

Guidance for Industry

Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes

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For questions on the content of this guidance, contact the Division of Emerging and Transfusion Transmitted Diseases at 301-827-3008.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
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This guidance updates the July 2007 guidance of the same title to extend the implementation date.

Contains Nonbinding Recommendations

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I. INTRODUCTION

Blood establishments are required under 21 CFR 610.40(a)(3) and (b) to test donations of human blood and blood components for hepatitis B virus using approved screening tests that are adequate and appropriate for this purpose. One test used to detect the presence of hepatitis B infection is the hepatitis B surface antigen (HBsAg) test. This document provides recommendations to manufacturers of HBsAg assays that are intended to be used to test donors of Whole Blood and blood components, including Source Plasma and Source Leukocytes, and to establishments using an HBsAg assay. This guidance represents the Food and Drug Administration's (FDA's) current thinking on minimum sensitivity standards for such HBsAg assays, as they relate to testing "to reduce adequately and appropriately the risk of transmission of communicable disease" under 21 CFR 610.40(b) (see Section III). Under 21 CFR 610.44, manufacturers of test kits used to test donations for hepatitis B virus must use a reference panel from FDA or an FDA-designated source when such panel is available and appropriate to verify acceptable sensitivity and specificity of such kits (see Ref. 1). This guidance document finalizes the draft guidance document entitled "Guidance for Industry: A Modified Lot-Release Specification for Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Blood, Blood Components, and Source Plasma Donations" dated April 2002.

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.

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II. BACKGROUND

Since 1975, we, FDA, have distributed Reference Hepatitis B Surface Antigen panels to manufacturers of HBsAg detection assays used to test donors of Whole Blood and blood components, including Source Plasma and Source Leukocyte donations. Manufacturers use these panels, suitable for testing HBsAg assays of so-called “third generation” sensitivity (mostly radioimmunoassays and enzyme immunoassays), to test manufactured kit lots of HBsAg detection assays for screening Whole Blood and blood components, including Source Plasma and Source Leukocytes, to ensure a minimum sensitivity for those kit lots. FDA also distributes the panels to unlicensed manufacturers who are developing such HBsAg assays. The panels are used to test the sensitivity of HBsAg assay lots, pre- and post-licensure, under our lot-release and surveillance programs.

The current Center for Biologics Evaluation and Research’s (CBER’s) panel, distributed since 1996, contains 10 plasma samples: eight reactive and two nonreactive for HBsAg. The eight reactive samples are estimated to contain about 0.02, 0.04, 0.5, 0.9, 1.0, 2.5 to 3.0, 5.0 to 6.0 and 7.0 to 8.0ng HBsAg/mL (see footnote to the table on page 3, under Section III.). The current lower limit of detection specification for HBsAg assays used to test blood donations corresponds to 1.0ng HBsAg/mL. The CBER panel sample estimated to contain about 1.0ng HBsAg/mL is detected by all HBsAg test kit lots used to test Whole Blood and blood components, including Source Plasma and Source Leukocyte donations.

Since this 1.0ng HBsAg/mL sensitivity specification for HBsAg assays was implemented, we acquired information that the different HBsAg detection assays, both licensed and investigational assays that are developed for eventual licensure, varied widely in relative sensitivity below this limit. Furthermore, we learned that some of these assays might have detection capabilities well below 1.0ng HBsAg/mL.

Therefore, we initiated a study comparing three (at that time) investigational and four licensed HBsAg detection assays and procedures, to evaluate whether newer HBsAg assays were more sensitive than the then-used licensed methods. The rationale for performing such a study was to ascertain whether newer assays might increase the capability of detecting donations that are potentially infectious for hepatitis B virus. Since that time, FDA has licensed all three previously investigational assays.

At a Blood Products Advisory Committee (BPAC) meeting held on March 15, 2001 (Ref. 2), preliminary data generated by FDA and industry were presented which indicated that the sensitivity of HBsAg licensed and investigational assays varies significantly. In particular, the lower limit of detection ranged from 0.07 to 0.13ng HBsAg/mL for the three investigational assays (all of which are now licensed) and for one licensed assay tested. On the other hand, a detection limit range from 0.27 to 0.62ng HBsAg/mL was observed for three licensed assays tested. Based on these observations, we asked BPAC whether the HBsAg donor screening assays should be capable of a lower limit of detection. BPAC voted in favor of a lower limit of detection, with 14 “yes” votes, 0 “no” votes and 0 abstentions.

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Taking BPAC's recommendation into consideration, we are recommending that assays used under 21 CFR 610.40(b) to test Whole Blood and blood components, including Source Plasma and Source Leukocyte donations have a capability of detecting at least 0.5ng HBsAg/mL. HBsAg assays that do not have this capability should not be used to test Whole Blood and blood components, including Source Plasma and Source Leukocyte donations, because FDA believes that tests that are incapable of identifying HBsAg at these limits are not adequate to reduce the risk of communicable disease transmission. If more HBsAg assays demonstrate greater capability to detect HBsAg at even lower levels, we will reconsider this recommendation.

III. RECOMMENDATIONS

We recommend that establishments using HBsAg detection assays to test Whole Blood and blood components, including Source Plasma and Source Leukocyte donations, use assays that have a lower limit of detection capability of 0.5ng HBsAg/mL or less in order to reduce adequately and appropriately the risk of transmission of communicable disease. HBsAg assays that do not have this capability should not be used to test Whole Blood and blood components, including Source Plasma and Source Leukocyte donations, because FDA believes that they are not adequate or appropriate for this purpose. FDA recommends that test kits that are used to test Whole Blood and blood components, including Source Plasma and Source Leukocyte donations, employ the following performance standard when testing the CBER HBsAg Lot-Release Panel #12:

Panel Sample	Estimated Concentration of HBsAg (ng/mL)	Expected Reactivity*
1201	1.0	+
1202	5.0 to 6.0	+
1203	0	-
1204	0.04 ^a	±
1205	0.5	+
1206	0	-
1207	2.5 to 3.0	+
1208	7.0 to 8.0	+
1209	0.02 ^a	±
1210	0.9	+

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* + = reactive; ± = reactive or non-reactive; – = non- reactive

^a <0.1 ng/mL; imputed value shown is based on dilutions

IV. IMPLEMENTATION

We recommend implementation of these recommendations on July 31, 2008.

V. REFERENCES

1. Requirements for Testing Human Blood Donors for Evidence or Infection Due to Communicable Disease Agents; Final Rule, June 11, 2001 (66 FR 31146).

- 21 CFR 610.40.
- 21 CFR 610.44.
2. Blood Products Advisory Committee Transcript, March 15, 2001.
(<http://www.fda.gov/ohrms/dockets/ac/01docsbc.htm>).