

Guidance for Industry
Screening and Testing of Donors of Human Tissue
Intended for Transplantation

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GUIDANCE FOR INDUSTRY: (1)
SCREENING AND TESTING OF DONORS OF HUMAN TISSUE INTENDED FOR
TRANSPLANTATION

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PURPOSE

This guidance provides general information on donor screening and testing procedures and practices for those entities involved in the recovery, screening, testing, processing, storage, or distribution of human tissue intended for transplantation and may assist in complying with the requirements in Title 21, Code of Federal Regulations (21 CFR) Part 1270.

SCOPE

Because the Food and Drug Administration (FDA) is in the process of revising 21 CFR 10.90(b), this document is not being issued under the authority of 21 CFR 10.90(b), and the document does not bind the agency and does not create or confer any rights, privileges, or benefits for or on any person. Tissue establishments may follow the guidance or may choose to use alternative procedures not provided in this guidance document. If a tissue establishment chooses to use alternative procedures, the establishment may wish to discuss the matter further with the agency to prevent expenditure of resources on activities that may be unacceptable to the FDA.

This guidance applies to human tissue intended for transplantation procured on or after the effective date of the final rule contained in 21 CFR 1270 and supersedes previous guidance issued by FDA on the screening and testing of donors of human tissue intended for transplantation. FDA may amend this guidance periodically as needed.

INTRODUCTION

On December 14, 1993, FDA published 21 CFR Part 1270 (1), entitled Human Tissue Intended for Transplantation, to reduce the risk of transmission of the human immunodeficiency virus (HIV) and hepatitis viruses through human tissue intended for transplantation. The regulation was issued as an interim rule under the authority of Sections 215, 311, 361, and 368 of the Public Health Service Act (42 U.S.C. 216, 243, 264, 271), because of an immediate need to protect the public health from exposure to the human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) viruses through transplantation of tissue from donors infected with these viruses. On July 29, 1997, FDA issued a final rule, 21 CFR Part 1270, clarifying and modifying provisions contained in the interim rule for human tissues intended for transplantation.

DONOR TESTING

Required Tests

All human tissue intended for transplantation should be procured from donors who are tested and found to be negative for antibodies to the human immunodeficiency virus, Type 1 and Type 2 (anti-HIV-1 and anti-HIV-2), hepatitis B surface antigen (HBsAg), and antibodies to the hepatitis C virus (anti-HCV) using FDA licensed tests. The testing should be performed by laboratories appropriately certified for these tests under the Clinical Laboratories Improvement Amendments (CLIA) of 1988. Tissue determined to be suitable for transplantation should be accompanied by a summary of records or copies of original records as required by 21 CFR Part 1270 indicating that the testing was performed and that the samples were found to be negative for anti-HIV-1, anti-HIV-2, HBsAg, and anti-HCV using an FDA licensed screening test. For samples of cadaveric blood, i.e., taken from a donor whose heart beat has ceased, screening tests which have been licensed for testing cadaveric blood should be used, when such tests become available.

FDA recommended that blood banks screen blood using HIV antigen testing. (2) At present, FDA is not recommending HIV antigen testing for donors of human tissue intended for transplantation. Because blood storage, temperature and other factors may affect test results; and because the test kit specificity and sensitivity has not been addressed for cadaveric blood, HIV antigen testing is not a requirement at this time. If, however, donors are tested using an HIV antigen test, or any other non-required HIV test, the tissue establishment should reject tissue from a donor who tests positive by that test.

Viral Marker Test Performance

All tissue from donors that test repeatedly reactive on a required screening test should be quarantined and should not be used for transplantation. Donor sample testing, using FDA licensed tests, should be performed and test results interpreted according to the manufacturer's instructions in the package insert for the particular viral marker. Below is a summary for conducting laboratory testing of donor samples using currently licensed kits (3,4,5,6):

- (1) A single test should be performed on a donor sample from each donor whose tissue is intended for transplantation. This test is referred to as the initial test.
- (2) If the initial test result is nonreactive, the donor sample is considered negative for the particular viral marker, and the tissue from the donor may be used for transplantation, provided all other donor suitability requirements are met.
- (3) If the initial test result is reactive, the donor sample is considered to be initially reactive. The sample should be

retested in duplicate, preferably within a single run (not necessarily the same test kit lot), using the same procedure and same manufacturer's test kit as that used for the initial test. If both repeat test results are non-reactive for the viral marker the donor sample is considered negative for the particular viral marker, and the tissue from the donor may be used for transplantation provided all other donor suitability requirements are met. If either one or both of the repeat test results are reactive, the test is considered to be repeatedly reactive, and the tissue from the donor should not be used for transplantation.

Plasma Dilution and Testing Algorithm

21 CFR Part 1270 states that tissue shall be determined to be unsuitable for transplantation if transfusion or infusion has been sufficient to affect test results. Transfusion or infusion in the absence of blood loss should not normally be sufficient to affect test results. When blood loss is known or suspected to have occurred, the potential tissue donor was transfused or infused, and no adequate pre-transfusion/infusion sample is available for infectious disease testing; then an algorithm should be used to determine that there has not been plasma dilution sufficient to affect test results. For adults, if administration of more than 2000 milliliters of whole blood, reconstituted blood, red blood cells (RBC) and/or colloid occurs within the 48 hours immediately preceding the collection of a blood sample for testing; or the administration of more than 2000 milliliters of crystalloids occurs within the one hour immediately preceding the taking of a blood sample for testing; or a combination of more than 2000 milliliters of the above occurs, and there is no pre-transfusion/infusion blood sample, then the algorithm defined in the tissue establishment's standard operating procedure (SOP) should be applied. If a donor is 12 years of age or under and there is no pre-transfusion/infusion sample, then an algorithm should be applied when any transfusion or infusion has occurred to determine that there has not been plasma dilution sufficient to affect test results.

The following is an example of a suitable algorithm (see Attachments 1 and 2):

For donors in the 45-100 kilogram range: the blood volume in milliliters may be determined by dividing the body weight in kilograms by 0.015, and the plasma volume in milliliters may be determined by dividing the body weight in kilograms by 0.025. In a circumstance of blood loss with replacement:

If the combined volume of colloid given in the 48 hours preceding sampling plus the volume of crystalloid given in the one hour preceding sampling exceeds the donor's total plasma volume or if the combined volume of the blood given in the 48 hours preceding sampling, plus the volume of colloid given in the 48 hours preceding sampling, plus the volume of crystalloid given in the one hour preceding sampling exceeds the donor's total blood volume then plasma dilution is sufficient to affect test results and the donor should be rejected. (If any one element has not

been transfused/infused then it is simply a zero in the calculation.)

For purposes of clarification and definition:

- (1) Blood - refers to whole blood, reconstituted blood, and/or red blood cells transfused in the 48 hours preceding sampling. Reconstituted blood is considered to be red blood cells suspended extracorporeally, in a volume of colloid or crystalloid sufficient to produce a product with a hematocrit in the normal range.
- (2) Colloid - refers to plasma, platelets, albumin, hetastarch, dextran, or a combination of these administered in the 48 hours preceding sampling.
- (3) Crystalloid - refers to saline, dextrose in water, Ringer s lactate, and other balanced electrolyte solutions administered in the one hour before sampling.

Because every possible clinical situation cannot be predicted, the medical director should determine additional circumstances where application of an algorithm would be applied, document the application, and explain the circumstances. Examples of these additional circumstances are a donor who has had blood loss previously, stabilizes, then expires, but has received fluids in the 48 hours prior to sampling; a donor who is obese; a donor who in the absence of bleeding may have received large amounts of infusions which the medical director or designee believes may affect test results; or a donor who is less than 45 kilograms or greater than 100 kilograms.

The establishment's SOP's should define those elements necessary to make a determination whether a pre-transfusion/infusion blood sample for infectious disease testing is adequate. For example, the amount of hemolysis, storage conditions, and age of the sample may be considered relevant. Therefore, the medical director or designee should review these factors and document that a determination of unsuitability of the sample was made.

The tissue establishment should include in its SOPs the algorithm established [see 21 CFR 1270.31(a)].

There should be written procedures prepared and followed for all significant steps in the infectious disease testing process under section 1270.21 which should conform to the manufacturers' instructions for use contained in the package inserts for the required tests. These procedures should be readily available to the personnel in the area where the procedures are performed. Any deviation from the written procedures should be recorded and justified.

Sources of Information

In addition to the testing and plasma dilution determination, 21 CFR Part 1270 requires identification of the donor and screening of all tissue donors for relevant behavioral high risk criteria and for clinical and physical evidence of HIV or hepatitis infection. This screening should include an interview with the donor, if living, or an interview with one or more individuals who can provide reliable information concerning the donor's medical history, if the donor is deceased. The donor medical history interview as defined in the final rule means a documented dialogue with an individual or individuals who would be knowledgeable of the donor's medical history and relevant social behavior. The relevant social history would include questions to elicit whether or not the donor met certain descriptions or engaged in certain activities or behaviors considered to place the donor at increased high risk for HIV and hepatitis. The individual interviewed may be the donor's next of kin, a relative, a member of the donor's household, an individual with an affinity relationship with the donor, or the donor's primary treating physician. In addition, a review of all available records including the donor's medical records, autopsy reports or any physical assessment reports including the medical examiner report, police records and other available information, should be used to make a donor suitability determination.

Review of such records should be performed by an individual who is qualified by profession, education and training and who is familiar with the intended use of the tissue. Determining the acceptability of each donor should be the responsibility of the medical director or designee, who, upon review of all available records makes such a determination following the establishment's standard operating procedures, existing medical standards, and federal, state or territorial laws and regulations. The medical director or designee should determine that adequate information has been obtained to assess donor suitability and should have the discretion to reject tissue where information is incomplete or should document the rationale for the release of such tissue based upon the available adequate information.

A number of state and territorial legislative consent laws permit corneal retrieval under specified circumstances of consent. FDA requires in 21 CFR Part 1270, consistent with the 1994 PHS guidelines (7) that the corneal tissue be accompanied by the summary of records documenting that the corneal donation was procured under legislative consent law and determined to be suitable in the absence of a donor medical history screening interview. For corneal tissue procured under legislative consent where a donor medical history screening interview has not occurred, a physical assessment of the donor is required and other available information should be reviewed and should support a determination that the cornea is suitable for transplantation. FDA recommends that, whenever possible, a donor medical history screening interview be performed.

Behavioral and High Risk Information

The donor medical history screening interview should include questions about the following behavioral and high risk criteria and tissue should not be accepted for transplantation from donors who have any positive evidence of the following exclusionary risk factors:

- (1) men who have had sex with another man within the preceding 5 years (7);
- (2) persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, and subcutaneous injections (7);
- (3) persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates (4,7,8);
- (4) persons who have had sex in exchange for money or drugs in the preceding 5 years (7);
- (5) persons who have had sex in the preceding 12 months with any person described in the 4 items above or with any person suspected of having HIV, hepatitis B virus, or hepatitis C virus infection (4,7);
- (6) persons who have been exposed within the last 12 months to known or suspected HIV, HBV, and/or HCV infected blood through percutaneous inoculation (e.g. needlestick) or through contact with an open wound, non-intact skin, or mucous membrane (4,7,8);
- (7) children 18 months of age or less born to mothers HIV-infected or at risk for HIV infection and who have been breast fed within the preceding 12 months, regardless of HIV status (7);

NOTE: Children over 18 months of age born to mothers infected with HIV or at risk for infection, who have not been breast fed within the preceding 12 months, and whose HIV antibody test, physical examination and review of medical records do not indicate evidence of HIV infection can be accepted as donors (7).

- (8) current inmates of correctional systems (including jails and prisons) and individuals who have been incarcerated for more than 72 consecutive hours during the previous 12 months (7,9);
- (9) persons who have had close contact with another person having viral hepatitis within 12 months preceding donation (3,8);
- (10) persons who have had or have been treated for syphilis or gonorrhea during the preceding 12 months (4);
- (11) persons who within 12 months of donation have undergone tattooing acupuncture, ear or body piercing in which shared instruments are known to have been used (3);

NOTE: Though not currently within the scope of 21 CFR 1270, FDA is aware that screening for possible risks of exposure to Creutzfeldt-Jakob disease is recommended in voluntary standards such as the

American Association of Tissue Banks and the Eye Bank Association of America.

The relevant factors are:

- (12) persons with a diagnosis of Creutzfeldt-Jakob Disease or known family history (blood relative) of a person with non-iatrogenic Creutzfeldt-Jakob Disease (10);
- (13) persons who have received injections of human pituitary-derived growth hormone (pit-hGH) (11); or
- (14) persons who are known to have received transplants of dura mater (10).

21 CFR 1270.31(b), states that written procedures should be prepared and followed for all significant steps for obtaining, reviewing, and assessing the relevant medical records. As noted in the definition of relevant medical records, those records include a donor medical history screening interview. FDA believes that the establishment should develop and follow SOPs incorporating direct questions addressing the above risk factors and that direct questions should be asked in the donor medical history screening interview to determine if these events occurred. The questions should be framed in a way to elicit the information being sought. Available records should also be reviewed to determine if any of the above risk factors are reported. If these risk factors are reported to have occurred within the specified time period the tissue should not be used.

Clinical Evidence

In addition to the requirements in 21 CFR Part 1270 that a donor should test negative on FDA screening tests for HIV, HBV, HCV and be screened and found to have none of the relative risk factors, a donor should also be free from clinical signs and symptoms of HIV and hepatitis. Based on the available information from a donor's medical history, physical examination, medical records, autopsy report and laboratory test results, tissue donors should be free from evidence of:

- (1) HIV infection or Acquired Immunodeficiency Syndrome (AIDS) which could include clinical signs and symptoms such as unexplained weight loss, unexplained night sweats, blue or purple spots on the skin or mucous membranes typical of Kaposi's sarcoma, disseminated lymphadenopathy of longer than one month, unexplained temperature of over 100.5F (38.6C) for more than 10 days, unexplained persistent cough or shortness of breath, opportunistic infections, unexplained persistent diarrhea (4,7), and
- (2) Hepatitis B or C infection, which could include clinical signs and symptoms of hepatitis such as unexplained yellow jaundice or hepatomegaly (records of laboratory data such as alanine aminotransferase (ALT), aspartate aminotransferase (AST),

bilirubin or prothrombin time may assist in making a donor suitability determination) (6).

Physical Evidence

Physical assessment of all tissue donors aids in donor suitability determinations because it provides an additional level of assessment for high risk behaviors or clinical evidence of infection with HIV or hepatitis. 21 CFR 1270 defines a physical assessment as a limited autopsy or recent antemortem or postmortem physical examination of the donor to assess for any evidence of high risk behavior and signs of HIV and hepatitis infection. If any of the following signs are observed on physical assessment and are deemed to be an indication of either high risk behavior or an indication of HIV or hepatitis infection then the tissue should be rejected.

For all donors, the following should be determined by limited autopsy and/or recent antemortem or postmortem physical examination, and noted if reported in any other available record:

- (1) Physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, syphilis, chancroid;
- (2) Physical evidence of anal intercourse including perianal condyloma;
- (3) Physical evidence of nonmedical percutaneous drug use such as needle tracks;
- (4) Disseminated lymphadenopathy;
- (5) Oral thrush;
- (6) Blue or purple spots consistent with Kaposi's sarcoma;
- (7) Needle tracks, including examination of tattoos which may be covering needle tracks;
- (8) Unexplained jaundice, hepatomegaly or icterus; or
- (9) If the body was rejected for routine autopsy due to infectious criteria or if the autopsy was done in an infectious disease control room or under any special precautions and the reasons for these procedures.

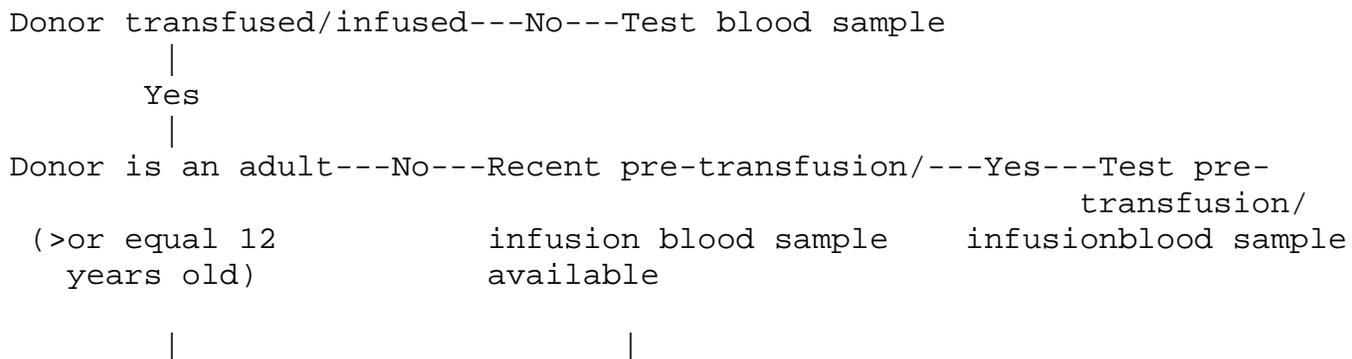
REFERENCES

1. FDA Interim Rule for Human Tissue Intended for Transplantation, December 14, 1993, Federal Register, Vol 58, No. 238, p 65514.
2. FDA Recommendations to Blood Establishments for "Donor Screening with a Licensed Test for HIV-1 Antigen," 8/8/95.

3. FDA Revised Recommendations to Blood Establishments for "Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)," 4/23/92.
4. FDA Revised Recommendations to Blood Establishments for "The Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," 4/23/92.
5. FDA Recommendations to Blood Establishments for "The Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBSAG)," 12/2/87.
6. FDA Recommendations to Blood Establishments for "Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis," 12/22/93.
7. PHS Guideline for Preventing Transmission of HIV through Transplantation of Human Tissue and Organs, MMWR 1994:43, 1-17.
8. PHS Guideline for Screening Donors of Blood, Plasma, Organs, Tissue and Semen for Evidence of Hepatitis B and Hepatitis C, MMWR 1991:40, 1-17.
9. FDA Recommendations to Blood Establishments for "Deferral of Current and Recent Inmates of Correctional Institutions as Donors of Whole Blood, Blood Components, Source Leukocytes, and Source Plasma," 6/8/95.
10. FDA Recommendations to Blood Establishments for "Precautionary Measures to Further Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease by Blood and Blood Products," 8/8/95.
11. FDA Recommendations to Blood Establishments for "Deferral of Blood and Plasma Donors based on Medications," 7/28/93.

ATTACHMENT 1

EXAMPLE OF A FLOW CHART FOR DETERMINING IF A DONOR SPECIMEN IS
SUITABLE FOR INFECTIOUS DISEASE TESTING



TOTAL: A = _____ ml

B. Total volume of Colloid Infused/48h

Volume of: dextran _____ ml

plasma _____ ml

platelets _____ ml

albumin _____ ml

hetastarch _____ ml

Other:

_____ ml

_____ ml

_____ ml

TOTAL: B = _____ ml

C. Total volume of Crystalloid Infused/1h

Volume of: saline _____ ml

dextrose in water _____ ml

Ringer's lactate _____ ml

Other:

_____ ml

_____ ml

_____ ml

TOTAL: C = _____ ml

DETERMINATION OF SUITABILITY

- | | | | |
|----|--------------------|---|---|
| 1. | Is B + C > PV? | Y | N |
| 2. | Is A + B + C > BV? | Y | N |

If answer to both 1 and 2 are NO then test sample.

COMMENTS: If answer to either 1 or 2 is YES then reject donor.

INITIALS: _____