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

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Draft Guidance for Industry

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U.S. Department of Health and Human Services
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Contains Nonbinding Recommendations

Draft – Not for Implementation

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I. INTRODUCTION

We, FDA, are providing you, establishments that make donor eligibility determinations for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps), with recommendations concerning the use of FDA-licensed nucleic acid tests (NAT) in donor testing for hepatitis B virus (HBV) deoxyribonucleic acid (DNA). We consider the use of FDA-licensed HBV NAT in testing HCT/Ps donors to be necessary to adequately and appropriately reduce the risk of transmission of HBV. The FDA-licensed HBV NAT can detect evidence of the viral infection at an earlier stage than the hepatitis B surface antigen (HBsAg) and total antibody to hepatitis B core antigen (anti-HBc tests). Therefore, we recommend the use of FDA-licensed HBV NAT, in addition to the use of licensed HBsAg and total anti-HBc Immunoglobulin G (IgG) and Immunoglobulin M (IgM), for testing donors of HCT/Ps for evidence of infection with HBV.[1] The draft guidance, when finalized, will supplement previous recommendations from FDA to HCT/P establishments concerning donor testing for HBsAg and total anti-HBc, in the document entitled "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated August 2007 (2007 Donor Eligibility Guidance) (Ref. 1).

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[1] FDA licensed donor screening tests can be found via the following link: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/TissueSafety/ucm095440.htm

II. BACKGROUND

HBV is a relevant communicable disease agent or disease (RCDAD) according to 21 CFR 1271.3(r). Section 1271.75 requires screening, and 21 CFR 1271.80 and 21 CFR 1271.85 require testing for HBV to adequately and appropriately reduce the risk of transmission of this RCDAD. The 2007 Donor Eligibility Guidance recommends that HCT/P donors be tested for HBsAg and total anti-HBc (IgG and IgM) (Ref. 1). The 2007 Donor Eligibility Guidance also indicated that the FDA recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge.

A. HBV Epidemiology and Public Health Impact

HBV is a major global public health concern. According to the World Health Organization (WHO) there are 240 million people who are chronically infected with HBV. Approximately 780,000 persons die each year from HBV infections worldwide. Regional prevalence is highest in sub-Saharan Africa and East Asia, where between 5-10% of the adult population is chronically infected. Less than 1% of the population in Western Europe and North America is chronically infected (Refs. 2, 3). In 2013, in the United States, there were 3,050 cases of acute hepatitis B reported from 48 states to Centers for Disease Control and Prevention (CDC). The overall incidence rate for 2013 was 0.9 cases per 100,000 population. After adjusting for under-ascertainment and under-reporting, an estimated 19,764 acute hepatitis B cases occurred in 2013. Additionally, it is estimated that there are between 700,000 to 1.4 million persons infected with HBV in the United States, many of whom are unaware of their infection status (Ref. 4).

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. 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 and may depend on the age of the individual at the time of primary infection. About 1% to 3% of infected adults develop chronic infections that can be asymptomatic (i.e., a carrier state, a chronically infected individual that is able to spread the disease to others) (Ref. 5). Between 30% and 90% of infants and young children (< 5 years of age) infected with HBV develop chronic hepatitis. By comparison, only 2% to 10% of children older than 5 years of age infected with HBV develop chronic hepatitis (Ref. 5).

Potential sequelae of HBV infection include acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma. About 20% of chronically infected individuals develop cirrhosis. Chronically HBV infected subjects have 100 times higher risk of developing hepatocellular carcinoma than non-carriers (Ref. 6). It has been shown that HBV infection can occur in previously vaccinated individuals who are exposed to a different HBV genotype (Ref. 7).

B. Rationale for HCT/P Donor Testing Using HBV NAT

HBV is transmitted by blood transfusions more frequently than hepatitis C virus (HCV) or human immunodeficiency virus (HIV) (Ref. 2). HBV NAT is a more sensitive technology which could detect trace amounts of HBV DNA during the window period in HBsAg negative blood specimens (i.e., a potential reduction of the infectious window period of up to 40 days depending on sensitivity of the HBsAg test) (Ref. 2). In blood donors, adding HBV NAT testing for HBV reduces the residual risk of transmission of HBV infection beyond that which can be achieved by screening donors using only HBsAg and total anti-HBc tests (Refs. 2, 8). In addition, it can detect breakthrough infections in previously vaccinated individuals who are exposed to the virus, and HBV mutants appear to be more likely detected by HBV NAT than by HBsAg assays (Ref. 9).[2]

HBV has been transmitted by tissue transplantation (Refs. 10 through 14). Available literature has indicated possible transmissions of HBV by hematopoietic stem cells and blood with HBV NAT positive/hepatitis B surface antibody (anti-HBs) positive /HBsAg negative blood, irrespective of anti-HBc test results (Refs. 15 through 17).

The estimated probability of HBV viremia at the time of tissue donation was determined to be 1 in 34,000 (Ref. 10); this is higher than the probability of viremia in first-time blood donors. HBV NAT's potential utility in further reducing risk of HBV transmission by transplantation is mainly restricted to the early HBsAg-negative phase of infection. It was estimated that the probability of donor viremia could be reduced to 1 in 100,000 if HBV NAT individual testing were used (Ref. 10). Therefore, by analogy to the experience in the blood donor setting, it is reasonable to expect that the residual risk of transmission of HBV infection would be reduced by adding HBV NAT to the testing strategy for HCT/P donors.

In the United States, there are currently FDA-licensed HBV NAT assays with an indication for screening donor blood samples for 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 HIV, HCV, and HBV in a single blood specimen, thus improving the feasibility of routine NAT testing for HBV.

In summary, the available scientific data and the availability of FDA-licensed assays support a recommendation that all HCT/Ps donors should be tested using an FDA-licensed HBV NAT.

[2] According to the Blood Products Advisory Committee (BPAC), there is no assumption of non-infectivity to recipients of blood products from donors with breakthrough infections (Ref. 18). Similarly, there can be no assumption of non-infectivity of HCT/Ps from donors with breakthrough infections containing HBV DNA and vaccine-induced, HBV-neutralizing anti-HBs when transplanted into recipients.

III. RECOMMENDATIONS

In order to adequately and appropriately reduce the risk of relevant communicable disease agent or disease transmission (21 CFR 1271.85(a)(3)), we recommend that you test HCT/P donors for HBsAg and for total anti-HBc (IgG and IgM) (Refs. 1, 10, and 19).

In addition, FDA recommends that you test HCT/P donors for HBV using an FDA-licensed NAT donor screening test in accordance with the manufacturer's instructions.

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

- 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)).[3]

IV. IMPLEMENTATION

We recommend that you implement this guidance within six months after a final guidance is issued.

[3] Recommendations regarding donor screening for HBV can be found in sections IV.E. and F., and recommendations for donor testing for HBV, including interpretation of positive anti-HBs results, can be found in section VI.A. of the "Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" (Ref. 1).

V. REFERENCES

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