Guidance for Industry

Requalification Method for Reentry of Donors Who Test Hepatitis B Surface Antigen (HBsAg) Positive Following a Recent Vaccination against Hepatitis B Virus Infection

This guidance is for immediate implementation

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit one set of either electronic or written comments on this guidance at anytime. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the Docket No. FDA-2011-D-0829 for this guidance.

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance document is intended for blood establishments that manufacture Whole Blood and blood components for transfusion or for further manufacture, including Source Plasma and Source Leucocytes. This guidance provides recommendations for a requalification method or process for the reentry of deferred donors who test repeatedly reactive for hepatitis B surface antigen (HBsAg), confirmed positive by neutralization, following a recent vaccination against hepatitis B virus (HBV) infection, and who are not infected by HBV.

FDA issued a memorandum to all registered blood establishments on December 2, 1987, entitled, "Recommendations for the Management of Donor and Donations that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg)" (FDA 1987 Memorandum) (Ref. 1). This guidance supplements the FDA 1987 Memorandum.

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

II. BACKGROUND

Under Title 21 Code of Federal Regulations 610.40(a) (21 CFR 610.40(a)), you, blood establishments that collect blood and blood components, must test each donation of human blood or blood component intended for use in preparing a product for evidence of infection due to certain communicable disease agents, including HBV. Under § 610.40(h)(1), you must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to communicable disease agents, including HBV infection, except under certain circumstances. Similarly, donors that test reactive for HBV must be deferred, with certain

exceptions (§ 610.41(a)). Note that under § 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. Such a donor is considered no longer deferred.

The recommendations in the FDA 1987 Memorandum established procedures for reevaluating donors who were repeatedly reactive for HBsAg. This guidance supplements the FDA 1987 Memorandum by providing recommendations for a requalification method for reentry of deferred donors who test repeatedly reactive for HBsAg, confirmed by neutralization, following a recent vaccination against HBV, and who are not infected with HBV.

A. Prevalence, Transmission, and Testing for HBV Infection

1. Prevalence of HBV Infection

HBV infection is a severe global health problem due to its high prevalence. The world-wide number of infected individuals is estimated to be over 2 billion, and more than 400 million are in the chronic phase of infection (Ref. 2). In the United States (U.S.), approximately 200,000 to 300,000 acute HBV infections occur each year, more than 1 million individuals have chronic HBV infection and approximately 5,000 individuals die each year from HBV induced hepatocellular carcinoma and chronic liver disease (Refs. 3 and 4). Antigens and antibodies associated with HBV infection include HBsAg and antibody to HBsAg (anti-HBs), hepatitis B core antigen (HBcAg) and antibody to HBcAg (anti-HBc), and hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe). Currently, all donations of Whole Blood and blood components and Source Plasma are tested for HBsAg. The average time from exposure to detection of HBsAg is 30 days (range: 6 to 60 days) (Refs. 5 and 6).

2. Transmission of HBV Infection

HBV can be transmitted by blood transfusion, through puncture wounds acquired during work in the health-care field (medical, dental, laboratory or other), by sharing needles used for injection of drugs, and by unprotected sex with an HBV infected partner (Ref. 2). It has also been suggested that there is a possibility of HBV transmission through breast milk, as HBV markers such as HBsAg and HBV deoxyribonucleic acid (DNA) are detected in breast milk (Ref. 7). However, studies have shown that there is no increased risk of HBV transmission from infected mothers to their children through breast-feeding (Ref. 8).

3. Testing for HBV Infection

In accordance with § 610.40(a)(3), each donation of blood and blood components must be tested for infection with HBV. Consistent with the

FDA 1987 memorandum, donations of Whole Blood and blood components for transfusion are tested for HBsAg and anti-HBc. All Source Plasma collections in the U.S. are tested for HBsAg. However, FDA does not recommend that Source Plasma donors be tested for anti-HBc because plasma units that are untested, non-reactive or repeatedly reactive for anti-HBc are currently acceptable for manufacture of plasma derivatives. Under § 610.41(a)(4), a deferred donor, who otherwise is determined to be suitable for donation and tests reactive for anti-HBc may serve as a donor of Source Plasma. Under § 610.40(h)(2)(v), anti-HBc reactive donations, otherwise non-reactive when tested as required under this section, may be used for further manufacturing into plasma derivatives.

In addition, excluding anti-HBc reactive units in certain plasma products might compromise the safety of those products. Anti-HBc and anti-HBs usually occur together in pools used for the manufacture of plasma derivatives. If anti-HBc reactive units were excluded from these pools, titers of anti-HBs in the pools would be expected to diminish. Because the presence of neutralizing anti-HBs is believed to contribute to the safety of certain plasma products such as immunoglobulins, reducing the titers of anti-HBs would have a negative effect on the safety of these products.

B. Rationale for Requalification Method for Reentry of Deferred Donors Who Test Repeatedly Reactive for HBsAg Following Hepatitis B Vaccination

Hepatitis B vaccination has been shown to be a very effective measure to prevent HBV infection (Ref. 9). Since 1982, recommendations for hepatitis B vaccination have evolved into a comprehensive strategy to eliminate HBV transmission in the U.S. (Refs. 10, 11, and 12). These recommendations advise the vaccination of adults at risk for HBV infection as well as neonates, older children and adolescents.

Currently manufactured HBV vaccines consist of recombinant antigenic, non-infectious HBsAg protein that elicits production of protective, neutralizing, anti-HBs when injected into individuals. As viral HBsAg forms the outer envelope of HBV, anti-HBs neutralizes HBV, thus providing protection to the vaccinated individual from HBV infection. Recombinant, non-infectious HBsAg from the vaccine remains in the circulation for several weeks after vaccination. This circulating, non-infectious recombinant HBsAg tests repeatedly reactive using screening tests for HBsAg, and it is confirmed positive by HBsAg neutralizing tests. Consequently, many donors who have been vaccinated against HBV and who do not have hepatitis B infection are deferred. The deferral of non-infected hepatitis B vaccinated individuals is consistent with the FDA 1987 memorandum (Ref. 1).

Following hepatitis B vaccination, HBsAg can be transiently detected in blood for

up to 21 days in neonates (Ref. 13) and up to 18 days in adults (Refs. 14 and 15). In these cases, the presence of HBsAg in the vaccine recipients does not signify infection with HBV, as anti-HBc and HBV DNA are not detectable and there are no clinical signs and symptoms of viral hepatitis. Based on the transient detection of HBsAg, a deferral period of 28 days after the date of Hepatitis B vaccination should rule out the possibility of a positive screening test due to the vaccination. However, if vaccination has been given to a previously exposed individual (exposure by needle stick, risk behavior, etc.) as a prophylactic measure, a non-reactive test result for HBsAg up to a period of 28 days after exposure does not necessarily rule out HBV infection.

Based on the possibility of a positive screening test due to Hepatitis B vaccination, FDA is providing recommendations for a requalification method for reentry of donors deferred due to repeatedly reactive screening tests for HBsAg, confirmed by neutralization, following a recent vaccination against HBV, and who are not infected with HBV.

III. RECOMMENDATIONS

Consistent with FDA 1987 Memorandum, a donor who tests repeatedly reactive for HBsAg, is confirmed positive by neutralization[1], and who tests non-reactive for anti-HBc, is permanently deferred and the donation must not be used (Ref. 1). Donors may be informed of the possibility for reentry based on Hepatitis B vaccination history when they are notified of their deferral.

A. When Hepatitis B vaccination was given for protection from possible future exposure or as a part of an approved Source Plasma HBV immunization program:

The donor would be eligible for reentry 56 days after the donation that tested repeatedly reactive for HBsAg and confirmed positive by neutralization[2], if:

1. The blood establishment determines that the donor received the vaccination against HBV infection within 28 days prior to collection of the specimen that tested confirmed positive for HBsAg;

[1]Some HBV NAT assays received a limited supplemental indication for repeatedly reactive HBsAg test results. If a donor tests HBsAg repeatedly reactive and positive for HBV DNA using an HBV NAT with such a limited supplemental test indication, the HBsAg test result can be considered as HBsAg positive without performing HBsAg neutralization. These test results are indicative of HBV infection and are not caused by Hepatitis B vaccination. Therefore, such a donor should be deferred permanently. If a donor tests HBsAg repeatedly reactive in a screening test and negative for HBV DNA using an HBV NAT with such a limited supplemental test indication, an HBsAg neutralization test should be performed. The result of the neutralization test serves as the test of record.

[2] While not yet eligible for routine donation, Source Plasma donors actively participating in an approved HBV immunization program may be eligible for reentry into the HBV immunization program prior to 56 days, provided the donor tests non-reactive for HBsAg and all other donor suitability criteria are met at the time of the next donation.

2. The vaccination was given solely to protect the donor from possible HBV infection because of potential future exposure to HBV or as part of an approved HBV immunization program for Source Plasma donors (i.e., it was not performed for the purpose of HBV infection prophylaxis following a specific incident of potential exposure, such as needlesticks, risk behavior, etc.); and

3. All other donor suitability criteria are met when the donor presents to donate.

Additional testing (for the purpose of reentry) prior to the next donation is not recommended.

B. When Hepatitis B vaccination was given as a prophylaxis following a specific incident of potential exposure:

The donor would be eligible for reentry after the donation that tested repeatedly reactive for HBsAg and confirmed positive by neutralization, if:

1. The blood establishment determines that the donor received the vaccination against HBV infection within 28 days prior to collection of the specimen that tested confirmed positive for HBsAg for the purpose of HBV infection prophylaxis following a specific incident of potential exposure;

2. A follow up sample, collected at least 12 months after the potential exposure, tests non-reactive for HBsAg, non-reactive for anti-HBc and negative for HBV DNA by individual donation (ID) NAT; and

3. All other donor suitability criteria are met when the donor presents to donate.

Note:

1) A donation that tests repeatedly reactive for HBsAg should not be used, whether or not it is confirmed positive.

2) If test results for anti-HBc are repeatedly reactive, whether or not HBsAg test results are positive, refer to FDA's published recommendations and guidance (Refs. 16 and 17).

3) A donor who was deferred because of previous HBsAg test results, whether or not these test results were caused by infection with HBV, may donate Source Plasma for use in the preparation of Hepatitis B Immune Globulin (Human), provided the current donation tests non-reactive for HBsAg and the donor is otherwise determined to be suitable (§ 610.41(a)(3)).

IV. IMPLEMENTATION

We consider the recommendations in this guidance to be an acceptable requalification method or process, within the meaning of § 610.41(b), for reentry of donors deferred due to repeatedly reactive screening tests for HBsAg, confirmed positive by neutralization, following a recent vaccination against HBV.

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 § 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.

Section 610.41(b) requires that a donor requalification method or process used to requalify a donor be acceptable to FDA. Accordingly, before you implement an alternative requalification method or process from that described in this guidance, FDA must first find the alternative method or process to be acceptable for such purpose. Licensed establishments intending to use an alternative requalification method must submit a supplement for prior approval, as required under § 601.12(b). Similarly, FDA must find an alternative requalification method proposed by an unlicensed establishment to be acceptable before it is implemented.

V. REFERENCES

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