; 49: 2454-2489.
15. Centers for Disease Control and Prevention. Prevention of Hepatitis B infection in the United States: Recommendations of the Advisory Committee of Immunization Practices. Morb Mortal Wkly Rep 2018; 67(1): 1-31. https://www.cdc.gov/mmwr/volumes/67/rr/rr6701a1.htm.
16. Wen WH, et al. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol 2013; 59:24–30.

17. De Feo TM, et al. Risk of transmission of hepatitis B virus from anti-HBc positive cadaveric organ donors: a collaborative study, Transplant Proc, 2005; 37: 1238-1239.
18. Fabrizio F, et al. Transplanting kidneys from donors with prior hepatitis B infection: one response to the organ shortage. J Nephrol, 2002; 15: 605-613.
19. Yen RD, et al. Case report of lamivudine-resistant hepatitis B virus infection post liver transplantation from a hepatitis B core antibody donor. Am J Transplant 2006; 6: 1077–1083.
20. Eastlund T, Warwick RM. Diseases Transmitted by Transplantation of Tissue and Cell Allografts. Chapter 4 in Tissue & Cell Clinical Use: An Essential Guide. Blackwell Publishing Ltd., 2012.
21. Solves P, et al. Hepatitis B Transmission by cell and tissue allografts: How safe is safe enough? World J Gastroenterol 2014; 20(23):7434-7441.
22. Hoft RH, et al. Clinical evidence for hepatitis B transmission resulting from corneal transplantation. Cornea 1997; 16:132.
23. Morris A, et al. Use of Aortic Valve Allografts from Hepatitis B Surface Antigen-Positive Donors. Ann Thorac Surg 1990; 49(5): 802-805.
24. Locasciulli A, et al. Allogeneic bone marrow transplantation from HBsAg + donors: a multicenter study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood 1995; 86:3236–3240.
25. Berry WR, Gottesfeld RL, Alter HJ, Vierling JM. Transmission of hepatitis B virus by artificial insemination. JAMA 1987; 257:1079–1081.
26. Zou S, et al. Probability of Viremia with HBV, HCV, HIV, and HTLV among Tissue Donors in the United States. N Eng J Med 2004; 351: 751-759.
27. Stramer SL, et al. Hepatitis B virus Testing by Minipool Nucleic Acid Testing: Does It Improve Blood Safety? Transfusion 2013; 53(10 Pt 2): 2449-2458.
28. Zou S, et al. Current Incidence and Residual Risk of Hepatitis B Infection Among Blood Donors in the United States. Transfusion 2009; 49(8): 1609-1620.
29. Dodd RY, et al. Screening Blood Donors for HIV, HCV, and HBV at the American Red Cross: 10-Year Trends in Prevalence, Incidence, and Residual Risk, 2007 to 2016, Transfusion Medicine Reviews, Volume 34, Issue 2, 2020, 81-93.
30. Food and Drug Administration, Guidance for Industry: Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products (May 2023). https://www.fda.gov/media/164829/download.
31. Assessing Donor Variability And New Concepts in Eligibility (ADVANCE) Study; https://www.advancestudy.org.
32. Caffrey N, Goldman M, Lewin A, Grégoire Y, Yi Q-L, O'Brien S, Removing the men who have sex with men blood donation deferral: Informing the risk models using Canadian public health surveillance data, Transfusion Clinique et Biologique, 2022; 29:198-204.
33. O'Brien SF, Goldman M, Robillard P, et al., Donor screening question alternatives to men who have sex with men time deferral: Potential impact on donor deferral and discomfort, Transfusion 2021; 61:94–101.
34. Goldman M, Lewin A, Ren'ud C, O'Brien SF. Implementation of sexual risk behavior donor screening in Canada. Transfusion 2024 May 17.

35. Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO). Donor Selection Criteria Report. July 2017. https://www.gov.uk/government/publications/blood-tissue-and-cell-donor-selection-criteria-report-2017 .
36. FAIR. Can donor selection policy move from a population-based donor selection policy to one based on a more individualized risk assessment? Conclusions from the For the Assessment of Individualized Risk (FAIR) group; 2020.
37. Patel P, et al. Estimating per-act HIV transmission risk: A systematic review. AIDS 2014; 28:1509-1519.
38. NHS Blood and Transplant. Our Improved Donations Safety Check. https://www.blood.co.uk/news-and-campaigns/the-donor/latest-stories/our-improved-donation-safety-check/ .
39. White SL, et al. Infectious Disease Transmission in Solid Organ Transplantation: Donor Evaluation, Recipient Risk, and Outcomes of Transmission. Transplant Direct 2018 Dec 20; 5(1):e416.
40. Jones JM, et al. Assessing Solid Organ Donors and Monitoring Transplant Recipients for Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus – U.S. Public Health Service Guideline, 2020. Morb Mortal Wkly Rep 2020; 69(4): 1-16.
41. Public Health Service, Guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep 2013; 128:247-343
42. Mallick TK, et al. Reported Infections after human tissue transplantation before and after new Food and Drug Administration (FDA) regulations, United States, 2001-through June 2010. Cell Tissue Bank 2012; 13: 259-267.
43. Tang LSY, et al. Chronic Hepatitis B Infection: A Review. JAMA 2018; 319(17): 1802-1813.
44. Trepo C, et al. Hepatitis B virus infection. Lancet 2014; 384: 2053-2063.
45. Strong DM, Nelson K, Pierce M, Stramer SL. Preventing disease transmission by deceased tissue donors by testing blood for viral nucleic acid. Cell Tissue Bank 2005; 6: 255-262.
46. Nucleic acid amplification testing of blood donors for transfusion-transmitted infectious diseases. Committee Report. Transfusion 2000; 40: 143-159.
47. Pruss A, et al. Tissue donation and virus safety: more nucleic acid amplification testing is needed. Transplant Infectious Disease 2010; 12: 375-386.
48. Food and Drug Administration, 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/media/124225/download.
49. Vermeulen M, et al. Reassessment of hepatitis B virus window periods for two transcription-mediated amplification assays using screening data of South African blood donors. Transfusion 2019; Sept: 59(9): 2922-2930.
50. Biswas R, et al. Comparative sensitivity of HBV NATs and HBsAg assays for detection of acute HBV infection. Transfusion 2003 June; 43(6): 788-798.

51. Kleinman SH, Busch MP. Assessing the impact of HBV on window period reduction and residual risk. Journal of Clinical Virology. Vol 36, Supplement 1, May 2006: S23-S29.
52. Pondé RA. Atypical serological profiles in hepatitis B virus infection. Eur J Clin Microbiol Infect Dis 2013; 32:461–476.
53. Pondé RA, Cardoso DD, Ferro MO. The underlying mechanisms for the 'anti-HBc alone' serological profile. Arch Virol 2010; 155:149–158.
54. Esposito A, et al. Occult Hepatitis Infection in Transfusion Medicine: Screening Policy and Assessment of Current Use of Anti-HBc Testing. Transfus Med Hemother 2017; 44(4):263-272.
55. Hollinger FB, Sood G. (2010), Occult hepatitis B virus infection: a covert operation. Journal of Viral Hepatitis; 17: 1-15.
56. Gerlich WH, et al. Occult Hepatitis B Virus Infection: Detection and Significance. Dig Dis 2010; 28:116-125.
57. Launay O, et al. High levels of serum hepatitis B virus DNA in patients with 'anti-HBc alone': role of HBsAg mutants. J Viral Hepat 18 (2011); pp. 721-729.
58. Mikulska M, et al. Hepatitis B reactivation in HBsAg-negative/HBcAb-positive allogeneic haematopoietic stem cell transplant recipients: risk factors and outcome. Clin Microbiol Infect 20 (2014); pp. 694-701.
59. Yip TC, Wong GL. Current Knowledge of Occult Hepatitis B Infection and Clinical Implications. Semin Liver Dis. 2019; 39(2):249-260.
60. Pisaturo M, et al. An estimation of the prevalence of occult HBV infection in Western Europe and in Northern America: A meta-analysis. Journal of viral hepatitis 2020; Vol. 27(4), p.415-427.
61. Candotti D, Laperche S. Hepatitis B Virus Blood Screening: Need for Reappraisal of Blood Safety Measures? Front Med 2018; 5: 29.
62. Grob P, et al. Serological pattern "anti-HBc alone": report on a workshop. J Med Virol 2000; 62:450–455.
63. Silva AEet al. Hepatitis B virus DNA in persons with isolated antibody to hepatitis B core antigen who subsequently received hepatitis B vaccine. Clin Infect Dis 1998; 26:895–897.
64. Candotti D, et al. Occult hepatitis B infection in blood donors from South East Asia: molecular characterisation and potential mechanisms of occurrence. Gut 2012; 61:1744–1753.
65. Chou R, et al. Screening for Hepatitis B Virus Infection in Nonpregnant Adolescents and Adults: Systematic Review to Update the 2004 U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 110. AHRQ Publication No. 12-05172-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2014.
66. Public Health Service, Guideline for reducing human immunodeficiency virus, hepatitis B virus, and hepatitis C virus transmission through organ transplantation. Public Health Rep 2013; 128:247-343.
67. Piot P, Goilav C, Keels E. Hepatitis B: transmission by sexual contact and needle sharing. Vaccine 1990; Volume 8, Supplement 1, S37-S40.

68. Abara WE, et al. Hepatitis B Vaccination, Screening, and Linkage to Care: Best Practice Advice from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2017; 167(11): 794-804.
69. Bobashev GV, Zule WA, Osilla KC, Kline TL, Wechsberg WM, Transactional Sex among Men and Women in the South at High Risk for HIV and Other STIs. J Urban Health. 2009 Jul; 86(Suppl 1): 32–47.
70. Javanbakht M, Ragsdale A, Shoptaw S, Gorbach PM, Transactional Sex among Men Who Have Sex with Men: Differences by Substance Use and HIV Status. J Urban Health (2019) 96:429–441.
71. Keosha T, Bond 1, Yoon IS, et al., Transactional Sex, Substance Use, and Sexual Risk: Comparing Pay Direction for an Internet-Based U.S. Sample of Men Who Have Sex with Men. Sex Res Social Policy. 2019 September; 16(3): 255–267.
72. Armstrong HL, Jordan M. Sang, et al., Factors associated with transactional sex among a cohort of gay, bisexual, and other men who have sex with men in Vancouver, Canada. 30 November 2021.
73. Menza TW, Lipira L, Bhattarai A, Cali-De Leon V, Orellana ER, Prevalence and correlates of transactional sex among women of low socioeconomic status in Portland, OR. BMC Women's Health (2020) 20:219.
74. Moazen B, et al. Prevalence of Drug Injection, Sexual Activity, Tattooing, and Piercing Among Prison Inmates. Epidemiol Review 2018; 40(1): 58-69.
75. Pitasi MA, et al. Hepatitis B virus (HBV) infection, immunity and susceptibility among men who have sex with men (MSM), Los Angeles County, USA. AIDS Behav 2014; 18 Suppl 3:248-255.
76. Thompson ND, et al. Nonhospital Health Care-Associated Hepatitis B and C Virus Transmission: United States 1998-2008. Ann Intern Med 2009; 150(1): 33-39.
77. Assefa A, Kiros T, Delelegn B. Seroprevalence and Associated Factors of HBV and HCV among Pregnant Women Attending Antenatal Care at Debre Tabor Comprehensive Specialized Hospital, Northwest Ethiopia: A Cross-Sectional Study. Int J Microbiol Jul 31; 2023:2282673.
78. Weinbaum CM, et al. Hepatitis B, hepatitis C, and HIV in correctional populations: a review of epidemiology and prevention. AIDS 2005; 19: S41-S46.
79. Chang M, Nguyen M. Epidemiology of Hepatitis B and the role of vaccination. Best Practice & Research Clinical Gastroenterology 2017; 31(3): 239-247.
80. Smith JM, et al. Epidemiology and Treatment of Hepatitis B in Prisoners. Curr Hepatol Rep. 2017; 16(3): 178–183.
81. Messahel A, Musgrove B. Infective complications of tattooing and skin piercing, Journal of Infection and Public Health 2009; 2: 7-13.
82. Abiona TC, et al. Body art practices among inmates - implications for transmission of bloodborne infections. Am J Infect Control 2010; 38(2):121–129.
83. Wilkins T, et al. Hepatitis B: diagnosis and treatment. Am Fam Physician 2010; 81 (8): 965-972.
84. Snowden J, et al. Papular Acrodermatitis. In StatPearls, Treasure Island (FL): StatPearls 2021.
85. Steele WR, et al. Prevalence of human immunodeficiency virus, hepatitis B virus, and hepatitis C virus in United States blood donations, 2015 to 2019. The Transfusion-

Transmissible Infections Monitoring System (TTIMS). Transfusion 2020; 60;(10); 2327-2339.

86. Custer B, Stramer SL, Glynn S, Williams AE. Transfusion-transmissible infection monitoring system: a tool to monitor changes in blood safety. Transfusion 2016; 56:1499-1502

87. Steele WR, et al. HIV, HCV, and HBV incidence and residual risk in US blood donors before and after implementation of the 12-month deferral policy for men who have sex with men. Transfusion 2021 Jan 18.