

Guidance for Industry

Recommendations for Obtaining a Labeling Claim for Communicable Disease Donor Screening Tests Using Cadaveric Blood Specimens from Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

FDA is issuing this guidance for immediate implementation in accordance with 21 CFR 10.115(g)(4)(i). Submit comments on this guidance at any time to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance 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>.

For questions on the content of this guidance, contact Melissa Greenwald, M.D., at 301-827-2002.

**U.S. Department of Health and Human Services
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This guidance represents the Food and Drug Administration's (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. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides to you, medical device manufacturers of communicable disease tests, information about performing studies to support modifying the indication for use to include testing of cadaveric blood specimens to screen donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps). This guidance makes recommendations about:

- Sensitivity and specificity studies
- Reproducibility studies
- Number of test kit lots to include in studies
- Plasma dilution issues
- Information about specimen collection times to be included

This document contains information which has been provided in Center for Biologic Evaluation and Research's (CBER's) letters to manufacturers of communicable disease tests. We, FDA, continue to encourage manufacturers of communicable disease tests to evaluate these tests for cadaveric HCT/P donor use and seek such labeling.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

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II. BACKGROUND

Recognizing the need for appropriately evaluated and labeled test kits, we issued letters in 1995 to manufacturers of donor screening tests introducing the subject of expanding the indication for use of blood donor screening tests to include testing of cadaveric blood specimens and suggesting a minimum protocol. In the Federal Register of July 29, 1997 (62 FR 40429), we issued a final rule, “Human Tissue Intended for Transplantation,” (the tissue final rule) which requires “certain infectious disease testing, donor screening, and recordkeeping to help prevent the transmission of the human immunodeficiency virus (HIV), and hepatitis viruses through human tissue used in transplantation” (62 FR 40429 at 40429) (Ref. 1). Additionally, the tissue final rule requires that “FDA licensed screening tests labeled for cadaveric specimens must be used when available” (21 Code of Federal Regulations 1270.21(d)). Also, in the Federal Register of July 29, 1997 (62 FR 40536), we announced the availability of a “Guidance for Screening and Testing of Donors of Human Tissue Intended for Transplantation,” dated July 1997, which further discussed the use of donor screening tests (Ref. 2).

We approved two biologic license supplements with the modified indication for use to include testing of cadaveric blood specimens. On December 28, 1999, FDA approved the Genetic Systems Corporation's Supplement to its Product License Application for Antibody to Hepatitis B Surface Antigen (Mouse Monoclonal) Enzyme-Linked Immunosorbent Assay to modify the intended use of the Genetic Systems HBsAg EIA 2.0 and the Genetic Systems HBsAg Confirmatory Assay 2.0 to include the testing of cadaveric serum samples. On February 9, 2000, FDA approved the Genetic Systems Corporation's Supplement to their Product License Application for Human Immunodeficiency Virus Types 1 and 2 (Synthetic Peptide) to modify the intended use of the Genetic Systems HIV-1/HIV-2 Peptide EIA to include the testing of cadaveric serum samples. These approved tests detect antibodies to Hepatitis B Surface Antigen and antibodies to Human Immunodeficiency Virus (HIV)-1 and HIV-2, respectively, in a cadaveric donor's serum.

In June 2000, we issued a “Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens” (the June 2000 guidance), which informed establishments of the availability of these two licensed donor screening tests labeled for use with cadaveric blood specimens (Ref. 3). In the Federal Register of May 25, 2004 (69 FR 29786), we issued a final rule “Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products” (Ref. 4) which requires that donors of cells and tissue be tested for evidence of infection due to relevant communicable disease agents or diseases. Those relevant communicable disease agents include HIV, types 1 and 2; hepatitis B virus; and hepatitis C virus, and, for certain donors, Human T-Lymphotropic Virus, types I and II. Manufacturers of tests used to screen blood donors for communicable diseases have requested information on studies to support modifying the indication for use to include testing of cadaveric blood specimens from donors of HCT/Ps.

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III. DISCUSSION

We recommend you address the following areas when preparing a protocol to modify the indication for use to include testing of cadaveric blood specimens.

A. What data about specificity and sensitivity are recommended when matched pairs of pre- and post-mortem serum/plasma specimens are available?

1. Specificity

We recommend that you test at least 50 paired specimens (1 pre- and 1 post-mortem specimen from the same donor).

a. Clinical Specificity

Clinical specificity is a measure of how often the test is negative in non-diseased donors.

We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on frequency of false positive results.

b. Analytical Specificity

Analytical specificity measures a test's ability to exclusively identify a target substance rather than different substances.

We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on signal strength.

2. Sensitivity

We recommend that you test at least 50 paired reactive specimens (1 pre- and 1 post-mortem specimen from the same donor).

a. Clinical Sensitivity

Clinical sensitivity is a measure of how often the test is positive in diseased donors.

We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on frequency of false negative results.

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b. Analytical Sensitivity

Analytical sensitivity measures a test's ability to detect a low concentration of a given substance.

We recommend that you determine if a statistically significant difference exists between pre- and post-mortem specimens based on signal strength and endpoint dilutions of positive specimens.

B. What data about specificity and sensitivity are recommended when matched pairs of pre- and post-mortem serum/plasma specimens are not available?

1. Specificity

We recommend that you concurrently test at least 50 cadaveric (post-mortem) specimens from 50 different cadaveric donors and an equal number of random living donor specimens (unmatched pre-mortem specimen) with the same test kit lots.

a. Clinical Specificity

We recommend that you determine if a statistically significant difference exists between the cadaveric specimens and the random living donor specimens based on the frequency of false positive results, i.e., the number of pre-mortem nonreactives/post mortem reactives.

b. Analytical Specificity

We recommend that you determine if a statistically significant difference exists between the cadaveric specimens and the random living donor specimens based on signal strength.

2. Analytical Sensitivity

We recommend that you concurrently test at least 50 nonreactive cadaveric specimens from 50 different cadaveric donors with an equal number of random living donor specimens with the same kit lots, with both types of specimens spiked with the infectious disease marker at a potency near the assay's cutoff. You should use a minimum of 5 individual positive sources for the spiking experiment.

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We recommend that you determine if a statistically significant difference exists between the spiked living donor specimens and the spiked cadaveric specimens based on signal strength.

C. What is an example of a recommended reproducibility study?

We recommend that you conduct a reproducibility study to determine if a statistically significant difference exists between the coefficients of variations of cadaveric specimens compared to those of living donors. One possible experimental design might include comparing at least 20 random cadaveric specimens with at least 20 random living donor specimens (confirmed true positives may be excluded) spiked to be reactive near the cutoff. Test each specimen individually, in 6 separate runs on 6 separate days using each of 3 different kit lots (18 data points per specimen). We also recommend that the specimens to be tested on 6 separate days be stored at 4° Centigrade to avoid repeated freezing and thawing.

D. How many test kit lots are recommended to be included in the studies?

We recommend that you include at least three test kit lots in all studies.

E. What plasma dilution issues are recommended for consideration?

Prior to including a cadaveric blood specimen in these studies, we recommend that you determine whether the specimen has been appropriately evaluated for plasma dilution. You can obtain information about plasma dilution from FDA's "Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation," dated July 1997 (the July 1997 guidance). This document can be found on the Internet at www.fda.gov/cber/tissue/docs.htm. As stated in the July 1997 guidance, plasma dilution is due to the transfusion or infusion of fluids into the donor prior to specimen collection, and can result in false negative test results. In an adult donor, if blood loss is known or suspected to have occurred and there was transfusion/infusion of more than 2000 mL of blood or colloids within 48 hours, or more than 2000 mL of crystalloids within 1 hour, or any combination thereof, prior to the collection of the blood specimen, plasma dilution may have occurred. In this case, we recommend that you use a specimen taken from the donor prior to transfusion or infusion, or an algorithm designed to evaluate volumes administered in the 48 hours prior to specimen collection, to ensure that plasma dilution sufficient to affect test results has not occurred. An example of an algorithm can be found in the July 1997 guidance.

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F. What information about specimen collection times does FDA recommend I note?

1. We recommend that you note the time between death and specimen collection. In order to accurately document test kit performance, we recommend that the time at which cadaveric specimens are taken incorporate the full range of time points typically encountered during tissue recovery, e.g., 0-24 hours.
2. We recommend that you include hemolyzed specimens in the study, since a large percentage of cadaveric specimens are hemolyzed due to biological processes that occur immediately post-mortem. You should quantify the degree of hemolysis, if possible, of the cadaveric specimens.
3. We recommend that you note information about storage and handling conditions of both living donor specimens and cadaveric specimens.

G. Where do I submit my data?

We intend to review any applications for cadaveric blood specimens jointly in the Offices of Cellular, Tissue and Gene Therapies and Blood Research and Review.

1. If you seek an indication for use of cadaveric blood specimens and blood donor specimens, you may submit an Investigational New Drug Application (IND), or a Biologics License Application (BLA), as appropriate, with data for both intended uses, to:

Center for Biologics Evaluation and Research
Attn: Office of Blood Research and Review
HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448
2. If an IND or BLA has already been submitted for blood donor screening, and you seek to modify the indication for use to include testing of cadaveric blood specimens, you may submit an amendment to the IND, or a supplement to the BLA with cadaveric blood specimen data, as appropriate, to the same address as above.
3. If you seek to modify the indication for use to include testing of cadaveric blood specimens only, you may submit an IND or BLA with cadaveric blood specimen data, to:

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Center for Biologics Evaluation and Research
Attn: Office of Cellular, Tissue and Gene Therapies
HFM-99, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

If you have questions about this guidance, please contact Melissa Greenwald in the Office of Cellular, Tissue and Gene Therapies at 301-827-2002.

IV. REFERENCES

1. Human Tissue Intended for Transplantation; Final Rule, July 29, 1997 (62 FR 40429), (<http://www.fda.gov/cber/genadmin/frtissue.txt> or <http://www.fda.gov/cber/tissue/docs.htm>).
2. Guidance for Industry: Screening and Testing of Donors of Human Tissue Intended for Transplantation; Notice of Availability, July 29, 1997 (62 FR 40536), (<http://www.fda.gov/cber/gdlns/tissue2.txt> or <http://www.fda.gov/cber/tissue/docs.htm>).
3. Guidance for Industry: Availability of Licensed Donor Screening Tests Labeled for Use with Cadaveric Blood Specimens, June 2000, (<http://www.fda.gov/cber/gdlns/cadbld.htm> or <http://www.fda.gov/cber/tissue/docs.htm>).
4. Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule, May 25, 2004 (69 FR 29786), (<http://www.fda.gov/cber/tissue/docs.htm>).