

MEBTC

MIDWEST EYE-BANKS AND TRANSPLANTATION CENTER

August 19, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: FR Doc. 04-11246

Dear Sir or Madam:

The Midwest Eye-Banks (MEB) appreciates the opportunity to comment on the Food and Drug Administration's draft guidance document: **Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)**. MEB is a 501(c)(3) not-for-profit organization whose mission is to recover and provide donated human eye tissue of the highest quality for sight restoring transplantation procedures. MEB is comprised of the Michigan Eye-Bank, the Illinois Eye-Bank and the Watson Gailey Eye-Bank. These three eye banks provide over 2,500 corneas annually for transplant.

Midwest Eye-Banks are founding members of the Eye Bank Association of America (EBAA), and participate at all levels of the Association. We actively support the EBAA's programs for the establishment of Medical Standards and the accreditation of eye banks.

We strongly support the position of the EBAA regarding this FDA guidance document. Our comments on the draft guidance document are attached.

Sincerely,



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President and Chief Executive Officer

2004D-0193

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Midwest Eye-Banks Comments

FDA Draft Guidance: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Midwest Eye-Banks (MEB) comments have been drafted in the following format: the FDA section will be identified, followed by MEB comments specific to that section.

FDA Section II.C. What is a “relevant communicable disease agent or disease?”

The rule states that a communicable disease agent or disease not named in the rule is relevant under this rule if the communicable disease agent or disease is one:

For which there may be a risk of transmission by an HCT/P, either to the recipient of the HCT/P or to those people who may handle or otherwise come in contact with the HCT/P, such as medical personnel, because the disease agent or disease:

- is potentially transmissible by an HCT/P; and
- either (1) has sufficient incidence and/or prevalence to affect the potential donor population, or (2) may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection (§1271.3(r)(2)(i);
- That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure (§1271.3(r)(2)(ii); and
- For which appropriate screening measures have been developed and/or an appropriate screening test for donor specimens has been licensed, approved, or cleared for such use by the FDA and is available (§1271.3(r)(2)(iii).

MEB Comments:

The Guidance Document lists West Nile Virus (WNV) as a disease that meets the standards for identification of a relevant communicable disease not specifically identified in the regulation. The FDA’s current recommendation is for donor screening. Routine use of a licensed serologic test would be recommended once such a test becomes available. The statistics cited for blood establishments (601 blood donations out of approximately 2.5 million tested reactive for WNV by investigational NAT testing, or 0.002%); the number of deaths from WNV reported to the CDC in 2003¹ (264 out of U.S. population of 293,580,925, or 0.00009%); and the limited timeframe for occurrences (99% of the human cases occurred between July 1 and October 31, 2002) does not appear to warrant serologic testing of all donors of surgical eye tissue at all times for all geographic locations. In addition, EBAA Medical Standards contraindicate

the use of tissue from donors with active viral encephalitis, encephalitis of unknown origin, progressive encephalopathy and death with neurologic disease of unestablished diagnosis. The MEB requests that the FDA treat WNV in a manner similar to its treatment of SARS: “FDA believes it is prudent to recommend donor screening for this illness **when CDC lists SARS-affected areas on their website**”.

FDA provides no definitions regarding the meaning of key terms in the determination of relevance for communicable disease agents or diseases. In the absence of meaningful standards for “potentially transmissible”, “sufficient incidence and/or prevalence”, “appropriate screening measures” or “appropriate screening test”, regulated entities can never have a basis for challenge to the FDA’s assertions, such as: “FDA believes that there is a risk of transmission of WNV through HCT/Ps because it is potentially transmissible by HCT/Ps and that WNV has sufficient incidence or prevalence to affect the potential donor population”. FDA should identify criteria based on epidemiological evidence rather than on its own beliefs.

FDA provides no evidence that appropriate measures exist to screen cadaveric donors for WNV. FDA even admits that “signs and symptoms of WNV can be nonspecific” (section III. F. 5), and that “donor exclusions based on donor health screening will have limited effectiveness” (section II. C. 2). It would be inappropriate to exclude donors based on nonspecific information, the benefit of which in protecting the public health has not been established.

FDA’s indication that it “would recommend routine use of appropriate licensed donor screening tests to detect acute infections with WNV once such tests are available” is premature and unsupported. Absent from FDA’s analysis are consideration of the direct cost of testing, the benefit to the public in terms of disease prevented, the feasibility of performing additional testing on limited quantities of available specimens, or the impact of unavailable or false-positive results on the availability of safe tissue for transplantation.

In the absence of appropriate screening or testing measures, WNV is not a relevant communicable disease agent.

Transmission of WNV through corneal transplantation has not been documented in the current environment of screening and testing. When FDA ventures into situations of hypothetical disease transmission, it must apply scientific methods and cite specific evidence demonstrating particular levels of theoretical risk. The guidance document’s reliance on speculative belief of possibilities conveys the image of concern for the public’s health but does not demonstrably add to the safety of human tissue for transplantation.

Eye banks are small entities engaged in the charitable purpose of facilitating the use of gifts made by donors and their families. In performing this mission, the necessity to maintain the public’s trust far exceeds the requirements imposed by the rules and recommendations of the FDA. Because FDA sanctions can destroy public trust

independent of their value in protecting public health, eye banks have little ability to challenge rulings which are based on FDA's beliefs. In establishing guidance that has the effect of coercing compliance, FDA has the responsibility to develop and cite sources of information demonstrating public benefit, and a responsibility to look at the costs to achieve that benefit. In this guidance document, the FDA has not provided clear indication of benefits or costs of screening for TSE, syphilis, WNV, SARS, vaccinia or sepsis.

FDA section II.E. What procedures must I establish and maintain?

The rule states that procedures must be available to personnel either in the area where the procedures are performed, or if this is not practical, in a nearby area.

MEB Comments:

Physical assessment of the cadaveric donor is required under the definition of relevant medical records, §1271.3(s). This procedure is performed during tissue recovery at locations outside of the eye bank laboratory, and the procedure for performing this body inspection would not be available in the area or in a nearby area. Because it is not feasible to have controlled copies of procedures available in the area where recoveries occur, we ask the FDA to limit this requirement to apply only to those activities that occur on our own premises.

FDA section III. C. What sources of information do I review?

The document states that one must review "relevant medical records for risk factors, clinical evidence and physical evidence of the relevant communicable diseases listed in section III. A. (§1271.75(a)". In this section, FDA believes that "available means that the record or information exists and is obtainable within a reasonable amount of time. A reasonable amount of time is a period of time that would allow the effort to collect important information without compromising the usefulness of the tissue."

MEB Comments:

The definition of "reasonable" is problematic, because it does not reflect the scope of the search, or amount of effort required. It means that information is available to us if it "is obtainable within a reasonable amount of time". That is a theoretical concept. Assume that crucial information is not in the donor medical record but is known to someone we are not aware of. Under this definition, FDA could maintain that the information was available, because we could have obtained it had we performed a large number of medical/social interviews. MEB suggests the following definition for available: "is recorded and can be obtained through reasonable diligence within a reasonable amount of time".

FDA section III.E. What risk factors do I look for when screening a donor?

The document states that you must review relevant medical records and ask questions about the donor's medical history and relevant social behavior.

Statements E.5 and E.9 refer to contact with persons with viral hepatitis. Statement E.5 is: “persons who have had sex in the preceding 12 months with any person described in the previous 4 items of this section or with any person known or suspected to have HIV infection, clinically active hepatitis B infection, or hepatitis C infection”. Statement E.9 is: “persons who have had close contact within 12 months preceding donation with another person having clinically active viral hepatitis (e.g., living in the same household, where sharing of kitchen and bathroom facilities occurs regularly)”.

MEB Comments:

Does the statement “clinically active” apply to hepatitis C infection, as well? Per the FDA draft guidance, *Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Human Donors of Blood and Blood Components*², sexual contact or household contact with a person with asymptomatic hepatitis C does not constitute a donor deferral for blood donors. MEB requests that the same guidance apply to donors of HCT/Ps and that statement E.9 be amended to: “persons who have had sex in the preceding 12 months with any person described in the previous 4 items of this section or with any person known or suspected to have HIV infection, clinically active hepatitis B infection, or symptomatic hepatitis C infection.”

FDA Statement E. 11 states: “persons who have had a past diagnosis of clinical, symptomatic viral hepatitis after age 11, unless evidence from the time of illness documents that the hepatitis was identified as hepatitis A (e.g., a reactive IgM anti-HAV test).

MEB Comments:

MEB has several concerns regarding this question. MEB believes it will be extremely difficult to obtain accurate information due to the fact that medical and social history is obtained from someone other than the donor. In other words, the appropriateness of screening based on a third-party interview has not been established. The third-party may be able to answer relevant medical/social history questions but may have limited knowledge of the details. Evidence from the time of illness will be equally as difficult to obtain, because medical records may not be available. Furthermore, the CDC reports that serologic testing for diagnosis of hepatitis A, IgM anti-HAV, began in 1981, so this evidence would not exist for donors over age 34³. According to EBAA’s 2003 Eye Banking Statistical Report, approximately 84% of eye donors in the U.S. were over age 40⁴. A review of EBAA eye banking activity reports for the past 10 years showed approximately 80% of donors each year were over age 40.

FDA Statement E.16: “persons who have had both a fever and a headache (simultaneously) during the 7 days before donation, FDA recommends that the donor be deferred from donation; or donor be deferred for 28 days after the interview of living donors who may donate at a later date.”

MEB Comments:

There could be many causes of fever and headache in a potential donor, other than West Nile Virus, which would not constitute contraindications to donation. Fever and

headache may be symptoms seen in patients with cancer, autoimmune diseases, heatstroke, menstruation, on certain medications, etc. Since eye donors cannot be deferred, under the proposed statement, these donors would be determined to be ineligible for eye donation. In this regard, fever and headache do not constitute an appropriate screening measure for WNV.

FDA Section IV. E When do I collect a specimen for testing?

You must collect the donor specimen for testing at the same time as cells or tissue are recovered from the donor, or, if this is not feasible, within seven days before or after the recovery of cells and tissue (§1271.80(b)).

MEB Comments:

Although the FDA does allow the use of a premortem specimen for donors in whom plasma dilution sufficient to affect the results of communicable disease testing is suspected (§1271.80(d)(2)(i)(A)), the guidance, as written, suggests that a postmortem sample is preferable. This contradicts the current FDA Final Rule, Human Tissue Intended for Transplantation and the flowchart for determining specimen adequacy in Appendix 1. It may be feasible, but not appropriate, to test a specimen collected at the time of recovery, especially if there are questions about plasma dilution.

The inclusion of complicated requirements for evaluation of potential plasma dilution indicates the FDA's own understanding that specimens collected before administration of large fluid volumes can provide a higher level of assurance than cadaveric specimens. Determination of which available specimen is most appropriate for communicable disease testing should be left to the discretion of the professional staff of the (often multiple) entities involved in recovering tissues from a particular donor. FDA should remove the language, "You must collect the donor specimen at the time of recovery..." from §1271.80(b), or make clear through guidance that use of premortem specimens is acceptable.

FDA Section V.A. For what diseases must I test all donors of HCT/Ps, and what tests should I use?

You must test all donors of HCT/Ps, unless subject to an exemption in §1271.90(a), for the diseases listed as 1-5 of this section, as required in §1271.85(a). You must use an FDA licensed, approved, or cleared test, and if a test specifically labeled for use with cadaveric specimens is available, you must use that test, if applicable to your HCT/P. (§ 1271.80(c)). At this time we recommend that you use the tests listed in parentheses because we believe these tests adequately and appropriately reduce the risk of transmission of relevant communicable disease. Our recommendations on specific tests may change in the future due to technological advances or evolving scientific knowledge:

1. HIV, type 1 (FDA-licensed screening test either for anti-HIV-1 or combination test for anti-HIV-1 and anti-HIV-2);

2. HIV, type 2 (FDA-licensed screening test either for anti-HIV-2 or combination test for anti-HIV-1 and anti-HIV-2);
3. HBV (FDA-licensed screening test for Hepatitis B surface antigen (HBsAg) and for total antibody to Hepatitis B core antigen (anti-HBc)—(IgG+IgM));
4. HCV (FDA-licensed screening test for anti-HCV);
5. *Treponemal pallidum* (FDA-cleared serological test for syphilis).

Exception for syphilis test results: a donor whose specimen tests reactive on a non-Treponemal screening test for syphilis and negative on a specific Treponemal confirmatory test may nevertheless be considered eligible, as long as all other required testing and screening are negative. A donor whose specimen tests reactive on a Treponemal confirmatory test is not eligible.

Nucleic Acid Testing (NAT): FDA may recommend these tests for use in cadaveric tissue donors.

MEB Comments:

The FDA is recommending serologic testing for anti-HBc IgG and IgM in addition to HBsAg. EBAA Medical Standard, G1.240 Hepatitis B Screening, requires that all member eye banks use an FDA-approved test for HBsAg for all donors of surgically designated tissue⁶. As a result, there have been no cases of transmission of hepatitis B virus via corneal transplantation since serologic testing for HBV became mandated by EBAA in 1986. Since current practices successfully screen out donors with Hepatitis B, there is insufficient evidence to justify the addition of a secondary serologic test⁵. The current anti-HBc test may have as high as a 30% false positive rate. In addition, the test is not approved for use on cadaveric specimens. As a result, the false positive rate may increase resulting in the needless disposal of human tissues.

Zou et al.⁷ reported a prevalence rate for confirmed positive serologic tests in tissue donors as 0.093% for anti-HIV, 0.229% for HBsAg, 1.091% for anti-HCV and 0.068% for HTLV. The estimated incidence rates were 30.118 for anti-HIV, 18.325 for HBsAg, 12.380 for anti-HCV and 5.586 for HTLV per 100,000 person-years. This study estimated the probability of viremia at the time of donation as 1 in 55,000 for HIV, 1 in 34,000 for HBV, 1 in 42,000 for HCV and 1 in 128,000 for HTLV.

Although an HIV-1/HCV NAT test was approved by the FDA for cadaveric specimens in June 2004, the FDA is not requiring its use for testing donors of HCT/P at this time. The rule requires “an FDA licensed, approved, or cleared test, and if a test specifically labeled for use with cadaveric specimens is available, you must use that test, if applicable to your HCT/P”. FDA intends to issue guidance documents to notify tissue establishments if use of a new test is required. If the FDA issues such a requirement, will you allow a grace period for tissue establishments to comply, or will testing be required immediately?

FDA appears to confuse the term “living donor” with “premortem specimen”. Specimens collected before death may be available for cadaveric donors, and may be preferable to

cadaveric specimens under a number of circumstances. FDA should demonstrate that it understands this distinction, and should clarify its guidance. Is NAT testing recommended for use with premortem specimens from cadaveric donors?

FDA Section VII.A When is a donor eligibility determination not required?

The Guidance lists three situations in which organizations are not required to make a determination of donor eligibility or to perform donor screening and testing. Donor eligibility determination is not required for:

1. cells and tissues for autologous use;
2. reproductive cells or tissue donated by a sexually intimate partner of the recipient for reproductive use; or
3. cryopreserved cells or tissue for reproductive use, originally excepted under (1) and (2) at the time of donation.

MEB Comments:

EBA Medical Standards G1.230, HIV Screening; G1.240, Hepatitis B Screening; and G1.250, Hepatitis C Screening require testing of all donors of surgically designated tissue⁶. Medical Standard H1.000, Non-Surgical Donor Tissue, requires that tissue used for purposes other than surgery, (e.g., research, practice surgery, etc.), and not screened for HIV or hepatitis be labeled with “potentially hazardous biologic material” or some other designation acceptable under CDC guidelines. As a result, **tissue for research and training may not be screened thoroughly or tested**. MEB recommends clarifying this section so that it is understood that it pertains to clinical use of HCT/Ps.

FDA Section VII.D Are there any other uses for HCT/Ps from donors determined to be ineligible?

The rule allows nonclinical use of HCT/Ps as long as they bear the biohazard legend and are labeled “For Nonclinical Use Only”.

MEB Comments:

Does FDA require that their language be used (For Nonclinical Use Only) or is other language acceptable?

What is not included in the Guidance Document, but what should be included:

In §1271.55(a), FDA states “Once a donor-eligibility determination has been made, the following must accompany the HCT/P at all times:....”

MEB Comments:

FDA does not define “accompany”. Presumably, it means that paperwork with the required information must go with the tissue when it is shipped, but that we are not required to store these papers in physical proximity to tissues in our possession, such as in the refrigerator. Also, once a tissue is delivered to a hospital or surgery center, it

is not within our scope to guarantee that the information continues to accompany the tissue. Finally, FDA should clarify that this requirement pertains only to tissues intended for clinical use.

References

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2. Food and Drug Administration. Guidance for Industry: Acceptable Full Length Donor History Questionnaire and Accompanying Materials for Use in Screening Human Donors of Blood and Blood Components dated April 2004.
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4. Eye Bank Association of America. *2003 Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America, March 2004.
5. Mattern RM, Cavanaugh, HD. Should Antibody to Hepatitis B Core Antigen Be Tested in Routine Screening of Donor Corneas for Transplant? *Cornea* 1997;16: 138-145.
6. Eye Bank Association of America. *Medical Standards*. Washington, DC: Eye Bank Association of America, November 2004.
7. Zou S, Dodd RY, Stramer SL, Strong DM. Probability of Viremia with HBV, HCV, HIV and HTLV among Tissue Donors in the United States. *New England Journal of Medicine* 2004; 351:751-759.

cm:Eligibility guidance document final comments