

Testing for antibody to Anti-HBc (9/10/91)

DATE: September 10, 1991

FROM: Acting Director, Center for Biologics Evaluation and  
Research

SUBJECT: FDA Recommendations Concerning Testing for Antibody to  
Hepatitis B Core Antigen (Anti-HBc)

TO: All Registered Blood Establishments

The Food and Drug Administration (FDA) is now regulating as licensed biologic products test kits that detect total (IgG and IgM) antibody to hepatitis B core antigen (anti-HBc). After 31 March 1991 anti-HBc kits shipped in interstate commerce and labeled for use in screening blood and blood products must bear a U.S. license number.

When initially marketed, anti-HBc test kits were intended for use as diagnostic devices only, and were regulated by the FDA under the premarket approval application (PMA) mechanism. In 1987 blood banks in the United States voluntarily introduced anti-HBc screening of blood and blood components intended for transfusion as a surrogate, non specific, test for non A, non B hepatitis. Thus, anti-HBc test kits were being used to screen licensed, transfusable, biological products and determine donor suitability. After review of this situation in a public meeting on 18 November 1988, the FDA Blood Products Advisory Committee recommended that FDA regulate these kits as licensed biologic products. The FDA announced in the Federal Register (20 February 1990) that total (IgG and IgM) anti-HBc detection kits would be regulated as licensed biologic products after 31 March 1991. On 18 January 1991, the policies and procedures for screening blood and blood components for anti-HBc as described in this document were discussed in a public meeting of the Blood Products Advisory Committee.

Studies of transfusion associated hepatitis prior to anti-HBc testing indicated that hepatitis B still occurred despite the use of sensitive tests for hepatitis B surface antigen (HBsAg). It has also been demonstrated that transfusions of blood reactive for anti-HBc, but negative for HBsAg, are associated with the development of hepatitis in some recipients. Thus, FDA has concluded that testing Whole Blood and components intended for transfusion for anti-HBc contributes to the safety of the blood supply by reducing the incidence of transfusion associated hepatitis B infection.

Therefore, FDA now recommends that all donations of blood and blood components intended for transfusion be screened by an FDA licensed test to detect products that are repeatedly reactive for anti-HBc and prevent their distribution for use in transfusion. FDA is not recommending the exclusion of repeatedly reactive

anti-HBc plasma from pools for further manufacture into plasma derivatives because the exclusion of such products might result in decreased safety of plasma derivatives by a likely reduction of antibody to hepatitis B surface antigen (anti-HBs). For this reason, testing of Source Plasma for further manufacturing is not recommended at this time. Although recovered plasma is harvested from donations that have been tested for anti-HBc, it may be shipped for further manufacturing under a valid short supply agreement regardless of the test results.

Donations intended for transfusion should be tested to determine whether they are negative or repeatedly reactive. Only negative units are suitable for transfusion, with the exception of - autologous donations under specified conditions. Donors should be deferred indefinitely from donating transfusable blood components whenever they test repeatedly reactive for anti-HBc on more than one occasion regardless of the time interval between the two repeatedly reactive tests. A donor reentry protocol for anti-HBc cannot be recommended at this time for lack of an available confirmatory test.

The attached recommendations provide guidance on the testing, labeling, quarantine, storage and shipment of units of blood and blood components with respect to anti-HBc testing. Labeling, informed consent forms, standard operating procedures, deferral registries and recordkeeping procedures should be revised as necessary to reflect the blood establishment's implementation of anti-HBc testing. Licensed blood establishments may adopt labeling consistent with this memorandum concurrently with submitting revised labeling for licensed products for review to the Division of Product Certification, OBPR, CBER.

The recommendations for the labeling of units intended for use in further manufacturing (Section III) will be of special interest to those involved in supplying Source Plasma, recovered plasma and red blood cells for research and for further manufacturing into non-injectable products. The Labeling recommendations in Sections II and III should be implemented within 90 days.

Questions may be directed by telephone to the Division of Transfusion Science, Laboratory of Hepatitis, (301) 496-4288, or in writing.

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RECOMMENDATIONS FOR TESTING FOR ANTIBODY  
TO HEPATITIS B CORE ANTIGEN  
(ANTI-HBc) IN BLOOD ESTABLISHMENTS

I. PERFORMANCE OF ANTI-HBc TESTING

- A. For blood and blood components intended for transfusion, anti-HBc testing should be performed, using an FDA-licensed test kit, and test results interpreted according to the manufacturer's instructions as described in the package insert. Instructions for testing may be summarized as follows:
1. A single test for anti-HBc should be performed on a donor sample for each unit of blood or blood component intended for transfusion (the initial test).
  2. If the initial test result is nonreactive, the test is interpreted as negative and the product may be released for transfusion if all other donor suitability criteria are met.
  3. If the initial test result is reactive, the donor sample is initially reactive. The sample should be retested in duplicate in a single test run, using a test kit of the same format and from the same manufacturer as the kit used for the initial test.
    - a. If both duplicate repeat test results are nonreactive, the test is interpreted as negative for anti-HBc, and the unit may be released for transfusion if all other donor suitability criteria are met.
    - b. If one or both of the duplicate repeat test results are reactive, the test is interpreted as repeatedly reactive for anti-HBc. In this case:
      - i. The products should not be used for transfusion. No further screening tests for anti-HBc should be performed on the products in an effort to qualify them as suitable for transfusion.
      - ii. Blood establishments should include in their donor deferral system a method for identifying any previous anti-HBc test results which were repeatedly reactive.
      - iii. Blood establishments should include in their donor history questionnaire a question regarding any previous anti-HBc test results which were repeatedly reactive.

- B. If the donor is repeatedly reactive for anti-HBc on a second occasion, regardless of the time interval (even if less than 8 weeks), the donor should be indefinitely deferred and the product(s) should not be used for transfusion. An explanation and evaluation of the role of anti-HBc testing in donors is provided in the following article: Hoofnagle, J. H., Post transfusion Hepatitis B, *Transfusion* 1990; 30: 384-386. In addition, general guidance in regard to the testing, counseling, and evaluating of donors tested for hepatitis viruses is described in the Public Health Service Interagency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C. *MMWR* 1991; 40 (RR-4); 1-17.
- C. FDA believes that public health considerations dictate the need for caution in the distribution and autologous use of anti-HBc reactive products. Accordingly, repeatedly reactive units for autologous use should bear a restrictive label as recommended below in Section II.B. Additionally, use of autologous blood repeatedly reactive for anti-HBc is acceptable on the condition that a report of the test result has been made available to the patient's physician. This recommendation differs from those which issued on 12 February 1990 concerning the use of autologous blood positive for disease markers. The physician's written request is necessary for release of units that test - reactive for anti-HIV and HBsAg, but is not required for release of autologous products reactive for anti-HBc.
- D. Test reactivity may represent a "false positive" reaction. In the absence of a licensed confirmatory test, it is suggested that an aliquot of serum or plasma from each repeatedly reactive unit be frozen at -20 C or colder and stored for possible future use in verifying the screening test result in the context of a donor reentry algorithm.
- E. In the absence of licensed confirmatory tests for anti-HBc, the blood center may wish to utilize related test results when counseling the donor. The alanine aminotransferase (ALT) level of an HBsAg nonreactive donor sample may assist in the evaluation of the significance of a repeatedly reactive anti-HBc screening test result. However, regardless of the risk assessment from evaluation of related tests, donors who are repeatedly reactive for anti-HBc on more than one occasion should be deferred indefinitely from donation of whole blood and components for transfusion (See Section I.B.).

II. LABELING OF WHOLE BLOOD AND COMPONENTS INTENDED FOR TRANSFUSION

A. Whole Blood and Blood Components Intended for Homologous Transfusion

Consistent with the labeling for other infectious disease marker tests as described in 21 CFR 606.121 and in the current Guideline for the Uniform Labeling of Blood and Blood Components, negative anti-HBc test results need not appear on-the container label but should be included in the instruction circular. An appropriate statement is:

"...nonreactive for anti-HBc."

This statement may be combined with other statements concerning tests for infectious disease markers. For example, the following combined statement is acceptable:

"A sample from each donation intended for homologous use has been tested by FDA-licensed tests and found negative for antibody to human immunodeficiency virus (anti-HIV-1), and nonreactive for hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis C virus (anti-HCV), and antibody to human T-cell lymphotropic virus, type I (anti-HTLV-I)."

B. Whole Blood and Blood Components Intended for Autologous Transfusion

The guidance for autologous blood and blood components issued on 15 March 1989 includes recommendations for labeling autologous blood. When the test for anti-HBc is repeatedly reactive, the blood product should be permanently labeled with the "Autologous use only" and special BIOHAZARD labels described in the current Guideline for the Uniform Labeling of Blood and Blood

Components. The Circular of Information distributed with blood products should be amended to include use of the biohazard label when an autologous unit tests repeatedly reactive for anti-HBc.

C. Units of Whole Blood or Components Not Tested for Anti-HBc.

On rare occasions, it may be necessary to ship a unit not tested for anti-HBc because a tested unit is not available. For example, untested Red Blood Cells, Frozen, with no serum or plasma available, may be

required to meet an emergency need for a rare phenotype. The container label of such an untested product should include a statement such as the following:

"Caution: Test for anti-HBc has not been done."

### III. LABELING OF BLOOD AND BLOOD COMPONENTS INTENDED FOR FURTHER MANUFACTURING OR RESEARCH

#### A. Plasma Intended for Further Manufacture into Injectable Products

At this time, Source Plasma and recovered plasma under short supply agreements may be shipped to U.S. licensed fractionators for further manufacture into injectable products without labeling as to anti-HBc test status. Additional recommendations for the labeling of such units are being considered.

Note: Source Plasma and recovered plasma for further manufacture into injectable products by licensed manufacturers are prepared, labeled, shipped, and accepted, using approved procedures. Products and samples being shipped under other circumstances, however, need to be appropriately labeled, as addressed below.

#### B. Plasma and Red Blood Cells Intended for Further Manufacture into Noninjectable Products; Whole Blood, Blood Components, and Samples for Research Use

Products intended for further manufacture into in vitro diagnostic reagents or for use in research studies (Section IV.B.) are often provided to consignees on an "as needed" basis, rather than as routine shipments. Therefore, FDA is recommending that such products be labeled with one of the following statements to indicate test status:

1. "Negative by an FDA licensed test for anti-HBc."
2. "Not tested for anti-HBc."
3. "Reactive by an FDA licensed test for anti-HBc."

If the product is not tested for anti-HBc or is reactive for anti-HBc, labels should also include:

"CAUTION: For further manufacture only into in vitro diagnostic reagents for which there are no alternative sources."

or

"For laboratory research only."

If the product is not licensed or is not provided to a U.S. licensed in vitro diagnostics manufacturer under a short supply agreement, the following statement should also appear on the label:

"Not for use in products subject to license under Section 351 of the Public Health Service Act."

#### IV. QUARANTINE AND DISPOSITION OF REPEATEDLY REACTIVE DONATIONS

Whole blood and blood components that are repeatedly reactive for anti-HBc should be quarantined and either destroyed as if infectious for hepatitis or restricted to appropriate use other than transfusion. Provisions of FDA's 6 April 1988 memorandum to all registered blood establishments, Control of Unsuitable Blood and Blood Components, apply.

- A. Whole Blood or blood components that have been found to be repeatedly reactive for anti-HBc should be moved from the general quarantine area for storage of untested units to a special quarantine area designated for units unsuitable for transfusion due to infectious disease test results.

NOTE; Recovered plasma may remain in general quarantine with other units intended for manufacture of plasma derivatives. A mechanism should be in place, however, to ensure that a unit of anti-HBc reactive plasma will not be released inadvertently as plasma for transfusion.

- B. Anti-HBc repeatedly reactive blood and blood components should not be used for homologous transfusion. FDA suggests that establishments destroy the blood or blood components (and laboratory samples, except as noted in I.D.) by autoclaving at 121.5 C maintained for 60 minutes by saturated steam, or by incineration. While awaiting destruction, the whole blood or blood components should be prominently labeled "NOT FOR TRANSFUSION; anti-HBc reactive" in accordance with 21 CFR 606.121(f).
- C. Whole Blood and blood components repeatedly reactive for anti-HBc should be distributed to consignees in a manner consistent with 21 CFR 606.40(a)(7), 606.100, and 606.165. Additional information concerning the shipment of biological products and clinical

specimens, including donor blood samples, may be found in the following CFR sections:

1. Postal Service: 39 CFR Part 111. See also  
(a) the Domestic Mail Manual, which is incorporated by reference into the CFR, and  
(b) the International Mail Manual, for materials to be transported by air.
2. Department of Transportation: 49 CFR Part 173
3. Department of Health and Human Services, Centers for Disease Control: 42 CFR Part 72

- D. The FDA's 26 October 1989 guideline for collection of blood or blood products from "high risk" donors need not be applied at this time to collections from donors known to be anti-HBc repeatedly reactive, whose blood or plasma may be needed for use in research or further manufacture. It is emphasized, however, that all staff should be instructed to follow universal blood and body-fluid precautions in all situations where contact with human blood can be anticipated.

#### V. "LOOKBACK"

A targeted "lookback" program in relation to previously collected products from donors testing repeatedly reactive for anti-HBc is not recommended at this time.

#### VI. PLASMA FOR FURTHER MANUFACTURE

- A. Source Plasma: The FDA does not currently recommend that Source Plasma donors be tested for anti-HBc. If anti-HBc reactive units were excluded from pools used for the manufacture of plasma derivatives, titers of anti-HBs in those pools would be expected to diminish, as both these antibodies usually occur together in plasma. The presence of anti-HBs is believed to contribute to the safety of certain plasma products such as the immunoglobulins. '
- B. Recovered plasma: Plasma units that are untested, nonreactive, or repeatedly reactive for anti-HBc are currently acceptable for the manufacture of plasma derivatives under short supply agreements (see 21 CFR 601.22) with U.S. licensed plasma fractionators.