

December 20, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. 98N-0581: Rule and Proposed Rule; Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents and Requirements for blood, Blood Components, and Blood Derivatives

To Whom It May Concern:

The American Association of Blood Banks (AABB) is the professional association for approximately 2200 institutions engaged in the collection and transfusion of blood and blood products, including all American Red Cross blood services regions, independent community blood centers, hospital-based blood banks and transfusion services, and more than 8500 individuals engaged in all aspects of blood collection, processing and transfusion. Our members are responsible for virtually all of the blood collected and more than eighty percent of the blood transfused in this country. The AABB's highest priority is to maintain and enhance the safety of the nation's blood supply. The AABB appreciates the opportunity to comment on the Food and Drug Administration's (FDA) rule and proposed rule on the requirements for testing human blood donors for evidence of infection due to communicable disease agents and requirements for blood, blood components, and blood derivatives.

The AABB appreciates the efforts of FDA to revise and update the general biological product standards. In particular we commend the incorporation of information pertaining to required testing into one set of regulations. The following comments are divided into two sections. First AABB responds to specific questions posed by the FDA. Second, we provide additional comments on other sections of the proposed rule.

I. Response to specific questions posed by FDA

The agency solicited comments with supporting data from the public in regard to the value of donor testing for syphilis as a marker of high risk infectious diseases, and in preventing the transmission of syphilis through blood transfusion.

The requirement for serological testing for syphilis (STS) has been in place since 1938. However, there have been no well-documented cases of transfusion associated

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syphilis in the past 30 years, and it is clearly recognized that the vast proportion of STS positive donations reflect treated historical infection or non-specific test reactivity.

The question of whether STS is necessary has resulted in considerable debate. In 1995 a NIH Consensus Conference strongly considered recommending that the STS requirement be dropped, but ultimately concluded that additional data were needed to rule out the possibility that dropping the testing requirement would result in post transfusion syphilis.

To address the infectivity issue, carefully controlled pilot phase studies of 100 STS positive samples were assessed for *T Pallidum* DNA by the American Red Cross (ARC) ARCNET program. As reported at the FDA public meeting on November 22, 1999, to date all results have been negative (Transfusion 39(10s), P6-020C) The AABB strongly supports the continuation of these studies toward a sample size that will reasonably reflect a conclusion that STS positive samples do not harbor treponemes.

Another reason cited for STS testing is its possible surrogate value for behavioral risk. In 1997 Herrera, et al from the CDC published data showing that STS had very limited value as a surrogate marker for recent HIV infection (Transfusion 1997 37:836-840). Recent data collected by the NHLBI REDS Study have indicated that STS seropositive donors do not have a level of important deferrable risks that is significantly higher than background (A. Williams, comments presented at 11/22/99 FDA public meeting). Due to the difficulty in measuring rare transfusion transmitted disease (TTD) outcomes, this single study may be the sole source of data that directly addresses the surrogate test issue and it clearly demonstrates a lack of benefit. With the projected licensure of a NAT test for HIV, utilization of STS as an admittedly poor surrogate has even less utility.

On a national basis, reports of primary and secondary syphilis have been declining in the United States since 1990. In 1998 primary and secondary syphilis declined to the lowest rates ever reported in the US, with syphilis transmission increasingly concentrated in limited geographic areas (MMWR October 8, 1999). Rates of syphilis transmission are now sufficiently low that elimination of syphilis (defined as an absence of sustained transmission) in the US has now become a realistic goal.

Current STS procedures result in the loss of many otherwise qualified blood donors and create a situation requiring the notification of individuals about STS test results that almost invariably reflect historical infection or test non-specificity.

The AABB applauds the FDA's reconsideration of the STS issue and reiterates its past position that continued testing is unnecessary for the maintenance of a safe blood supply and an unnecessary drain on both blood supply adequacy and blood donor trust.

FDA requested comment on whether to exempt from testing for evidence of infection due to communicable disease agents listed in proposed 610.40(a) each donation of dedicated apheresis donors. Specifically FDA asked whether the proposed rule when finalized should be revised to permit testing proposed in 610.40 (a) to be completed only once at the beginning of a 30 day period of donation by a dedicated apheresis donor for a single recipient.

The discussion of the proposed rule cites several precedents for such a practice, specifically clinical situations in which apheresis products are collected from HLA matched donor or dedicated family donor for transplant recipients or patients with certain hematological conditions.

The *AABB Standards for Blood Banks and Transfusion Services* has specifically permitted this practice since 1997. Standard H2.510 states “For a cytapheresis donor dedicated to the support of a specific patient, testing required by E5.000 shall be performed prior to transfusion of the first apheresis component and at least every 30 days thereafter.”

Implementation of a proposal of this type does not, we believe, present significant safety concerns, because the patient would be exposed to the (infectious disease marker tested) component of this donor with transfusion of the first donated product. The health and social history screening that takes place immediately prior to each donation would retain the element of safety conferred by that process. From a clinical practice perspective, this product may actually be preferred, because availability of products donated subsequently in the donation period would be expedited.

The AABB supports the concept of this proposal from a philosophical perspective, but requests consideration of modification in its practice. We request that consideration be given to the following

- The final recommendation allow infectious disease marker testing to be performed close to but not necessarily at the time of the first donation. Such pre-screening would permit expedited release of the first donated unit.
- The proposal be extended to include dedicated granulocyte donors. The factors in favor of this approach are similar to those for dedicated plateletpheresis donations.

The agency requested comments on alternatives including the rationale to testing each donation that may be applied to autologous donations as well as dedicated apheresis donors for a single recipient.

We believe that **dedicated apheresis donors** who have been completely screened do not need to be treated any differently from routine donors. Use of an abbreviated donor history questionnaire would be desirable, and could be identical to an abbreviated questionnaire should such a questionnaire be developed for long time donors. Units do not need to be labeled as untested. Even though each subsequent donation has not actually been tested, in fact the test results are known as the test results will not be expected to change within the 30 day timeframe. The establishment must have a process for identifying a dedicated donor and a method of labeling the unit to identify the

intended recipient, but it is unnecessary for the FDA to specify those details in a regulation.

Autologous donations do need different processes. These processes may vary depending upon whether the autologous donation is collected at a blood center or at the hospital where the unit is to be transfused. The *AABB Standards for Blood Banks and Transfusion Services*, 19th Ed details the current AABB requirements. (see Attachment No. 1). We believe that these requirements provide sufficient safeguards and should be incorporated into the proposed rule. We wish to highlight the following points:

- For autologous units which are collected at the blood center and then shipped to the transfusing hospital, complete infectious disease testing should be required as per L1.321. Only the first unit of those collected during a 30-day period need be tested.
- As per L1.321, infectious disease testing should not be required for autologous units to be transfused within the collecting facility.
- Prohibit “crossover” into the allogeneic inventory as per L 1.120.
- All autologous units should be permanently labeled “For Autologous Use Only as per L1.430.
- L1.430 describes the current FDA recommendations for Biohazard labeling dependent on the particular test. There is considerable confusion about the use of Biohazard labels, and the AABB believes that it would be less confusing to simply require that any reactive/positive screening test would require the autologous unit to be labeled Biohazard.

Although it is not currently an AABB Standard, we would consider supporting the additional application of a Biohazard label for autologous units, which have not been tested.

Omitting testing for units to be transfused in the collecting facility is a safe alternative providing that 1. Crossover is not permitted 2. a labeling system is in use which very conspicuously and irreversibly identifies units collected for autologous use and 3. All untested units are labeled with a Biohazard label.

Since these requirements are consistent with present *AABB Standards for Blood Banks and Transfusion Services*, these practices are already widely in use. Implementation of the AABB Standards by the FDA would be less disruptive than introducing an entirely new set of requirements, particularly if the new requirements have not been demonstrated to be superior.

The FDA has described a number of rationales for requiring testing of autologous units. The AABB submits the following comments on these rationales.

- **Rationale: Reduce the risk of transmission of communicable disease by untested units inadvertently entering the blood supply. Further examples of errors and accidents are cited as being erroneous transfusion of an autologous unit to an**

unintended recipient and clerical errors in inventory management including inadvertent crossover of autologous units to the allogeneic inventory.

AABB Comment: Requiring testing for all autologous units will not resolve this concern as long as test positive units are retained in inventory. We do not believe that it would be prudent to require the destruction of all test positive units. The 1998 Supreme Court decision in *Bragdoon v Abbott* may make it unlawful for hospitals to deny HIV-infected patients the opportunity to use their own blood. Institutions are unlikely to refuse autologous services. The AABB supports the current requirements to segregate all autologous units, and label test positive units with Biohazard labels when the autologous units are to be collected at one institution and shipped to another for transfusion. Labeling to more clearly distinguish autologous units from allogeneic units, and to distinguish test positive autologous units from test negative autologous units is also essential.

We believe that attention to other quality systems would provide a better method of reaching this goal for institutions that collect autologous units and transfuse them within their own facility. The most important safeguard is to clearly distinguish autologous units from allogeneic units. This can be accomplished through the use of both labeling and processing controls. If testing is not required then autologous units can have a totally separate processing path, and are less likely to be confused with allogeneic units. Use of a label that clearly identifies and distinguishes autologous units is an important safeguard. An example of the label as currently required by FDA compared to a second label, which more clearly distinguishes, the autologous unit is attached (Attachment No. 2). Addition of a Biohazard label to identify that all autologous units are untested would add an additional safeguard.

The real issue is the effectiveness of the institution's processes for ensuring that the unit of blood intended for Mr. Smith is transfused to Mr. Smith and not to Mr. Jones. Requiring testing of autologous units will not have any impact on this process. The emphasis should be on the organization's quality system to ensure that no units (allogeneic or autologous) are transfused to unintended recipients.

The AABB feels very strongly that the use of autologous units for allogeneic transfusion should not be permitted. Permitting the use of autologous units for allogeneic transfusion eliminates whatever safety margin would be introduced by testing. i.e. if there are circumstances in which autologous units can be made available for allogeneic use, and if units with reactive screening tests are allowed to remain in the autologous inventory, the test results are in effect not being used as they were intended, since the potential would remain for infectious units to be mistakenly transfused to allogeneic recipients. The number of autologous units, which are crossed over into the allogeneic inventory, is very small. Hence, forbidding this practice would have a minimal effect on the national blood supply.

A substantial proportion of autologous blood is collected at donor centers and is already tested per AABB Standards. Since a larger fraction of the autologous units collected in hospitals is presently untested, the impact of required testing, for units to be transfused within the collection institution would be more significant.

FDA requested industry comment on the anticipated number of affected units of autologous blood and their distribution across hospitals in the industry, particularly those units collected by hospitals that can be classified as small entities.

The National Blood Data Resource Center has provided data from the 1998 Nationwide Blood Collection and Utilization Survey. Of 2400 hospitals that replied, 251 indicated that they drew only autologous donors. The total number of autologous units collected by these hospitals was 73,069. The vast majority of these hospitals drew fewer than 400 units per year. Only 13 drew more than 1000 units per year. The survey did not ask whether autologous units were tested, but since these hospitals draw only autologous units, it is unlikely that autologous units are tested.

At least some of these hospitals are located in rural areas where donation at a blood center may be very difficult because of distance. Even those in big cities may represent much more accessible donation location than a blood center, particularly for older or orthopedic patients who might already be at a doctor's appointment at the hospital. Requiring testing would undoubtedly force these facilities to discontinue autologous services, and thus restrict access to the safest form of transfusion.

- **Rationale: Reduce the risk of infection due to communicable disease agents to blood product recipients and to individuals handling blood or blood products.**

AABB Comment: Individuals handling blood or blood products are already required to follow OSHA requirements for Universal Precautions. Labeling all autologous untested units as Biohazard will provide adequate information for appropriate handling.

- **Rationale: The agency also cites inappropriate salvage of plasma from autologous units.**

AABB Comment: It is very unlikely that a hospital collecting autologous blood currently subject to the existing exemption is even preparing plasma for further manufacture. If the hospital wishes to prepare plasma for further manufacture, then the exemption should not apply and testing all autologous donations would be required.

The agency requested comment on the use of vaccinated donors for HBV as an alternative to using donors previously showing evidence of infection due to Hepatitis B virus in the preparation of Hepatitis B Immune Globulin (Human).

Hepatitis B Immune Globulin (Human) (HBIG) is an essential product used in the treatment of individuals (mostly healthcare workers) who have had an exposure to individuals and the treatment of individuals who have had a liver transplant for liver disease caused by Hepatitis B. Currently both vaccinated donors and donors showing evidence of infection due to Hepatitis B are used in manufacturing HBIG. It has been difficult for production to keep pace with demand, especially as the demand is rising. In order to ensure availability of HBIG, manufacturers must be permitted to use all available resources.

II. Additional comments

610.40 (a)

We agree with the approach of defining testing for evidence of infection due to communicable disease agents using screening tests approved for such use by FDA rather than specifying the specific markers. This is especially important so that as advances in testing technology are achieved, these tests may be implemented rapidly, while still maintaining up to date regulations.

It is essential however, that FDA adhere to its stated plan of issuing draft guidance describing those tests it thinks are adequate and appropriate, and that public input on such guidance be sought early and often. Public comments should be incorporated into the final guidance as appropriate, and an explanation of consideration of the comments, which are not incorporated, should also be made public.

610.40 (c) Further Testing requires that each donation found to be repeatedly reactive by a screening test ... shall be further tested whenever FDA has approved a supplemental test for such use.

We believe that additional specific testing is necessary in order to determine the possibility of a false positive test and for purposes of donor notification and counseling. We are concerned that the currently available approved supplemental tests may not be the best methods of doing additional testing and therefore this policy should not be codified. For example, nucleic acid amplification testing (NAT) is generally recognized to be the gold standard of tests, but is not yet approved for use by FDA in blood donor testing. However NAT is already being performed under IND for HCV, will be implemented soon for HIV, and NAT tests are available for other infectious disease agents. These results should be acceptable as additional specific testing when appropriately validated. Indeed a recent review of supplemental testing for blood donor screening tests (to be published in the April 2000 issue of Transfusion Medicine Reviews Vol 14, No 2 Dodd and Stramer, "Indeterminate results in blood donor testing: What you don't know can hurt you") indicates that blot technology is counterproductive due to documented high rates of indeterminate and false positive results. For donor counseling, when possible, blots should be eliminated and replaced by a second EIA/NAT strategy

It is not necessary to require supplemental testing on each donation when the repeatedly reactive test is one of a series of donations. In instances of serial donations,

supplemental testing should only be required on the initial repeatedly reactive donation. The AABB does not believe it is necessary to require supplemental testing for autologous donors. The autologous donor physician should be informed of the screening results and decide whether supplemental testing is necessary.

640.41 Donor Deferral

This section proposed to except deferral from future donations of autologous donors who test repeatedly reactive for evidence of infection due to a communicable disease agent(s) listed in 610.40(a) or reactive for a serologic test for syphilis. We believe that when criteria for allogeneic deferral occur in an autologous donor, the autologous donor should also be deferred from future allogeneic donations. The purpose of deferral is to identify unsuitable donors and prevent distribution of blood components from such donors. Although the autologous donation may be distributed, it is important to defer such donors from allogeneic donation and provide a mechanism for preventing distribution should the donor appear in the future as an allogeneic donor.

Once again, the AABB appreciates the opportunity to comments on the proposed rule. If you have any questions, please contact Kay R. Gregory, AABB's Director of Regulatory Affairs at 301-215-6590 or by e-mail at kayg@aabb.org.

Sincerely,

A handwritten signature in black ink that reads "Paul M. Ness". The signature is written in a cursive, slightly slanted style.

Paul M. Ness, MD
President

Enclosures

NINETEENTH
XIX
STANDARDS FOR BLOOD BANKS
AND TRANSFUSION SERVICES
EDITION

L. AUTOLOGOUS BLOOD

L1.000 BLOOD COLLECTION FOR STORAGE AND LATER AUTOLOGOUS TRANSFUSION

L1.100 General Principles

L1.110 Blood collection for later autologous transfusion requires the order of the donor-patient's physician and the agreement of the medical director. Informed consent as described in B3.200 shall be obtained.

L1.120 The unit shall be segregated and used solely for autologous transfusion.

L1.121 When exceptional circumstances warrant the transfusion of autologous blood to another recipient, this decision shall be approved by the medical director on a case-by-case basis, and records of the indications shall be maintained.

L1.130 A process shall be maintained for all autologous donor selection and collection procedures.

L1.200 Criteria for Collection

Because of the special circumstances attending autologous blood transfusion, rigid criteria for donor selection are not required. In situations where requirements for allogeneic donor selection or collection are not applied, alternate requirements shall be established by the medical director and recorded. Individual deviations from the alternate requirements shall be approved by the blood bank medical director, usually in consultation with the donor-patient's physician. Alternate requirements shall include:

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- L1.210 The volume of blood collected shall comply with established weight provision. B1.200 and H1.210 applies.
 - L1.220 The hemoglobin concentration of the donor-patient's blood should be no less than 11 g/dL. The packed cell volume, if substituted, should be no less than 33%.
 - L1.230 The blood bank shall establish procedures for scheduling a phlebotomy for autologous transfusions. Blood shall not be drawn from the donor-patient within 72 hours of the time of anticipated surgery or transfusion unless approved by the medical director.
 - L1.240 Preoperative donation for autologous transfusion shall not be undertaken when the donor-patient has, or is being treated for, bacteremia or has a significant bacterial infection that could be associated with bacteremia.

L1.300 Testing of Units

- L1.310 ABO group and Rh type shall be determined by the collecting facility as in E1.000, I4.100, and I4.200.
- L1.320 In the case of autologous blood or blood components that will be transfused outside the collecting facility, tests for HBsAg, HIV-1-Ag, anti-HIV-1, anti-HIV-2, anti-HCV, anti-HBc, and a serologic test for syphilis shall be performed prior to shipping on at least the first unit shipped during each 30-day period.
- L1.321 L1.320 does not apply to autologous blood that will be used within the collection facility.

L1.322 If an autologous unit is to be shipped to another facility, and the unit tests positive for any marker of transfusion-transmitted disease listed in L1.320, the shipping facility shall notify the receiving transfusion service.

L1.323 The patient's physician shall be informed of any abnormal results obtained for the tests listed in L1.320.

L1.400 Labeling Requirements

In addition to requirements for labeling at the time of collection or preparation and prior to issue (F3.000 and F5.000), the following information shall appear on a label or tie tag attached to the blood container:

L1.410 The donor classification statement "Autologous Donor" and "For Autologous Use Only."

L1.420 The patient's name and, if available, the name of the facility where the patient is to be transfused, and the patient's hospital registration number (or, if unavailable, social security number, birthdate, or similar identifying information).

L1.430 A biohazard label on each unit from a donor if the donor is tested as in L1.320 and:

- 1) A test for anti-HIV-1 is confirmed to be positive or is repeatedly reactive, and a confirmatory test is not performed.
- 2) A test for anti-HIV-2 is repeatedly reactive.
- 3) A test for HBsAg is confirmed to be positive or is repeatedly reactive, and a confirmatory test is not performed.
- 4) A test for anti-HCV is confirmed to be positive or is repeatedly reactive, and a confirmatory test is not performed.

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- 5) A test for anti-HBc is repeatedly reactive.
 - 6) A test for HIV-1-Ag is repeatedly reactive.
 - 7) A screening test result for syphilis is reactive and the confirmatory test is positive or is not performed.

L1.500 Pretransfusion Testing

Pretransfusion testing for autologous transfusion shall include ABO group and Rh type of donor blood and the recipient on a properly collected and identified sample.

WHICH IS BETTER?

Collection Date | **9036037** | EXPIRES **11-02-99**




AS-1 RED BLOOD CELLS
ADENINE-SALINE ADDED
 15.4 mEq Sodium Added 04210

from 450 mL
 CPD Whole Blood
 Store at 1 to 6 C.



See circular of information for indications, contraindications, cautions and methods of infusion.

VOLUNTEER DONOR

This product may transmit infectious agents.
 Rx only

PROPERLY IDENTIFY INTENDED RECIPIENT

Collected and Processed by
LIFE SOURCE
 1205 North Milwaukee Avenue
 Glenview, IL 60025
 U.S. License #



Registration #1472204

CODE 4R1423
LOT M99D17065

Baxter Healthcare Corporation
 Fenwal Division
 Deerfield, IL 60015 USA
 7-17-31-175 5MH019
PL 146 Plastic



Collection Date | **0026367** | EXPIRES | FORM #AP-1000



FOR AUTOLOGOUS USE ONLY

CPDA-1 WHOLE BLOOD

Approx. 450 mL plus 63 mL CPDA-1.
 Store at 1° to 6° C.

00160



See Circular of Information for indications, contraindications, cautions and methods of infusion.

AUTOLOGOUS DONOR

This product may transmit infectious agents.
 Caution: Federal law prohibits dispensing without a prescription.

PROPERLY IDENTIFY INTENDED RECIPIENT

NOT TESTED FOR SYPHILIS, HIV p24 antigen, HTLV-I/II, HBsAg, HIV-Ab, ALT, ANTI-HBc, HTLV-I Ab, AND ANTI-HCV.

EVANSTON NORTHWESTERN HEALTHCARE

Evanston Hospital
 2650 Ridge Ave.
 Evanston, Illinois 60201
 Registration #1473456

DONOR NAME _____ SURGERY DATE: _____

HOSPITAL _____ BLOOD GROUP: _____

Social Security # _____