

Autologous blood collection (2/12/90)

DATE: February 12, 1990

FROM: Director, Center for Biologics Evaluation and Research

SUBJECT: Autologous Blood Collection and Processing Procedures

TO: All Registered Blood Establishments

The FDA has received an unusually large number of inquiries about the 15 March 1989 recommendations on autologous transfusion. Therefore, we are providing this additional information to assist blood establishments in developing procedures consistent with good manufacturing practices.

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AUTOLOGOUS BLOOD COLLECTION  
AND PROCESSING PROCEDURES:

JANUARY, 1990

ADDENDUM TO FDA GUIDANCE FOR AUTOLOGOUS BLOOD AND BLOOD

COMPONENTS MEMORANDUM OF MARCH 15, 1989

1. If the 15 March 1989 memo reflects the FDA's "recommendations," why did it refer to "required tests?"

The "required test" wording is meant to distinguish between anti-HIV-1, HBsAg and syphilis (STS) tests which are required, and other tests such as anti-HTLV-I, ALT and anti-HBc which are not required by FDA regulations, but have been incorporated into standard operating procedures by blood establishments for all transfusion products. Product labeling, including package inserts or directions-for-use circulars, should correctly identify which tests were performed.

2. Must the tests required by 21 CFR 640.5(a) and (f), 610.40(a) and 610.45(a) and recommended in the 15 March 89 memorandum actually be performed on autologous blood donations?

There have been numerous questions concerning the applicability of testing requirements to blood collected for autologous transfusion. Blood establishments are implementing various strategies to avoid homologous transfusion. The Report of the Presidential Commission on the Human Immunodeficiency Virus Epidemic recommended that

health care facilities implement all reasonable strategies including pre-deposit autologous transfusion to avoid homologous transfusion. It is apparent that many facilities have initiated autologous programs.

Blood establishments are aware of the tests required by 21 CFR 610.40(a), 610.45(a) and 640.5(a) and (f). In the preamble to the final rule for the test for antibody to HIV-1 (FR January 5, 1988 p. 114) it was noted that FDA intends to send a written memorandum to blood establishments setting forth the conditions for an exemption to the HIV-1 testing requirement for blood or blood components for autologous use only. This answer is in part intended to satisfy that commitment.

The existing regulatory requirements are also being examined-as they apply to the collection, testing and labeling of autologous blood to determine whether revisions or additions must be proposed. An example of such a revision might be an addition to 21 CFR 610.40 that parallels 21 CFR 610.45(a).

- a. The CFR recommends that all FDA required tests described at 21 CFR 610.40 (HBsAg), 610.45 (anti-HIV-1) and 640.5 (syphilis) be performed on a sample of blood, taken from the donor at the time of collection of the unit of blood. (15 March 1989 memorandum)
- b. An exception to the HIV-1 testing requirement for blood or blood components can be made however, under the following conditions:
  - 1) The establishment collects and uses autologous blood products only for the autologous donor,
  - 2) These products are used at the site of collection
  - 3) All products not used by the donor are destroyed.

If the above conditions are met, the facility may substitute rigid control procedures outlined in an SOP and cautionary labeling per 21 CFR 606.121(i)(4), as an alternative to HIV-1 antibody testing.

The use of precautionary procedures equivalent to those applied for donors known to be positive for anti-HIV is recommended. See 26 October 1989 memorandum: "Guideline for Collection of Blood or Blood Products from Donors with Positive Tests for Infectious Disease Markers ("High Risk" Donors)"

If these control conditions are in place the blood establishment also may consider exempting other tests such as those for HBsAg and syphilis if doing so will not compromise the safety of the recipient.

- c. Establishments that routinely ship autologous units interstate must be licensed. The units must be fully tested and appropriately labeled.
  - d. Any autologous units that are used homologously must come from a donor who meets all donor suitability requirements (21 CFR 640.3) and whose products meet all test requirements (21 CFR 640.5, 610.40 and 610.45).
3. Are there alternatives to testing all of the autologous products collected for anti-HIV-1, HBsAg and syphilis?

Yes. Provided that no part of the blood is used for any purpose other than autologous transfusion, it is acceptable to perform the required laboratory tests only on the first unit of blood collected from each donor in a 30-day period; subsequent units may be labeled: "Collected from a donor known to be ..." FDA recommends that the date of testing also be indicated on the label. Although some establishments may want to establish donor suitability by "prescreening", only test results from samples collected at the same time as the products meet FDA labeling requirements. [21 CFR 640.4(g)(2)i.

4. What should be done with units that are repeatably reactive in screening tests, but not confirmed to be positive by additional, more specific tests for anti-HIV-1 or HBsAg?

When screening tests are repeatably reactive, but additional more specific tests for anti-HIV-1 (e.g., Western blots) or confirmatory HBsAg tests are negative, the unit must be labeled for autologous use only, but products do not require the special precautions applicable to shipping positive products. The donor's name must be placed on a deferral list to prevent future distribution for homologous transfusion or further manufacturing of any products collected, unless the donor has satisfied all the requirements of the FDA donor re-entry algorithm.

5. Can test results from outside laboratories be used if the hospital does not perform tests for anti-HIV-1 and HBsAg on autologous donors?

Yes. Tests using licensed reagents may be performed in an outside laboratory; any registered blood establishment or HCFA certified laboratory is acceptable. However, the laboratory must register with FDA pursuant to 21 CFR 607 and is subject to FDA inspection. The establishment

responsible for blood collection must ensure that all FDA good manufacturing practices are met. The contractual agreement between the establishments should include procedures for test interpretation and record keeping.

6. Why wasn't HTLV-I testing mentioned? Can HTLV-I positive units be used? "

HTLV-I testing is not recommended by FDA for autologous transfusion purposes; test results, if known to be HTLV-I positive, do not limit use for autologous transfusions. Because HTLV-I testing is not recommended for plasma for further manufacturing, there is less concern about the possible inadvertent shipment of untested or HTLV-I test-positive units of recovered plasma. However, fractionators or other receivers of recovered plasma may require in product specifications that products have negative test results.

If the cellular components are not used by the autologous donor, HTLV-I testing is recommended before the release-of cellular products to another patient. Therefore, many blood banks will choose to do all of the testing at the time of blood collection. Note: If HTLV-I testing procedures do not address both autologous and homologous donors similarly, appropriate labeling changes should be made in the package insert and on containers (if applicable) to reflect only those tests actually performed.

7. Why did the FDA limit storage of products collected intraoperatively to 6 hours?

We are aware that the AABB Standards permit up to 24 hours storage at 1 - 6 degree Celsius for products collected under sterile conditions. CBER is not aware of data from controlled trials that would support a 24 hour storage period for the subject products and, therefore, applied the more conservative 6 hour recommendation. However, the medical director of each facility should take responsibility for the standard operating procedures adopted in his institution for these medical procedures.

8. What will happen if the FDA discovers that we did not call back the donors of previously frozen, stored autologous products to permit anti-HIV-1, HBsAg and STS testing to be done?

It will not be considered a deficiency if previously collected frozen autologous blood products remain untested, provided that labeling accurately reflects the status of all products distributed, the units are restricted to autologous use only and the applicable SOP's are followed.

9. Why does the 15 March 1989 memo differ from the 2 December 1987 memo in regard to donor deferral when HBsAg screening tests are reactive, but neutralization tests don't confirm a positive result?

The 2 December 1987 memo is misleading on this point. The term permanent deferral in the 15 March 1989 memorandum does not exclude the possibility that a donor might successfully complete a reentry program. Donor deferral is not necessary when confirmatory HBsAg tests are not positive and the necessary follow-up testing is done in accordance with the approved algorithm for donor reentry. However, the confusion caused by such test results in routine homologous donors usually does not warrant continued recruitment of that donor. On the other hand, the autologous blood unit which has already been collected can be used without prejudice.

10. If a blood establishment already has licenses for Whole Blood and components for homologous use, must another license be requested for autologous blood?

Autologous blood prepared from donors who meet the standards for whole blood donation would, of course, be included under existing licenses. There are no additional standards in 21 CFR, Part 640 for an autologous blood product prepared from donors who do not meet the requirements for homologous blood donation. There are, however, GMP labeling requirements in 21 CFR 606.121(i) for autologous blood that include instructions for labeling products that are collected from donors who do not meet whole blood standards (21 CFR Part 640). For the present, to extend a license to include autologous blood products prepared from donors who do not meet the homologous whole blood standards (21 CFR Part 640), the applicant need only define the procedures which will prevent inadvertent release of restricted units and request that product license applications be amended to include products prepared from those donors. The firm also must submit labels that meet the requirements of 21 CFR 606.121(i)(4).

11. Some hospitals do not like the autologous use only label prescribed by 21 CFR 606,121(i)(4) because 1) the space for hand-writing the patient identification information is too small and 2) this label may not be compatible with computerized systems that utilize bar coded ABO labels. Is this label required? If so, can the standard ABO label be used in addition to this label?"

The regulations are specific in that the "for autologous use only" label is to appear in place of the blood group label. The rationale for this requirement was that exclusion of the usual blood grouping label on blood intended for autologous purposes assures that the

autologous blood is not mistaken for blood intended for routine homologous transfusion purposes. One solution would be to label as prescribed by the regulations but add a tie-tag that displays the standard ABO label and any other information that hospitals may require.

12. Of there is no cross-over of any autologous blood and all units are labeled "for autologous use only", can the autologous donor classification statement recommended in the 15 March 1989 memorandum be deleted?

Although the statement is not yet required by regulation, we strongly recommend that labeling be kept as uniform as possible to minimize any potential confusion for staff encountering units that look "different".

13. For blood that may be "crossed over", where should the permanent autologous donor label described in the 15 March 1989 memorandum be placed? How big should the print be? What color print?

Since this label has not yet been incorporated in the uniform labeling guidelines, there are no definitive answers; however, guidance consistent with current practice would include the label being added to the container in the upper left-hand corner designated for the collection date. The collection date is rarely included for homologous use products. Labels could also be placed immediately above or below the base label. Size and color should be consistent with the volunteer/paid donor classification statements.

14. The 15 March 1989 memorandum states that, "Establishments collecting autologous blood ... that are routinely shipped in interstate commerce must be licensed...". What is FDA's definition of routine? Does it relate to the number of shipments?

"Routinely" refers to functions performed on a regular basis. A regular basis could be 4 times per year. If the establishment maintains an SOP for the collection and shipment of autologous blood, and it is known that the establishment will provide this service in interstate commerce, the practice would not fit the criteria of unplanned or emergency, and the establishment should seek licensure. Most autologous collections will not be associated with emergencies.

15. Can a hospital elect to omit infectious disease marker testing and institute rigid controls for licensed, interstate shipments of autologous blood?

No. Testing is a necessary component of an approvable license application. Products which are not tested should not leave the collecting establishment for any purpose.

16. Are there any regulations that prohibit the hand carrying of autologous blood in interstate commerce (no sale, barter, or exchange) by the donor?

No.

17. Are there any recommended procedures to be followed when a donor elects to hand carry his/her own blood to the receiving hospital?

Yes. When a donor elects to hand carry his/her blood, the donor or the attending physician must be responsible for making the necessary arrangements between the collecting and receiving hospitals and any commercial carriers. The blood establishments (collecting and receiving facilities) must have appropriate SOP's, to describe this service in sufficient detail, if provided.

The following suggestions will help protect the integrity of the product in such situations.

#### Labeling

The autologous donation should be labeled as any other autologous unit, in accordance with 21 CFR 606.121(i), except that the use of the blood or any of its components must be restricted to the donor only, 21 CFR 606.121(i)(4). The package label should include the maximum length of time that a package may be in transit.

#### Packaging

The autologous units should be packaged by the collecting facility and under no circumstances by the donor. A thermometer should be included inside the shipping container and the blood should be packaged by the usual procedures for shipment by common carrier. The sealed shipping container should not be opened by anyone other than authorized personnel at the receiving hospital. If delay in transit requires addition of ice, the blood should be taken to the nearest blood bank for repackaging.

#### Storage and Shipping Conditions

21 CFR 640.2(3) requires whole blood to be stored at 1 to 6 degree celsius and shipped between 1 and 10 degree celsius. There are no specific regulations that state that blood must be shipped within a certain length of time. The transit time limit should be established based on the amount of coolant needed to maintain the blood at the appropriate temperature. The in-transit time limit should be placed on the label of the outer shipping container. This should be discussed between the donor, the collecting facility, and the receiving facility as part of the acceptance criteria.

## Handling Instructions

The donor should be given written instructions by the collecting facility with regard to handling of autologous blood.

The donor needs to be informed of the storage requirements, storage temperature, and transit time limits. The donor needs to be informed of the Department of Transportation (DOT) regulations in the event that the autologous donations are tested and found infectious, thereby requiring biohazard labeling and special packaging for shipment by air freight. Such units may not be permitted on board commercial airline flights.

## Records for the Disposition of Autologous Blood That is not Transfused

The receiving blood establishment should have documentation that all unused components from the donation-are destroyed by an appropriate method. Blood should not be given back to the donor for destruction by the donor.