Guidance for Industry

Requalification Method for Reentry of Blood Donors Deferred Because of Reactive Test Results for Antibody to Hepatitis B Core Antigen (Anti-HBc)

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

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I. INTRODUCTION

We, FDA, are issuing this guidance to provide you, establishments that collect Whole Blood or blood components intended for transfusion, with recommendations for a requalification method or process for the reentry of deferred donors into the donor pool based on a determination that previous tests that were repeatedly reactive for antibodies to hepatitis B core antigen (anti-HBc) were falsely positive and that there is no evidence of infection with hepatitis B virus (HBV). Currently, donors who are repeatedly reactive on more than one occasion for anti-HBc (samples from more than one collection from the same donor are repeatedly reactive for anti-HBc) must be indefinitely deferred in accordance with Title 21 Code of Federal Regulations, section 610.41(a) (21 CFR 610.41(a)). Although it may seem unlikely that two anti-HBc tests would be falsely positive, such situations have occurred with some frequency because of the relative non-specificity of these tests. The result is that many otherwise suitable donors are indefinitely deferred because of their anti-HBc test results, even though medical follow-up of such donors indicates that they are not infected with HBV.

The availability of FDA-licensed hepatitis B virus nucleic acid tests (HBV NAT), which are particularly sensitive when single samples are tested, provides an additional, powerful method of determining whether a donor who has been deferred because of anti-HBc reactivity is truly infected with HBV. Due to the availability of FDA-licensed HBV NAT and the improved specificity of anti-HBc assays, we are recommending in this guidance a reentry algorithm for donors deferred due to falsely positive repeatedly reactive tests for anti-HBc. This guidance finalizes the draft guidance of the same title dated May 2008.

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

A. Clinical Significance of Donor Screening for Hepatitis B Virus Infection

HBV is an enveloped virus with a partially duplex circular deoxyribonucleic acid (DNA) genome of approximately 3,200 bases. It is a major human pathogen that causes acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma (Ref. 1). The mortality of acute HBV infection is about 1%. Most primary infections in adults are self-limited. The virus is cleared from the blood and liver, and individuals develop a lasting immunity. However, 2% to 6% of persons above the age of 5 years, and 30% to 90% of infected children under the age of 5 years (Ref. 2) develop chronic infections that generally are asymptomatic (i.e., a carrier state), but may not be benign. About 20% of chronically infected individuals develop cirrhosis, and chronically infected subjects have 100 times higher risk of developing hepatocellular carcinoma than non-carriers. In the United States, deaths from chronic HBV infection are estimated to range from 3,000 to 5,000 individuals per year (Ref. 2).

Currently, HBV is transmitted by blood transfusions more frequently than hepatitis C virus or human immunodeficiency virus. The residual risk of post-transfusion HBV infection from donations screened for hepatitis B surface antigen (HBsAg) and anti-HBc has been estimated as 1 in 205,000 (Ref. 3) to 1 in 269,000 (Ref. 4) per donated unit. The major cause of HBV transmission by blood is attributable to donations from asymptomatic donors with acute HBV infections who have not yet developed HBsAg or anti-HBc (i.e., donors in the seronegative window period) and, in some cases, from donors with chronic infections in which serological markers are not detected (occult hepatitis B). Seronegative blood donations from infected individuals can transmit hepatitis B. In such cases, lookback studies using polymerase chain reaction have shown that HBV DNA can be detected at low levels in the donor's blood (Ref. 5).

HBsAg becomes detectable in blood 30 to 60 days after infection followed by the emergence of anti-HBc. Viremia develops several weeks before HBsAg is detected, and can reach 10^9-10^{10} virions/ml in acute infections (Ref. 1). Upon clearance of the HBV infection by the immune response, the HBsAg disappears from the blood of individuals, while detectable anti-HBc and antibody to hepatitis B surface antigen (anti-HBs) usually persist indefinitely. However, there is evidence that anti-HBc can decrease and even disappear over a period of decades in resolved infections (Ref. 6). Nonetheless, in chronically infected individuals, tests for HBsAg and anti-HBc usually remain positive for life and lower viral titers can be detected in blood for a long period although they tend to decline over time.

HBV NAT assays for detection of HBV DNA have been developed, and have been licensed for screening blood donations using a minipool sample format. These assays are also indicated for testing samples from individual donations, thus increasing test

sensitivity. In a meeting of the Blood Products Advisory Committee (Committee or BPAC) on October 21, 2004 (Ref. 7), we requested scientific comment on a reentry algorithm for donors deferred for repeatedly reactive anti-HBc test results on more than one occasion. The algorithm was based on follow-up testing of the donor for HBsAg, anti-HBc, and HBV DNA by sensitive HBV NAT. Under this plan, HBV DNA testing using an FDA-licensed NAT would replace a previously considered recommendation for donor reentry that included antibody to hepatitis B surface antigen (anti-HBs) testing. We no longer propose additional testing for anti-HBs as part of donor reentry because extensive hepatitis B vaccination programs have been in place for a number of years, resulting in many individuals having anti-HBs from vaccination. As a result, anti-HBs now has questionable value as a marker of hepatitis B infection. While the Committee did not take a formal vote on the algorithm, the Committee discussed this approach and did not express concerns about the adequacy of this plan as a reentry algorithm.

Since the 2004 BPAC meeting referred to above, we have licensed qualitative tests for the direct detection of HBV DNA in human plasma from donors, including donors of Whole Blood and blood components, Source Plasma and other living donors, that have sensitivities of <2 International Units (IU)/mL (about 10 copies HBV DNA/mL) at 95% detection for HBV DNA when specific procedures are used.[1] The availability of sensitive, FDA-licensed, HBV NAT assays provides an additional, powerful method of determining whether a donor, who has been deferred because of anti-HBc reactivity, is truly infected by HBV. Due to the availability of FDA-licensed HBV NAT assays and the improved specificity of anti-HBc assays, we are recommending a reentry algorithm for anti-HBc in this guidance. Empirical studies support utility of this algorithm (Ref. 8).

B. Rationale and Procedure for the Requalification Method for Reentry

Under 21 CFR 610.40(a), you must test each donation of human blood or blood component intended for use in preparing a product, including donations intended as a component of, or used to prepare, a medical device, for evidence of infection due to HBV, among other communicable disease agents. Testing for evidence of infection of HBV includes testing for the presence of HBsAg and anti-HBc. In addition, some blood establishments also test blood donations for HBV DNA by HBV NAT.

Under 21 CFR 610.41(a), as a general matter, you must defer donors who test reactive[2] with respect to the battery of screening tests required under 21 CFR 610.40. However, donors who test repeatedly reactive for anti-HBc on only one occasion do not need to be

[1] COBAS AmpliScreen HBV Test (Roche Molecular Systems, Inc., Pleasanton, California): Triplicate testing using the multiprep specimen processing procedure.
Procleix® ULTRIO® Assay (Gen-Probe, Inc., San Diego, California): Testing 6 replicates.

[2] In 21 CFR 610.41(a), FDA requires that blood establishments defer donors who test reactive by a screening test for evidence of infection due to a communicable disease agent(s) listed in section 610.40(a). In section 610.41(a)(1), however, a donor who tests reactive for anti-HBc on only one occasion is not required to be deferred. In this guidance, we refer to reactive test results for HBsAg and anti-HBc as "repeatedly reactive" to accurately describe the testing algorithms for HBsAg and anti-HBc.

deferred (21 CFR 610.41(a)(1)). Donations collected from these donors are not suitable for allogeneic transfusions (21 CFR 610.40(h)(1) and (2)) (Ref. 9), but such donations, if otherwise nonreactive when tested for communicable disease agents as required under 21 CFR 610.40, may be used for further manufacturing into plasma derivatives without FDA prior approval. (21 CFR 610.40 (h)(2)(v). Donors who test reactive on more than one occasion do not fall within this exception and must be deferred (21 CFR 610.41(a)).

Under 21 CFR 610.41(b), "a deferred donor subsequently may be found to be suitable as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA."[3]

Until now, we have not recommended a requalification method for reentry of donors deferred due to repeatedly reactive test results for anti-HBc because there was no supplemental (additional, more specific) test available. Although donor screening for anti-HBc has contributed to blood safety, a large proportion of donors with anti-HBc reactivity who fulfill all other donor suitability criteria have been indefinitely deferred on the basis of potentially false positive anti-HBc test results (Refs. 10, 11). It is estimated that as many as 21,500 potentially eligible donors were deferred annually in the late 1980s and 1990s because of false positive anti-HBc results, and that over 200,000 donors could be eligible for reentry (Ref. 10).

For purposes of reentering into the donor pool, a donor who has been indefinitely deferred because of having tested repeatedly reactive for anti-HBc on more than one occasion, we recommend in Section III of this guidance that, after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you obtain from the donor a new, pre-donation blood sample (i.e., a blood sample that is obtained before the next donation) for follow-up testing, using FDA-licensed tests for HBsAg, anti-HBc and HBV DNA by NAT. If the new, pre-donation blood sample test results are negative for HBsAg, anti-HBc and HBV DNA, the donor may return to donate blood. When the donor returns to donate, after the tests for HBsAg, anti-HBc, and HBV DNA on the pre-donation sample have been determined to be negative, we recommend that you reenter the donor as eligible to donate Whole Blood and blood components, provided that the donor meets all eligibility criteria. Note that the reentry of a donor permits prospective donations from a reentered donor who meets donor suitability criteria. It does not affect the status of previous collections from that donor.

For donor retesting, we recommend that a minimum 8-week (56 days) period elapse following the last repeatedly reactive anti-HBc test, because this time period provides sufficient confidence that at least one of the three HBV markers (HBsAg, anti-HBc, and HBV DNA) will be detectable if the donor had been truly infected with HBV at the time of the last anti-HBc reactive donation (Ref. 1). In addition, eight weeks is the minimum time period permitted between donations of Whole Blood, with limited exceptions (21

[3] A deferred donor may serve as an autologous donor in accordance with 21 CFR 610.40 and 21 CFR 610.41. Note that a deferred donor that donates for autologous use is not deemed to be reentered and remains deferred, until the criteria for reentry are met.

CFR 640.3(b)).

For purposes of reentry, we recommend that you use an FDA-licensed HBV NAT labeled as having a sensitivity of ≤ 2 IU/mL at 95% detection rate [1 IU = ~5 copies]. Donors with negative results for HBV DNA at this level of sensitivity are highly unlikely to be infected with HBV (Ref. 12). Depending upon the assay and the platform used, this sensitivity may only be achieved when testing individual donor samples.

III. RECOMMENDATIONS

A. You may reenter into the donor pool, a donor who has been indefinitely deferred solely because of repeatedly reactive tests for anti-HBc on more than one occasion if (see flow chart in the Appendix):

1. After a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you collect a follow-up sample from the donor, and this sample tests negative on FDA-licensed tests for HBsAg, anti-HBc, and HBV DNA by NAT (sensitivity at 95% detection rate of ≤2 IU /mL)

and

2. When the donor presents to donate, after the new, pre-donation blood sample tests negative on FDA-licensed tests for HBsAg, anti-HBc, and HBV DNA by NAT, you determine that the donor meets all eligibility criteria for donors of Whole Blood and blood components.

B. You should continue to indefinitely defer a donor who was deferred for anti-HBc reactivity on more than one occasion and whose sample or donation tests: 1) repeatedly reactive on the HBsAg test (whether or not the neutralization test is positive); 2) repeatedly reactive on the anti-HBc test; or 3) reactive on the HBV NAT. Positive results on tests for HBsAg, anti-HBc or HBV DNA by NAT may be useful in donor counseling.

C. If you wish to perform follow-up testing on a donor who is deferred because of anti-HBc test results, you may do so before the end of the 8-week waiting period for donor notification purposes or for medical reasons. Negative test results on follow-up for HBsAg, anti-HBc, and HBV DNA by NAT (sensitivity at 95% detection rate of ≤ 2 IU/mL), may be useful in donor counseling. However, only negative results for all three tests (HBsAg, anti-HBc, and HBV NAT), obtained at least 8 weeks after the last repeatedly reactive anti-HBc result, would qualify the donor for reentry. If you obtain a reactive HBV NAT, or repeatedly reactive HBsAg or anti-HBc, or positive HBsAg result on any of these tests during this 8-week waiting period, the donor would not be eligible for reentry, and we recommend that you defer the donor indefinitely.

A donor who has been requalified as described above in Section III. A. 1 and 2 may on subsequent occasions be indefinitely deferred solely because of repeatedly reactive tests for anti-HBc on more than one occasion. You may reenter such a donor into the donor pool by again following all procedures described in Section III. A.

IV. IMPLEMENTATION

We consider the recommendations in this guidance to be an acceptable requalification method for reentry of donors deferred due to falsely positive repeatedly reactive tests for anti-HBc. Licensed establishments implementing these recommendations must report this change to FDA as required under 21 CFR 601.12(a). We consider implementation of recommendations in this guidance in their entirety and without modification to be a minor change to an approved license application. Therefore, licensed establishments are not required to have FDA prior approval and may submit a statement of this change in an annual report under 21 CFR 601.12(d), indicating the date that the revised standard operating procedures were implemented. Unlicensed establishments implementing recommendations in this guidance in their entirety and without modification are not required to report this change.

We do not consider implementation of an alternative requalification method from that described in this guidance to be acceptable, unless approved by FDA for such purpose. In accordance with 21 CFR 610.41(b), you must not reenter a donor unless the requalification method or process is found acceptable for such purposes by FDA. Licensed establishments intending to use an alternative requalification method must submit a supplement for prior approval, as required under 21 CFR 601.12(b). Similarly, under 21 CFR 610.41(b), FDA must find an alternative requalification method proposed by an unlicensed establishment to be acceptable before it is implemented.

V. REFE RENCES

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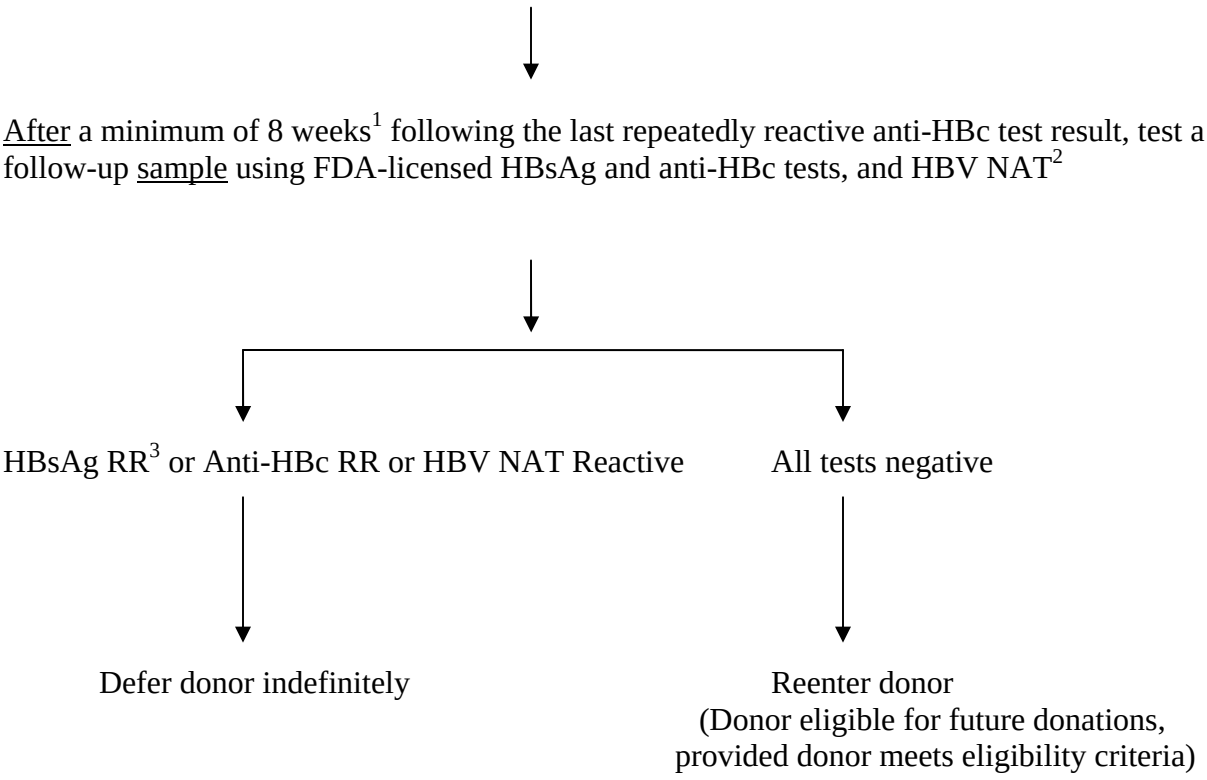
APPENDIX

REQUALIFICATION PROCESS FOR DONORS DEFERRED BECAUSE OF REPEATEDLY REACTIVE TEST RESULTS FOR ANTI-HBc



[1] If, for donor notification purposes or for medical reasons, you wish to perform follow-up testing on a donor who is deferred because of repeatedly reactive anti-HBc test results before the end of the 8-week waiting period and the blood sample tests HBsAg RR or anti-HBc RR or HBV NAT reactive, the donor should be indefinitely deferred. If, however, the sample tests negative on all three of these tests, the donor should be retested after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test result using licensed HBsAg and anti-HBc tests, and HBV NAT. If, at that time, the sample tests negative on all three of these tests (HBsAg, anti-HBc, and HBV NAT), the donor may be eligible to donate.

[2] The sensitivity of the HBV NAT used should be $\leq$ 2 IU/mL, at 95% detection rate.

[3] Regardless of the neutralization test result.