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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should identify with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this draft guidance document are available from: the Office Of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by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.

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U.S. Department of Health and Human Services
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Center for Biologics Evaluation and Research (CBER)
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This draft guidance represents FDA's current thinking on this topic.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. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

I. INTRODUCTION

This document provides recommendations to manufacturers of assays for the detection of HBsAg that are intended to be used to test blood, blood components, and Source Plasma donations. This guidance represents the agency's current thinking on minimum sensitivity specifications for HBsAg assays used to test blood, blood components, and Source Plasma donations (see Section III). Under 21 CFR 610.44, manufacturers of assays used to test donations for hepatitis B virus must verify acceptable sensitivity and specificity of such kits by testing kit-lots using an FDA reference panel.

II. BACKGROUND

Since 1975, FDA's Center for Biologics Evaluation and Research (CBER) has distributed Reference Hepatitis B Surface Antigen panels to manufacturers of HBsAg detection assays used to test blood, blood components, and Source Plasma 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 blood, blood components, and Source Plasma donations, to ensure a minimum sensitivity of those kit lots. They are also distributed to unlicensed manufacturers who are developing such HBsAg assays. CBER uses the panels to test the sensitivity of HBsAg assay lots, pre- and post-licensure, under its lot-release and surveillance programs.

The current CBER panel, distributed since 1996, contains 10 plasma samples: 8 reactive and 2 nonreactive for HBsAg. The 8 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 8.0 ng HBsAg/mL (see footnote to table). The current lower limit of detection specification for HBsAg assays used to test blood donations corresponds to 1.0 ng HBsAg/mL. The CBER panel member estimated to contain about 1.0 ng HBsAg/mL is detected by all HBsAg test kit lots used to test blood, blood components, and Source Plasma donations.

Since establishing this 1.0 ng HBsAg/mL sensitivity standard in 1996, FDA has acquired information that the different HBsAg detection assays, both licensed and investigational assays that are developed for eventual licensure, vary widely in relative sensitivity below this limit. Furthermore, FDA has learned that some of these assays might have detection capabilities well below the 1.0 ng HBsAg/mL standard.

Therefore, FDA initiated a study comparing 3 investigational and 4 licensed HbsAg detection assays and procedures, to evaluate whether newer HBsAg assays are more sensitive than currently 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.

At a Blood Products Advisory Committee (BPAC) meeting held on March 15, 2001, 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 0.18 ng HBsAg/mL for the 3 investigational assays and for one licensed assay tested. On the other hand, a detection limit range from 0.27 to 0.62 ng HBsAg/mL was observed for 3 licensed assays tested. Based on these observations, FDA asked the Committee whether FDA should lower the HBsAg lot-release specification. The Committee voted in favor of lowering the lot-release specification, with 14 "yes" votes, 0 "no" votes and 0 abstentions.

Taking BPAC's recommendation into consideration, FDA is recommending that assays used to test blood, blood components, and Source Plasma donations should have a capability of detecting at least 0.5 ng HBsAg/mL. This selected lower limit of detection standard is intended as an interim measure. When assays with yet lower limits of detection for HBsAg become generally available, FDA will once again review the lower limit of the detection standard. FDA is currently considering developing a future recommendation of a lower limit of detection standard at 0.2-0.3 ng HBsAg/mL, based on the sensitivity of the investigational tests once they are licensed. This approach would permit a stepwise decrease in the lower limit of detection specifications for lot-release of HBsAg detection assays used to test blood, blood components, and Source Plasma donations. FDA believes that this will result in minimal or no disruption in the availability of HBsAg assays for blood establishments, during the implementation of changes in lot-release specifications.

III. RECOMMENDATIONS

FDA recommends that HBsAg detection assays that are used to test blood, blood components, and Source Plasma donations have a lower limit of detection capability of 0.50 ng HBsAg/mL or less. The expected performance of test kits that are used to test blood and Source Plasma donations when testing the CBER HBsAg Lot-Release Panel #12 is shown in the following Table:

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	+

* + = reactive; ± = reactive or non-reactive; – = non- reactive
[a] <0.1 ng/ml; imputed value shown is based on dilutions

IV. IMPLEMENTATION

This guidance is intended for implementation by October 31, 2002.

V. REFERENCES

Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents; Final Rule, June 11, 2001.
21 CFR 610.40
21 CFR 610.44