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販売名(企業名)	合成血-LR「日赤」(日本赤十字社) 照射合成血-LR「日赤」(日本赤十字社)			

研究報告の概要

○業界向けガイダンス案:B型肝炎コア抗体(抗HBc抗体)検査陽性により供血延期となった供血者の供血再開(リエントリー)についての適格性確認方法

米国食品医薬品局(FDA)は、B型肝炎コア抗体が陽性となったために供血延期となった供血者のリエントリー・アルゴリズムを提案するガイダンス案を発表した。これまで、HBc抗体が2回以上陽性となった供血者は無期限に供血延期とされていた。FDAの試算では、1980年代後半から90年代にかけて、HBc抗体が偽陽性だったために供血延期となった人は毎年約21,500名にのぼり、これまでに20万人以上の供血適格者が供血できなくなっている。

本ガイダンスでは、HBc抗体検査が2回目に陽性となった後、8週間以上経ってから高感度のHBV NATによってHBV感染が否定された場合は供血可能となる。フォローアップの際に、HBV NAT陽性、HBs抗原繰り返し陽性、HBc抗体繰り返し陽性のいずれかに該当する場合は無期限供血延期となる。

報告企業の意見	今後の対応
米国食品医薬品局(FDA)は、B型肝炎コア抗体が陽性となったために供血延期となった供血者のリエントリー・アルゴリズムを提案するガイダンス案を発表したとの報告である。米国ではもともとHBV感染者が少なくワクチンも普及していることから、日本と状況は異なるが、偽陽性者のリエントリーの方法としては参考になると考えられる。	日本赤十字社では、HBs抗原検査及びHBc抗体検査を実施することに加えて、HBVについて20プールでスクリーニングNATを行い、陽性血液を排除している。HBV感染に関する新たな知見等について今後も情報の収集に努める。また、これまでの凝集法と比べて、より感度の高い化学発光酵素免疫測定法(CLEIA)及び精度を向上させた次世代NATを導入した。

使用上の注意記載状況・その他参考事項等

合成血-LR「日赤」
照射合成血-LR「日赤」

血液を介するウイルス、細菌、原虫等の感染
vCJD等の伝播のリスク

(2)

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)

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact Robin Biswas, M.D., at 301-827-3011.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
May 2008

Contains Nonbinding Recommendations

Draft –Not For Implementation

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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)

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternate approach if the approach satisfies the requirements of the applicable statutes or regulations. If you want to discuss an alternate approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

We, FDA, are providing recommendations to you, establishments that collect human blood or blood components, 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 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 false positives, 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 an FDA-licensed hepatitis B virus nucleic acid test (HBV NAT), which is 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 by HBV. Due to the availability of this 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.

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 a major human pathogen that causes acute and chronic hepatitis, cirrhosis and hepatocellular carcinoma (Ref. 1). HBV is an enveloped virus with a partially duplex circular deoxyribonucleic acid (DNA) genome of approximately 3,200 bases. Most primary infections in adults are self-limited; the virus is cleared from the blood and liver, and individuals develop a lasting immunity. Fewer than 5% of infected adults develop chronic infections that can be asymptomatic (i.e., a carrier state). About 20% of chronically infected individuals develop cirrhosis. Chronically infected subjects have 100 times higher risk of developing hepatocellular carcinoma than non-carriers. The mortality of acute HBV infection is about 1%. 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 (HIV). The residual risk of post-transfusion HBV infection from donations screened for hepatitis B surface antigen (HBsAg) and anti-HBc have been estimated as 1 in 63,000 donations (Ref. 3) to 1 in 180,000 donations (Ref. 4). 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 (i.e., donors in the seronegative window period), and 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 emergence of anti-HBc. Viremia develops by the time 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 antigen disappears from the circulation and detectable anti-HBc and antibody to hepatitis B surface antigen (anti-HBs) usually persists indefinitely. There is evidence that anti-HBc can decrease and even disappear over a period of decades in resolved infections (Ref. 6). 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 but tend to decline over time.

HBV NAT assays for detection of HBV DNA have been developed. So far, one test has been licensed for screening blood donations using a minipool sample format. This assay is also indicated for testing samples from individual donations, thus increasing test sensitivity. In a BPAC meeting on October 21, 2004 (Ref. 15), we proposed a revised reentry algorithm in which subsequent testing of the donor for HBsAg and anti-HBc is

retained, but sensitive HBV DNA testing using a licensed NAT would replace anti-HBs testing. While the Committee did not take a formal vote on FDA's proposed algorithm, the Committee did not raise any objections to FDA's proposal. We are not proposing 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.

Since October 21, 2004, we have licensed a qualitative test for the direct detection of HBV DNA in human plasma from donations of Whole Blood and blood components for transfusion, and Source Plasma. The availability of a sensitive, FDA-licensed HBV NAT assay, particularly 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 by HBV. Due to the availability of a licensed HBV NAT and the improved specificity of anti-HBc assays, we are proposing a reentry algorithm for anti-HBc in this guidance.

B. Rationale 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. Testing for evidence of infection includes testing for the presence of HBsAg and anti-HBc. In addition, some blood establishments also test blood donations for HBV DNA by NAT.

Under 21 CFR 610.41(a), blood establishments must defer donors who test reactive[1] by a screening test for evidence of infection due to a communicable disease agent(s) listed in 21 CFR 610.40(a). However, donors who test repeatedly reactive for anti-HBc on only one occasion need not be deferred (21 CFR 610.41(a)(1)), although the donation collected would be unsuitable (Ref. 11). Donors who test reactive on more than one occasion do not fall within this provision and must be deferred under 21 CFR 610.41(a).

Under 21 CFR 610.41(b), we provided for reentry of a deferred donor who is subsequently "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."

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

[1] 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 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 algorithm for anti-HBc.

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. 7, 16). 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. 7).

III. RECOMMENDATIONS

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 that, after a minimum of 8 weeks following the last repeatedly reactive anti-HBc test, you obtain a pre-donation blood sample (i.e., a blood sample which is obtained prior to any next donation) from the donor for follow-up testing, using licensed tests for HBsAg, anti-HBc and HBV DNA by NAT. Provided that the blood sample test results are negative for HBsAg, anti-HBc and HBV NAT, the donor may, at a later date, return to donate blood. When the donor returns to donate, subsequent to the negative tests for HBsAg, anti-HBc, and HBV NAT on the pre-donation sample, we recommend that you reenter the donor as eligible to donate Whole Blood and blood components, provided that all other suitability criteria are met.

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 that last anti-HBc reactive donation (Ref. 1). In addition, 56 days is the minimum time period permitted between donations of Whole Blood (21 CFR 640.3(b)).

For purposes of reentry, we recommend that you use a licensed HBV NAT labeled as having a sensitivity of $\leq$ 10 copies /mL (at 95 % detection rate). This sensitivity reflects the current technological capabilities regarding sensitivity of HBV NAT assays. Depending upon the assay and the platform used, this sensitivity may only be achieved when testing individual donor samples.

Donor reentry following deferral for repeatedly reactive tests for anti-HBc on more than one occasion:

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 licensed tests for HBsAg, anti-HBc, and HBV DNA by NAT (sensitivity at 95% detection rate of ≤ 10 copies/mL)

and

2. When the donor presents to donate, subsequent to the negative tests for HBsAg, anti-HBc, and HBV 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 repeatedly reactive on the: 1) HBsAg test (whether or not the neutralization test is positive), 2) anti-HBc test, or 3) HBV NAT. Positive results on tests for HBsAg, anti-HBc or HBV 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 NAT (sensitivity at 95% detection rate of ≤ 10 copies/mL), may be useful in donor counseling. However, only negative results for all three tests, 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.

IV. IMPLEMENTATION

This guidance is being distributed for comment purposes only.

V. REFERENCES

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