



EYE BANK ASSOCIATION of AMERICA

Dedicated to the Restoration of Sight since 1961

7507 '00 JUL 18 10:11

EXECUTIVE COMMITTEE

CHAIRPERSON
Wing Chu, M.D.
New York, NY

CHAIR ELECT
Barbara L. Crow, CEBT
Portland, OR

SECRETARY
Ginger Miller, RN, CEBT
Baton Rouge, LA

TREASURER
Michael Hettinger, M.D.
Overland Park, KS

IMMEDIATE PAST CHAIR
Mary Beth Dannelfel, RN, CEBT
Houston, TX

AT-LARGE MEMBERS
Gerald J. Cole
Baltimore, MD

Joel Sugar, M.D.
Chicago, IL

EX-OFFICIO MEMBER
Edward Holland, M.D.
Minneapolis, MN

BOARD OF DIRECTORS
Ronald Blanchett, BS, CEBT
Indianapolis, IN

Scott Davis, CEBT
Phoenix, AZ

Florence Johnston, RN, MS
Ann Arbor, MI

Mark Mannis, MD
Sacramento, CA

Tessie Smith, MS
Irvine, CA

Lee Williams, MS, CEBT
Memphis, TN

REGIONAL PRESIDENTS
NORTH EAST REGION
Patricia Dahl, CEBT

NORTH CENTRAL REGION
G. Scott Bryan, CEBT

SOUTH CENTRAL REGION
Edmund Jacobs, CEBT

SOUTH EAST REGION
Gail Walsh-Hudson, CEBT

WESTERN REGION
Monty Montoya, CEBT

ASSISTANT TREASURER
Woodford Van Meter, MD
Lexington, KY

PRESIDENT/CEO
Patricia Alken-O'Neill, Esq.

December 22, 1999

Jane Henney, M.D.
Commissioner
The Food and Drug Administration
5630 Fishers Lane
Rockville, MD 20852

Ref: Docket No. 97N-484S; Suitability Determination for Donors of Cellular and Tissue-Based Products; 64 Federal Register 189; September 30, 1999.

Dear Commissioner Henney:

On behalf of our more than 100 U.S. member eye bank organizations, the Eye Bank Association of America (EBAA) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) proposed rule: **Suitability Determination for Donors of Human Cellular and Tissue-Based Products**. Our membership represents a participation rate of 99% of the entire U.S. eye banking community and provides 97% of all corneal tissue for transplantation. All eye banks are 501(c) (3) organizations whose mission is to procure and provide donated human eye tissue for sight restoring transplantation procedures. The Association strives to ensure the superior quality of banked human eyes through the adoption and implementation of stringent medical standards.

Introduction:

The eye banking community is proud of its history. The first corneal transplant was performed in 1905 and the first eye bank opened in New York in 1944; this bank marked the first organized attempt to facilitate the transfer of tissue from donor to patient. The eye banking model was successfully replicated in other communities across the United States. Following the development of the eye banking system, the EBAA was founded in 1961 by the American Academy of Ophthalmology. The Association was the first transplant association and the first to establish medical standards. The Association also established and administers a comprehensive education and certification program for technicians and other eye bank professionals, continuing education programs for ophthalmologists and researchers, and an institutionalized program of accreditation for eye banks. EBAA's Medical Standards and certification program are used as models for other programs.

97N-484S

C 489

Page two, EBAA Comments

[The FDA has been provided copies of EBAA's Medical Standards and supporting documents.]

The EBAA's Medical Standards are specific to banked human eye tissue, scientifically-based and developed to ensure safe transplantation. EBAA's Medical Standards are twice-yearly peer-reviewed and revised when necessary to ensure the practice of state-of-the-art safety procedures. Such standards and procedures are also reviewed annually by the American Academy of Ophthalmology. It should be noted that the EBAA was the first transplant organization to institute mandatory testing of transplant donors for the presence of HIV. The Association was among the first transplant organizations to institute mandatory testing and screening procedures for hepatitis B and C as testing became available.

FDA's Proposal:

FDA proposes to broadly regulate human tissue and requires most establishments to test for syphilis and screen for transmissible spongiform encephalopathies (TSE), including Creutzfeldt-Jakob disease (CJD); exceptions are made in certain limited situations. The proposal ignores the agency's statement on page 52713 of the Federal Register, which states that the risks of disease transmission vary by cellular and tissue-based product.

EBAA's Position:

The American corneal tissue supply is safe. No public health threat exists; there has been zero transmission of systemic-infectious disease in over 560,000 corneal transplants, for the last 13 consecutive years. The present regulatory system, consisting of current FDA regulation under Part 1270, the eye bank communities adherence to stringent community-specific and self-imposed standards, and protections afforded by the legal system in this country, is effective as noted by the community's safety history. :

The proposed regulation places corneal transplant tissue under a generic and all inclusive regulatory framework not warranted by experience or scientific evidence. This proposed rulemaking, inclusive of all tissue, mimics the practice of defensive medicine -- "defensive rulemaking" -- where tests are ordered beyond the scope of practice parameters, are costly, and add no determined medical benefit. Generic and broad-based safety standards will undermine specific requirements that are peer-reviewed for the eye banking community. The adoption of FDA's broad regulatory approach may actually foster problems in a community that has experienced no transmission of systemic-infectious disease for over 13 years. These issues are specifically addressed later in this response.

The economic impact of the proposed rule is significantly understated. The requirements under the proposed rule would produce a cost with no related increase in safety. The burden of potentially paying a user fee in the future for this type of unnecessary oversight will further add to acquisition costs. Cost increases are not easily absorbed by the not-for-profit eye bank community. At some point, access will be impaired for no justifiable reason.

Page three, EBAA Comments

Corneal tissue destined for human transplant is not a manufactured device or drug, but is a living tissue with a very limited period of viability. The cornea must be recovered, evaluated, medically screened including serological testing for viral markers and provided for transplantation as soon as possible. Ideally, this occurs in one to two days after tissue recovery. Beyond five days, a cornea is unlikely to be acceptable to a U.S. surgeon. Unlike other human tissue, time is of the essence in screening and releasing corneal tissue in the effort to achieve the optimal surgical outcome for the patient/recipient. The FDA's proposed requirements under this rule will increase testing time with no proven benefit, thus pushing the acceptable time limit for transplantation, posing quality problems.

The American Corneal Tissue Supply is Safe:

Since the adoption of EBAA's Medical Standards in 1980, there have been only two reported cases of systemic disease transmission by corneal transplantation in over 850,000 corneal transplants in the United States. Both, cases of hepatitis B, occurred in the early 1980s prior to the development of hepatitis testing. As noted above, the EBAA was among the first transplant organizations to institute mandatory screening and testing procedures for hepatitis B. **With the advent of hepatitis B testing, there have been no cases of any systemic infectious disease transmission in over 560,000 U.S. corneal transplants. This record is testimony that the present self-regulatory approach is working. A 100% safety record cannot be improved.**

On the rare occasion when transmission of systemic infectious disease has occurred, the community has immediately responded, risen to the challenge, reviewed the case vis-à-vis relevant standards and available scientific knowledge, and adopted changes to prevent future occurrence. In sum, in emerging situations there is a mechanism to institute new eye bank community standards to safeguard the donor cornea pool.

EBAA medical standards require routine screening of donors for the following: active viral hepatitis, human immunodeficiency virus (HIV), or HIV seropositive donor, active viral encephalitis or encephalitis of unknown origin, Cruetzfeldt-Jacob Disease (CJD), and rabies. EBAA requires screening of donors for symptoms of transmissible spongiform encephalopathies (TSE) or CJD despite the fact that no known corneal recipients have contracted TSE or CJD in the last twenty-five years in the U.S. This fall, the EBAA convened a group of medical experts to further evaluate standards and procedures for safety relative to TSE and CJD concerns presented outside the United States. We believe this data is critical to determining appropriate eye banking practice. This model, a peer-reviewed scientific approach to public health concerns, is necessary to protect public health and ensure the integrity of the eye banking system.

In the Case of Corneal Tissue, No Public Health Threat Exists:

The FDA fails to demonstrate any compelling public health threat or need to justify the imposition of a broad regulatory approach for all tissue to include human corneal/eye tissue. **Zero transmission of systemic infectious disease in over 560,000 consecutive corneal transplants does not constitute a public health threat.**

Page four, EBAA Comment

The Present Regulatory System Provides Sufficient and Effective Oversight:

- 1) All U.S. eye banks are subject to present FDA regulation pursuant to part 1270 relative to HIV and hepatitis screening and testing procedures. It is misleading to allow the public to believe there are not universal standards in place, when clearly there are for HIV and hepatitis.
- 2) The FDA currently inspects eye banks for compliance with part 1270.
- 3) Should public health problems be generated from a certain eye bank, the FDA has other enforcement powers to call upon.
- 4) In the private sector, the EBAA provides a self regulated accreditation program for member banks. There is one eye bank operating outside the EBAA system in the State of Florida. This Florida eye bank is inspected and monitored for quality compliance under Florida State law, which has incorporated the EBAA's standards by reference.
- 5) The U.S. has a well defined tort system in place through its courts. Scientifically-based standards adopted by accrediting bodies would be used to define the standard of medical practice. If a bank were to significantly deviate from a community adopted standard, this standard would be referenced in a malpractice proceeding.

The EBAA believes there is sufficient oversight of the present eye banking system. Adding new broad-based regulatory requirements will not improve a 100% safety record. In fact, generic and broad-based safety requirements, inclusive of almost all types of human tissue used in transplantation, will replace the value of tissue specific safety requirements already developed and peer reviewed by specific tissue communities. This creates a situation where safety is diminished in certain communities leaving the transplant population more vulnerable to disease transmission or other quality problems.

FDA's Economic Impact Estimates Are Significantly Understated:

Human corneal tissue is a donated human gift. Under Public Health statute (P.L. 98-504; 42 USC 273 et seq., the National Organ Transplant Act of 1984) corneal tissue cannot be purchased or sold. Only the costs of acquiring tissue are reimbursable. As noted earlier, all eye banks are 501 (c)(3) organizations.

A great deal of tissue is necessarily lost throughout the medical screening process due to test results indicating contraindication to transplant or risk factors identified during construction of a donor profile. Eye banks only invoice an acquisition fee for a cornea that is transplanted. In some instances, tissue is provided by an eye bank as a charitable service for indigent care, or for furthering the advancement of the science of sight. The donating eye bank incurs all the costs associated with the procurement and distribution of the eye tissue. While there is generally no acquisition reimbursement for this tissue, in some cases the eye bank receives nominal payment for a portion of the direct costs associated with the procurement, testing, and/or transporting the tissue. In all cases, there is a financial loss to the eye bank.

Page five, EBAA Comments

Today, we are fortunate to meet the demand for corneal tissue. Tissue shortages could result in the near future given the number of new procedures which alter the cornea to improve sight (e.g. LASIK, PRK). Such individuals cannot be donors. We must be careful not to discard viable tissue for non-scientific based concerns. Cost and access problems will result.

The EBAA has reviewed the FDA's estimated economic impact of the proposed regulations and believes them to be significantly understated. The agency states the areas likely to be affected are donor screening, donor testing, record keeping, quarantine, donor suitability determinations, donor documentation, allograft documentation, and labeling.

The FDA only estimated the time needed for one person to "compare the proposed regulations against the facility's current standards". As communicated elsewhere in our response, the EBAA takes issue with the overall necessity of the proposed regulations as well as certain specific provisions. However, if implemented in their current form, the proposed regulations would necessitate changes for every one of the operational functions identified by the FDA (listed above) and others not identified for every eye bank in the United States. The time and resources necessary to comply would not be limited to "comparing" or identifying items for compliance.

For example, any identified area for change after comparing the FDA regulations to an eye bank facility's operating standards is just the first step. Typically, management and an eye bank's Medical Director must provide oversight, direction and approval of any change. Corrective action must be promulgated. Changes in the eye bank facility's standard operating procedures must be made and implemented. Most likely forms and/or logs must be changed. The most significant amount of time and resources is related to the retraining of all affected staff and subsequent quality assurance to insure compliance.

The EBAA has not performed a cost impact study but plans to do so. The economic impact is certainly more than the FDA's estimate of \$45 to \$229. Unfortunately, the comment period did not provide sufficient time for a thorough cost assessment of the provisions discussed therein. One authority on eye bank costs estimated the annual impact at \$10,000 to \$20,000 per average eye bank.

The EBAA is particularly sensitive to cost issues since the United States Health Care Financing Administration recently sought to significantly reduce Medicare reimbursement for the cost of eye banks providing a corneal tissue for transplantation. Eye Banking, as a non-profit community, inherently provides a subsidized service. An inaccurately low estimate of the impact of any additional regulation will severely harm our community's endeavors to provide our sight restoring service to the corneal blind.

The EBAA urges the FDA to correct the economic impact of the regulation. We will be happy to assist with this effort.

EBAA Proposal to the FDA:

The EBAA respectfully requests relief from the imposition of additional broad regulatory requirements established under this proposed rule for human eye tissue until a public health threat is founded. Specifically, the EBAA asks that banked human eye tissue be characterized as "Allogeneic banked human eye tissue" and that banked human eye tissue be subject to no "new" systemic-infectious disease requirements until a public health threat and need is demonstrated. Instead of being subject to unnecessary, broad-based regulatory requirements that diminish peer-reviewed tissue specific standards, the EBAA would support a mandatory reporting requirement for the transmission of systemic infectious disease through corneal transplantation.

Page six, EBAA Comments

The EBAA supported the registration provisions proposed in the Federal Register, May 14, 1998, the "Establishment, Registering, and Listing for Manufacturers of Human Cellular and Tissue-Based Products." As noted above, we would also support mandatory reporting of systemic infectious disease transmission. This requirement, coupled with mandatory registration, would provide a data collection vehicle to assess the need for additional government oversight. At this juncture, the Association believes this would be a prudent approach.

Specific Issues Contained in the Proposed Rule:

The attached pages (Attachment I, pages 1-9) address certain subject matter contained in the proposed rule. As you will note, the EBAA believes the most important issues raised in the proposed rule are not appropriate to the eye banking model. The provisions required in the proposed rule will add significant costs without the benefit of additional safety, and diminish quality standards developed by the community for tissue used in corneal transplantation procedures. In sum, the FDA could foster quality problems in a community where none have existed for over 13 years.

We appreciate the opportunity to comment on this proposed rule and hope that you find our arguments compelling. Please know that the EBAA is available to respond to any additional questions.

Sincerely,

Patricia Aiken O'Neill, Esq.
President/CEO

Enclosures

Attachment I:
Specific Issues in the Rule
Pages
(1-9)

EBAA Attachment I

- **“Manufacturer”, “Product”, and “Marketing”**

*These terms are found throughout the proposed rule and preamble
To describe eye banks corneal tissue, and donor matching.*

Under the definition, the organizations that recover, screen, test, process, store, label, package, or distribute human cellular, or tissue based products are referred to as “manufacturers”. Webster defines this term as “one that manufactures” or “makes into a product suitable for use; to make from raw materials by hand or machinery.” This term demeans the human aspect of what eye banks do which is to utilize, not manufacture, graciously and compassionately donated human tissue for the benefit of mankind. It would be more respectful of the thousands of donors and donor families to use a less offensive term.

“Marketing,” suggests a business model of competition and profitability. Corneas are neither sold nor bought under present law. There are no plans to alter corneas for other health care uses. This term is inappropriate for the community, and could potentially destroy a charitable education and donation network if the general public is led to believe banked human eyes are “marketed”.

In fact, using such terms puts regulation in conflict with several state statutes which declare “the procurement, processing, testing, storing, or providing of human tissue for human transplant” to be “a service” and that such “service does not constitute the sale of goods or products to which implied warranties of merchantability and fitness for a particular purpose are not applicable.” Designating eye banks as “manufacturers” (and tissue as a “product”) is false and misleading and raises potential legal issues, as well. It would establish expectations and standards different from the services an eye bank delivers; human eye tissue cannot be manufactured. It could subject eye banks to inappropriate product liability litigation.

EBAA Comment:

The EBAA recommends that the agency carefully evaluate such business terms for its impact on the donation system. The Association believes these terms are inappropriate to describe human anatomical donation and the provision of tissue for transplantation.

- **“Relevant Disease Risk”**

Section 1271.3-(y) (2)

Section 1271.3 (y) (2) defines “relevant” communicable disease agent or disease that warrants screening and testing of all donors. This definition and requirement thereto is overly broad. Such definition would subject all tissue entities to unfair malpractice claims, leaving the system vulnerable and subject to unnecessary costs.

EBAA Attachment I

If FDA's "relevant disease risk" for eye banks is represented by the Agency's tolerance for CJD and *Treponema pallidum*, one case and zero cases respectfully, it appears that the mere hypothetical threat of a disease or agent will make it eligible for required screening and testing.

The FDA does not identify a specific mechanism for community input, no advisory committee review, etc. This requirement would leave the tissue community vulnerable to the imposition of requirements not scientifically reviewed.

EBAA Comment:

The EBAA recommends deletion of this broad requirement. Appropriate rulemaking procedures and a demonstrated public health need must apply.

Syphilis

Section 1271.85-(a) (5)

Section 1271.85 (a) (5) requires screening for *Treponema pallidum* (syphilis). This disease has been repeatedly and intensively addressed by the eye banking community and, after a great deal of consideration, has been found to be not relevant to eye banking. As stated in the Federal Register page 52701, a communicable disease agent must be relevant. "First, for a communicable disease agent or disease to be "relevant," its prevalence among donors would have to be sufficient to warrant screening or testing of all donors. Second, "there will need to be a risk of transmission of disease agent or disease by human cellular or tissue based product...."

There has been no confirmed evidence, nor reported suspicion of transmission of *Treponema pallidum* (syphilis) by corneal transplantation. Respected studies have demonstrated no evidence of viability of *Treponema pallidum* under corneal storage conditions used by eye banks in the United States (Macasai, Norris, *Cornea*, 1995; 14:595-600). It has also been demonstrated (Goldberg, Laycock, Kinard, Wang, Pepose, *AMJ Ophthalmol*, 1995:119:1-6) that serologic testing for syphilis does not serve as a surrogate marker for HIV testing. In addition, the low incidence of new reported cases (less than 7,000 cases in the United States in 1998) makes this a poor screen to recommend.

Positive serologic tests for syphilis in pre-screened eye bank donors are almost always false positive tests and even if they were true positive tests, there has been no reported case of transmission of syphilis through transplantation of corneal tissue. Thus, requiring *Treponema pallidum* testing would reduce the number of available corneal donors, increase costs, and provide no additional protection for recipients.

EBAA Attachment I

EBAA Comment:

The EBAA recommends deletion of this requirement for screening and testing for treponema pallidum for those involved in eye banking.

Leukocyte – Rich Cells or Tissue

Section 1271.85 (b)

Section 1271.85 (b), requires additional testing for donors of viable, leukocyte-rich cells or tissue. Page 52705 of the Federal Register lists “stem cells” as “examples of leukocyte-rich cells or tissue.” This term should be better defined as “hemotologic” stem cells since, in eye banking, corneal epithelial stem cells are being more frequently used in transplantation and these cells are not leukocyte-rich and should not be included under the rubric “stem cells.” This problem could be eliminated if stem cells were better defined in the proposed rule.

EBAA Comment:

The EBAA believes this example is one among many that identify problems of appropriate applicability in the rule.

Transmissible Spongiform Encephalopathies (TSE) And Cruetzfeldt-Jakob Disease (CJD)

On page 52706 of the Federal Register, “the agency requests comment on the feasibility of testing for TSE/CJD in donors of corneal tissue.” In over 55 years of U.S. eye banking, only one reported case of CJD transmission has been documented. That particular tissue was recovered from a patient who died in a neurological institute. The donor tissue was never evaluated nor screened by the local eye bank. Zero cases have been reported since the EBAA implemented its medical standards in 1980. One case in over 55 years indicates a negligible prevalence in the donor pool. According to the FDA, “its prevalence among donors would have to be sufficient to warrant screening and testing of all donors.”

Due to reports of recent transmission outside the United States, the EBAA, concerned that “no future transmission occurs”, convened a group of internationally renown scientific experts in CJD, eye banking and epidemiology* to provide appropriate guidelines and parameters for TSE and CJD. The EBAA expects a report and scientific data on this subject soon and will forward it to the agency. It should be noted that the countries where recent transmission occurred do not adhere to standards as stringent as those adopted by EBAA member banks. Further, under current EBAA standards, the tissue would not meet EBAA donor criteria and would not have been transplanted.

EBAA Attachment I

At the present time, a brain biopsy is not a realistic way of screening donors for TSE, because of the time requirement involved. A brain biopsy would require consent for a brain autopsy to be performed. Brain autopsy results in donor disfigurement and delays in funeral arrangements, which would impact families and, we believe, would drastically reduce the number of people willing to donate. It would also add significant costs to eye banks. The length of time necessary to complete the microscopic study of brain tissue would result in expiration of the corneal tissue, i.e., aging of the cornea beyond the 7-10 days when a tissue could be placed for transplantation. In the absence of a serologic rapid test, the eye banking community is looking at possible historical screens for TSE as noted above.

EBAA Comment:

The EBAA recommends that the agency take no action in this area at this time. The EBAA will shortly receive recommendations from an Ad Hoc group of experts convened to examine CJD/TSE concerns. The group's findings will also be shared with the agency.

*Ad Hoc Committee for CJD:

(Advisory to EBAA Medical Advisory Board)

Robert Kennedy, MD, PhD, MBA, MPH
Associate Professor of Ophthalmology and Director of Oculo – Plastics
University of Texas, Southwestern Medical Center, Dallas, Texas

Robert Johnson, MD,
Professor of Neurology
Johns Hopkins University, School of Medicine, Baltimore, MD

Nicholas Hogan, MD, PhD
Assistant Professor of Ophthalmology and Neurology
University of Texas, Southwestern Medical Center, Dallas, Texas

Joel Sugar, MD
Professor of Ophthalmology
University of Illinois, Chicago, Illinois

Walter Stark, MD
Professor of Ophthalmology
Johns Hopkins University, School of Medicine, Baltimore, MD

Edward Holland, MD
Professor of Ophthalmology
University of Minnesota, Medical Center, Minneapolis, Minnesota

EBAA Attachment I

Paul Brown, MD

Senior Scientist

National Institute of Neurology and Stroke, National Institutes of Health, Bethesda, Maryland

Legislative Consent

Sections 1271.3 (o) and 1271.75 (d)

The Section 1271.3 (o) and Section 1271.75 (d) require a donor medical history interview. There is no evidence that there has been any increased risk of transmission of disease through corneas obtained under legislative consent absent a medical history interview. In the absence of such evidence, and given the lack of confirmation of the validity of such interviews, mandating such a requirement does not appear to have adequate scientific substantiation.

EBAA Medical Standards document that legislative consent cases can be screened for risk factors and an adequate donor profile can be constructed through the use of the investigator's reports, autopsy results, and other sources of donor history.

EBAA Comment:

The EBAA recommends no change in policy from present federal regulation. A 1998 report presented before EBAA's Medical Advisory Board by the EBAA Policy and Position Research Committee, specifically summarizes the EBAA position (see Attachment II).

Storage

Section 1271.65

Section 1271.65 requires separation of suitable tissue from "quarantine" tissue. Physical separation would require additional refrigerator storage units for quarantined tissues, and would present an unnecessary cost and space burden.

EBAA Comment:

No "storage" problems have resulted in the transmission of systemic-infectious disease. EBAA recommends that the agency permit eye banks to follow community standards for storage.

EBAA Attachment I

FDA - Licensed Tests

Section 1270.80 (c)

Section 1270.80 (c) requires the use of FDA-approved tests. Tests specifically labeled for cadaveric specimens shall be used instead of a more generally labeled test when applicable and when available.

No currently FDA-approved serological tests exist for cadaveric samples. Due to the nature of eye recovery, the majority of samples collected are cadaveric.

EBAA Comment:

Current EBAA's Medical Standards for labeling and testing requirements meet or exceed this proposed requirement. We encourage the FDA to work with laboratories and manufacturers of diagnostic tests to approve tests for cadaveric specimens.

Collection of Blood Samples

Section 1271.80 (b)

Section 1271.80 (b) of the proposed rule "...requires that the donor specimen be collected at the time of recovery of cells or tissue from the donor or within 48 hours after recovery; except that the specimen from a living donor may be collected up to 7 days prior to recovery...."

There are several problems with this proposal for eye banking:

- (1) The best sample is one that is obtained from the donor pre-mortem. A FDA-approved blood test kit would actually test the blood within the guidelines of the kit, since such kits are only approved for blood from living patients. Frequently, post-mortem samples are hemolyzed and this leads to false-positive tests.
- (2) Not permitting pre-mortem samples negates all blood samples taken pre-infusion and pre-transfusion in cases of blood loss (adults) and infusion of fluids and blood (adults with blood loss and all children under 12 years.) This whole proposal grossly contradicts FDA's final rule that requires pre-infusion and pre-transfusion samples in such cases. This requirement also conflicts with another section in the Proposed Rule, 1271.80 (d) (2) (i): "A specimen taken from the donor after blood loss but before the transfusion or infusion is available for relevant communicable disease testing."
- (3) Setting a standard of blood sample collection up to 48 hours after recovery establishes dangerous outer-testing limits for banked human eyes. The later the specimen collection, the more hemolyzed the blood, and the greater chance for testing errors.

EBAA Attachment I

EBAA Comment:

Allowing a donor specimen to be collected up to 48 hours after recovery is not recommended for purposes of eye donation. This requirement would foster quality problems for eye banks. This is one example of where the proposed rule is overly broad and actually relaxes community standards. This proposed standard could lead to dangerous quality problems not currently exhibited. The EBAA recommends deletion of these standards. Tissue specific community standards for eye banking must be allowed.

Plasma Dilution Algorithm

Section 1271.80 (d)(2) and (d)(2)(i)

Section 1271.80 (d)(2) and 1271.80 (d)(2)(i) of the proposed rule and previous FDA guidance documents provide direction for the final determination of serology test results. Nevertheless, direction under the proposed rule remains either vague or unsupported by scientific logic. For example, "blood loss" needs clarification. In addition, dilution algorithms are required if infusions and transfusions exceed 2000 mL over specific time periods. This becomes a practical issue of performance. How can you determine if the algorithm needs to be implemented due to the 2000 mL limit without actually performing the tabulation?

Most facilities have complied with this regulation by merely performing a dilution algorithm on all donor cases destined for transplant use. Finally, the inclusion of whole blood cell total volume in calculations does not meet scientific principles. The volume of the red blood cells does not contribute to plasma dilution, only the actual plasma volume of the whole blood or the components used to produce reconstituted whole blood prior to transfusion contribute to dilution of the plasma.

EBAA Comment:

The EBAA recommends no change from FDA's present policy on plasma dilution.

Screening and Confirmatory Testing

Section 1270.80 (d) (1)

Section 1270.80 (d) (1) of the Notice of Proposed Rulemaking (NPRM), declares a donor who tests "repeatedly reactive or positive for a particular agent unsuitable, thus the cells and tissues from that donor could not be used."

EBAA Comment:

Current clinical practice suggests that confirmatory tests be used when available to verify positive screening tests. In order to avoid discarding transplantable tissue, we urge the

EBAA Attachment I

FDA to follow current clinical practice and reconsider its position because of the lack of scientific information that negates current clinical practice. The FDA does accept confirmatory testing for Treponemal disease. Policy should be consistent with medical practice, allowing confirmatory tests (where available) to prevail in all cases.

Recordkeeping Requirement

Section 1271.55 (l) (i)

Section 1271.55 (l) (i) requires manufacturers to include a copy of the donor's relevant medical records in documentation to accompany the tissue.

Under FDA's proposed rule an eye bank would have to obtain permission to release the medical records of the donor. Any identification of the donor would have to be redacted. This requirement is cumbersome, costly, and would ultimately provide confusing and conflicting data to transplant physicians. It appears that eye banks would need to send copies of the donor's full hospital chart to the surgeon and hospital Operating Room. This would require a donor's medical chart be included with the recipient's hospital chart. This could create a confusing situation and lead to error. Identifying cause of death and including a brief summary of medical condition to be delivered with the tissue is more appropriate. This would shield sensitive materials. In the rule a definition of

Summary of Medical Records is given, however, the proposed rule does not appear to simply permit a summary to be sent with the donor.

EBAA Comment:

The EBAA recommends deletion of this requirement as excessively burdensome. EBAA practice, per Medical Standards, has effectively guarded against transmission of systemic-infectious disease.

Privacy

Section 1271.55 (d)

Section 1271.55 (d) requires deleting the donor's name from documentation accompanying the tissue.

The Department of Health and Human Services proposed rule addressing "Standards for Privacy of Individually Identifiable Health Information, Federal Register Vol. 64 No. 212 45 CFR Parts 160 through 164 RIN 0991-AB08," would require deletion of much more data than the "donor name" as required in this standard.

EBAA Attachment I

EBAA Comment:

The Association is currently providing comment to the Department of Health and Human Services, on the proposed rule regarding (Federal Register Vol. 64 No. 212 CFR Parts 160 through 164 RIN 0991-AB08) Standards for Privacy of Individually Identifiable Health Information. We believe the proposed HHS regulation would adversely impact the transplant community. The regulation would severely burden the transplant process because of mandatory preauthorization requiring consent to review medical records. The proposed regulation will also restrict the research community's access to corneal tissue. The Association will request an exemption from this proposed rule so that the transplant community can continue to have access to essential donor information, in a timely fashion, that is necessary to facilitate the transplant process.

Attachment II
(Pages 1-4)

MEDICAL EXAMINERS LAWS AND THE ISSUE OF TISSUE SAFETY

Increasing concern about disease transmission has led to increasing scrutiny of organ and tissue procurement practices. The recent proposed and final rulings by the Food and Drug Administration (21CFR1270) highlight this concern. Contained in these rulings is the requirement that information be obtained concerning donors through "a documented dialogue with an individual or individuals who would be knowledgeable of the donor's relevant medical history and social behavior..." but "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 shall be reviewed." This legislation appears to respect the importance of a medical history while at the same time allowing states which procure tissue under medical examiner laws to continue to do so, even without a direct interview. These rulings and the concerns of some members of the eye banking community have led to a request for re-appraisal of the issue of tissue obtained through medical examiner laws. At least two basic issues present themselves: one is the issue of the safety of medical examiner tissue; another is the ethical concern inherent in obtaining tissue without specific consent from the donor or donor family. This paper will attempt to deal only with the issue of safety. The issues related to ethics will be left to other arenas for debate.

Prior to discussing safety issues it would be appropriate to assess the impact of medical examiner legislation on the supply of corneas in the United States. The Lions Eye Bank of Texas at Baylor College of Medicine, through its executive director M.B.

Danneffel, surveyed United States eye banks and found that while 33 states have medical examiner laws only nine used them in 1996. Of the 43,711 usable corneas procured in the United States that year, 4,752 or 11% were procured under medical examiner legislation. Thus the impact is not great although in some areas it is substantial.

To evaluate the safety of medical examiner tissue we will first attempt to review the relevant literature. Direct comparisons between hospital and medical examiner tissue were sought. Very few such comparisons exist. Danneffel and A. Sugar¹ found almost an identical seropositivity for human immunodeficiency virus (HIV) in medical examiner cases (0.87%) and hospital cases (0.83%) screened from 1986 to mid 1988. Heck et al² found 5 of 205 prospective donors, already screened to attempt to eliminate high risk groups, positive by ELISA and Western blot for HIV. All prospective donors were medical examiner cases and no comparison group with non-medical examiner cases was evaluated. Hwang et al³ reviewed 4,451 consecutive potential donors from the Los Angeles County Medical Examiner and excluded 1,680 (37.7%) on the basis of history or physical examination. Of the remaining 2,771 potential donors 27, (0.97%) were repeatedly positive on ELISA screening for HIV. Again a non medical examiner group was not provided for comparison.

Another way of looking at the issue of safety is to assess adverse reactions reported. Through the EBAA adverse reaction reporting system, Kirk Wilhelmus found for adverse reactions reported from 1993 to 1997, 10 endophthalmitis cases were from medical examiner cases, 54 from hospital patients and in 16 the source was unknown. This makes medical examiner cases account for 15.6% of endophthalmitis cases where the tissue source was known. For primary donor failures, 1995 to Feb., 1998, 24 of 144

reported cases where the source was known were from medical examiner cases or 16.6%. The exact proportion of all grafts from medical examiner sources during this time period is uncertain but probably is somewhere between 11 and 25%. In a more limited but better controlled study Danneffel, Scardino, Wilhelmus, and Woodbury (written communication December 18, 1997 submitted as ARVO abstract) retrospectively reviewed all adverse reactions reported from 8,211 corneal tissues distributed by their eye bank from 1993 through 1996. 13 adverse reactions were from 5,580 medical examiner obtained tissues (0.24%) and 6 were from 2,631 next-of-kin consented sources (0.23%).

Specific cases of systemic disease transmission have been reported including 2 cases of Hepatitis B and 4 cases of Creutzfeldt-Jakob disease as well as cases of rabies. None of these were from medical examiner cases and all appeared to have histories available although in all United States cases transplantation took place prior to institution of the present medical standards. Nonetheless, the risk of transmission of systemic viral disease persists, even in the presence of a family history interview. The risk of prion-associated diseases such as Creutzfeldt-Jakob is low but certainly not zero. Hogan and Cavanagh⁴ and in revised figures Hogan, Heck, and Cavanagh (written communication January 9, 1998, submitted as ARVO abstract) suggest that approximately one donor per year would be expected in the United States donor pool to have Creutzfeldt-Jakob disease. They felt that historical exclusionary criteria, those already in place, would exclude such a donor. Whether medical examiner screening of tissue would exclude such a donor is unknown. The question persists as to the adequacy of medical examiner determination of causes of death but questions also exist as to the accuracy of family interviews as well.

In summary no data are presented here which demonstrate evidence of increased disease transmission risk from donor tissue derived from medical examiner sources. Whether such tissue, when lacking historical data, will present increased risks in the future is unknown. This review is limited by the scarcity of well designed studies of the predictive value of clinical and interview data collection in both medical examiner and hospital settings. Until data from appropriate studies are available, it is suggested that reasonable efforts be made to obtain historical information on all corneal donors. The Medical Advisory Board of the EBAA will need to continue to monitor and assess this issue. A scientific basis for altering present policies does not yet exist.

References:

1. Danneffel MB, Sugar A. Incidence of HIV antibody positive eye/cornea donors in hospital versus medical examiner cases. *Cornea* 1990;9:271-272
2. Heck E, Petty C, Palestine A, Luckenbach M, Salahuddin SZ, Nussenblatt R, Harris W, Baxter C, McCulley J. ELISA HIV testing and viral culture in the screening of corneal tissue for transplant from medical examiner cases. *Cornea* 1989;8:77-80.
3. Hwang DG, Ward DE, Trousdale MD, Smith RE. Human immunodeficiency virus seroprevalence among potential corneal donors from medical examiner cases. *Amer J Ophthalmol* 1990;109:92-93.
4. Hogan RN, Cavanagh HD. Transplantation of corneal tissue from donors with diseases of the central nervous system. *Cornea* 1995;14:547-553.

Accepted by the EBAA Medical Advisory Board
June, 1998

Eye Banking and the Potential Impact of Increased Screening for Creutzfeldt-Jakob Disease

Robert H. Kennedy, MD, PhD, MBA

R. Nick Hogan, MD, PhD

Paul Brown, MD

Edward Holland, MD

Richard Johnson, MD

Walter Stark, MD

Joel Sugar, MD

From the Department of Ophthalmology, The University of Texas Southwestern Medical Center at Dallas, Dallas, TX (R.H.K., R.N.H.); The Laboratory of Central Nervous System Studies, The National Institutes of Neurological Diseases and Stroke, Washington, DC (P.B.); the Department of Ophthalmology, The University of Minnesota, Minneapolis, MN (E.H.); the Department of Neurology (R.J.) and Ophthalmology (W.S.), The Johns Hopkins University, Baltimore, MD; and the Department of Ophthalmology, The University of Illinois, Chicago, IL (J.S.).

Address correspondence and reprint requests to Dr. R.H. Kennedy, Department of Ophthalmology, 5323 Harry Hines Blvd., Dallas, TX 75390-8895

Word Count = 3,914

ABSTRACT

Context: Emergence of new variant Creutzfeldt-Jakob disease (CJD) in the United Kingdom and other factors have raised concerns about the adequacy of current methods of screening tissue donors in the U.S. The Food and Drug Administration has issued a proposed rule that would require a "donor medical history interview" to identify possible indications of underlying disease.

Objective: To examine reported data on the occurrence of CJD, quantify the risk among cornea donors, and evaluate possible screening strategies.

Design and Setting: Reported information on deaths due to CJD, deaths from all causes, and total cornea donors was used to estimate the rate of CJD among cornea donors in the U.S. The impact of screening on risk of CJD and donor supply was estimated.

Main Outcome Measures: Numbers of donors with and without CJD that would be excluded by various screening approaches.

Results: Only 1.3 of the approximately 45,000 cornea donors in the U.S. each year might be expected to have CJD. Most of the estimated risk (91%) is due to preclinical (asymptomatic) disease, and therefore, could not be eliminated by screening for signs or symptoms. If only the highest risk age groups were screened and specificity were 90%, more than 21,000 otherwise acceptable donors would incorrectly be excluded for every potential donor with symptomatic CJD correctly excluded.

Conclusions: Currently, the risk of CJD transmission following cornea transplantation is remarkably low. Screening for symptoms of CJD would have minimal impact on safety, but would reduce the supply of donor corneas and result in many patients not receiving needed treatment.

It has been known since 1974 that Creutzfeldt-Jakob disease (CJD), a transmissible spongiform encephalopathy, can be transmitted from person to person through cornea transplantation. In the first reported case of transmission, the donor cornea was obtained from a 55 year-old man and transplanted before the characteristic findings of CJD were identified at autopsy.¹ The recipient, a 55 year-old woman, developed neurologic signs and symptoms approximately 18 months later and died shortly after that. The presence of CJD was confirmed by autopsy. Following that report, the Eye Bank Association of America established screening criteria to prevent those with a known diagnosis or family history of CJD from being selected as cornea donors.² Since then, more than 600,000 cornea transplants have been performed in the United States without any additional reported cases of transmission of CJD. Recently, however, several factors have raised concerns about the adequacy of current screening methods and have led to a re-examination of this issue by the Eye Bank Association of America, the Food and Drug Administration, and others.

In the United Kingdom, a new variant of CJD characterized by a relatively young age at onset has been identified and linked to the occurrence of "mad cow" disease (bovine spongiform encephalopathy).³⁻⁸ Because a large number of persons in the United Kingdom had likely been exposed to the causative agent (prion protein) from ingestion of affected beef during the 1980s and 1990s, the possibility could not be dismissed that CJD would occur with increasing frequency among potential cornea donors. Thus far, no cases of new variant CJD have been reported in the United States. Another factor that has focused attention on donor screening criteria has been the occurrence of two additional possible cases of transmission of CJD through cornea transplantation. One was reported from Japan in 1994 and the other from Germany in 1997.^{9,10} Also, two corneas and sclera were transplanted to three recipients in the United Kingdom from a woman who was found at autopsy to have had CJD.¹¹ Although she had exhibited characteristic neurological signs, the findings had been

attributed to central nervous system involvement from metastatic lung cancer. All three recipients underwent surgical removal of the donor tissue several months after placement, and none has yet developed CJD (approximately two years after removal).

Even though the risk of transmitting CJD through cornea transplantation is remarkably low, the question remains whether the benefits of implementing a more stringent screening process would outweigh the associated costs including decreased availability of donor corneas. An inadequate supply of donor tissue would have important public health consequences because of the generally favorable visual outcomes achieved with cornea transplantation and lack of satisfactory alternative therapies. In 1999, Hogan and associates¹¹ suggested that collection of additional information concerning previous neurologic findings among potential donors would reduce the risk of transmitting CJD. They did not estimate the costs associated with increased screening or the likely impact on individual eye banks and overall supply of donor corneas. Recently, the Food and Drug Administration has issued a proposed rule that would require a "donor medical history interview" to identify cognitive, behavioral, and other possible indications of underlying disease that would preclude tissue donation.¹² In response to those concerns and developments, the Eye Bank Association of America commissioned a committee to review available information on the occurrence and transmissibility of CJD as it relates to cornea transplantation. The committee's findings form the basis for this report.

METHODS

The frequency of occurrence of CJD among potential cornea donors in the United States was estimated from reported information on incidence and death rates of CJD,¹³ all cause death rates,¹⁴ and population figures by age.¹⁵ Holman and associates¹³ from the Centers for Disease Control and Prevention examined United States death records from 1979 through 1994, and calculated death rates of CJD by age, sex, and race. Because no statistically significant increase or decrease was identified over time, we used the average annual age-specific death rates to calculate expected numbers of deaths

due to CJD for the 1997 United States population (the most recent year for which final census estimates were available). The total numbers of deaths by age due to all causes were obtained from the National Vital Statistics Reports for 1997.¹⁴ Using those data, age-specific rates of CJD among all deceased individuals were calculated. The rates provide an indication of the level of risk of CJD by age among potential donors (all deceased individuals) if no screening criteria were used.

Since 1974, potential cornea donors with a known diagnosis or family history of CJD have been excluded. Also, the Eye Bank Association of America medical standards for documentation of cause of death require exclusion of tissue from potential donors who died of unknown causes or of unestablished neurologic disease.² Even with those safeguards, the possibility exists that a series of errors could potentially lead to transplantation of tissue from a donor who had the clinical diagnosis of CJD established before death. However, we believe this would be a very uncommon event; and we are not aware of it ever having occurred. An additional threat is posed by persons who die of CJD without ever having been diagnosed correctly. It is difficult to quantify how frequently this might occur, but it is probably uncommon, and any such potential donors could be excluded by other screening criteria (e.g., death of unknown cause). A consensus view of the authors is that no more than one percent of persons who die of CJD (approximately 2.6 cases per year) are not excluded by current screening criteria. This figure was used to estimate the frequency among cornea donors of CJD due to persons who had the diagnosis or died of the disease.

Separate estimates were made of the risk posed by potential donors who died of causes unrelated to CJD, but who had either preclinical disease (the phase before symptoms of CJD have developed) or symptomatic disease that had not yet been diagnosed. The numbers of potential donors by age with symptomatic (but not yet diagnosed) disease were calculated from age-specific death rates of CJD,¹³ the estimated duration of the interval from onset of symptoms to diagnosis, age-specific mortality rates based on all causes of death,¹⁴ and United States population estimates.¹⁵ Survival

following onset of CJD is generally no longer than a few months. In a recent review,¹¹ it was noted that the mean durations of disease before death reported from various case series were 7.0, 7.6, and 4.5 months. Consequently, there is a comparatively short period of time during which a person could potentially have symptomatic, undiagnosed disease but die of other causes and be selected as a cornea donor. We used a six-month interval to calculate the risk from this source. It was assumed that none of the potential donors that had symptomatic disease would be excluded by current screening criteria.

Given that the overall death rates of CJD have not changed significantly over time¹³ and that there is no evidence to suggest any change in mean duration of survival, the incidence rates of symptomatic disease are likely quite similar to the death rates. Therefore, the age-specific death rates and estimated mean duration of symptoms before diagnosis (6 months) were used to calculate age-specific prevalence rates of symptomatic disease. The prevalence rates were multiplied by the United States population figures and by age-specific death rates based on all causes of death to estimate the annual numbers of potential donors who had symptomatic (but not yet diagnosed) CJD.

A similar method was used to estimate the level of risk posed by potential donors who had preclinical disease (incubating CJD but not yet symptomatic). There is little reported information concerning the intervals from onset of preclinical disease to development of symptoms of CJD. In a report on 278 patients with CJD,¹⁶ most (234 patients) had sporadic disease (no known family history or exposure to other affected persons), 36 had familial disease, and 8 had iatrogenic disease (contracted from use of contaminated intracerebral electroencephalogram electrodes, treatment with cadaveric human growth hormone, or cornea transplantation). Among those with iatrogenic disease, the intervals from exposure to onset of CJD ranged from 16 months to 17 years. For estimation of the risk associated with preclinical disease, we used 10 years as the interval from onset of preclinical disease to onset of symptoms. The age-specific death rates of CJD,¹³ estimated duration of preclinical disease (10 years), and United States population figures¹⁵ were used to calculate age-specific expected numbers of

persons with preclinical disease. Those numbers were multiplied by age-specific death rates based on all causes of death¹⁴ to estimate the annual numbers of potential donors who had preclinical CJD. It was assumed that none of those potential donors would be excluded by current screening criteria.

The Eye Bank Association of America conducts an annual survey of eye banks in the United States to collect data concerning total numbers of cornea donors, demographic characteristics, and uses of donated tissue. The age distribution data for 1998 (the most recent data available) were used to estimate the proportions of all deceased individuals (potential donors) by age that meet the selection criteria and become donors.¹⁷ Those proportions (cornea donor fractions) were multiplied by the estimated numbers of deceased individuals who either died of CJD and were not excluded by the screening criteria or who had preclinical or symptomatic disease. This provided estimates of the annual numbers of donors by age that could potentially transmit CJD to cornea recipients. Data from the Eye Bank Association of America were also used to estimate the total number of donor corneas that have been transplanted in the United States from 1974 through 1999. Information concerning the age distribution of donors obtained through legislative consent was obtained from the Florida Lions Eye Bank, the Lions Eye Bank of Texas, and Tissue Banks International.

RESULTS

The average annual age-specific death rates of CJD based on a study of United States death records from 1979 through 1994 are shown in Table 1.¹³ During that 16-year period, CJD was reported as a cause of 3,642 deaths. Approximately 98% of deaths occurred among persons 45 years of age or older and 80% among those aged 60 years or older. The average annual age-specific rates peaked at 5.75 deaths per 1,000,000 population among the 70 to 74 year age group. The overall annual age-adjusted death rates remained quite stable during the study period, varying from 0.78 to 1.11 (average annual rate of 0.95 deaths per 1,000,000 population).

The expected numbers of deaths due to CJD based on the 1997 United States population are greatest in the 70 to 74 year age group (Table 1). By comparison, total deaths due to all causes continue to rise with increasing age, and are greatest among those 85 years of age or older. For this reason, the age-specific numbers of deaths due to CJD per 1,000,000 deaths due to all causes peak in the 60 to 64 year age group at 266.7 and decline substantially among older groups. Those rates provide an indication of the risk that a deceased person of any particular age would have had a diagnosis of CJD. To account for the impact of current cornea donor screening practices, estimates of the numbers of those who had the diagnosis or died of CJD and, for whatever reason, remain undetected in the pool of potential donors were based on one percent of expected deaths due to the disease.

The numbers of persons by age who at any given time would be expected to be symptomatic but not diagnosed as having CJD are shown in Table 2. Death rates based on all causes of death were used to calculate the numbers of such persons who would be expected to die each year. Also, the expected numbers of potential donors with preclinical disease (incubating CJD) were calculated. Because of the much longer assumed duration of the incubation period (10 years) than the symptomatic period (6 months), the estimated frequencies of preclinical disease are much greater.

The numbers of cornea donors were divided by total deaths to yield the proportions of all deceased individuals that become cornea donors within each age group (Table 3). Although the Eye Bank Association of America does not provide the data on age by 5-year intervals, the estimated proportions of cornea donors are quite similar over the age range of 21 to 70 years. The age-specific proportions of cornea donors were used to estimate the annual numbers of cornea donors that might be expected to have had preclinical or symptomatic disease or to have had the diagnosis or died of CJD (Table 4). Among the annual total of approximately 45,000 cornea donors in the United States, the estimates indicate that 1.3 donors might be expected to have had preclinical or symptomatic disease or

to have died of CJD. Most of the estimated risk (approximately 91% of total risk) is due to preclinical disease. The age-specific rates of CJD were 1.1 per 1,000,000 cornea donors aged 21 to 40 years, 20.2 among those 41 to 60 years, 52.1 in the 61 to 70 year group, and 31.1 among those older than 70 years.

DISCUSSION

Currently, there is no laboratory test that meets all criteria necessary to be used for widespread screening of potential cornea donors for CJD. The criteria would include reasonable cost in relation to expected improvements in safety, high sensitivity and specificity, completion of testing within the short period of time before a donor cornea must be used, and accessibility and availability of tissue for testing. Consequently, it is not possible at the present time to identify and exclude individual potential donors that had preclinical disease. Screening of blood for the presence of diagnostic prion protein (the etiologic agent of CJD) might eventually be useful, but no sufficiently sensitive methodology has yet been discovered.

Possible strategies to improve safety could be based on exclusion of potential donors in the age groups at highest risk or on more intensive efforts to identify the estimated small number of donors with a known diagnosis or symptoms of CJD that are missed by current screening methods. Hogan and associates¹¹ previously suggested the latter approach, and a requirement for a "donor medical history interview" to identify cognitive, behavioral, and other possible indicators of underlying disease is included in a recently proposed rule drafted by the Food and Drug Administration.¹² In order for any such program to be beneficial, it would need to have the capability of preventing the highly infrequent occurrence of cornea procurement from a donor that had a known diagnosis or symptoms of CJD. We estimate that approximately one such case would occur every 8.1 years (0.123 cases per year) at current annual volumes of cornea donation (Table 4). This would represent approximately one case among every 368,000 donors.

Even if a screening approach were available that could identify all potential donors with a known diagnosis or symptoms of CJD (sensitivity of 100%), it might not be practical to use it unless the specificity (proportion of those without disease that are correctly identified) were sufficiently high. In general, screening for an uncommon disease requires very high specificity to avoid misclassification of large numbers of subjects who do not have the disease. A critical question, therefore, is whether screening interviews to identify symptoms suggestive of CJD would have high enough specificity to avoid unacceptably large losses of otherwise suitable cornea donors.

Frequent clinical features of CJD include cognitive impairment (personality and behavioral changes, disorientation, and memory loss), myoclonus, cerebellar dysfunction, speech abnormalities, and visual impairment.^{11,16} Because of the overlap of symptoms with other neurologic disorders, histologic verification of CJD at autopsy is required to establish a definitive diagnosis. This overlap with common age-related findings among the elderly (e.g., mental deterioration) would tend to limit the specificity of screening based on symptoms suggestive of CJD. Also, the information would not generally be collected by neurologists or other physicians, but by technicians with limited medical training. Another factor is that family members and other respondents might have considerable difficulty in judging and agreeing whether a potential donor had a particular symptom.

The numbers of otherwise suitable donors that might incorrectly be excluded in order to correctly exclude a single donor with symptomatic or diagnosed disease (that without screening based on symptoms would remain in the donor pool) were calculated for various levels of specificity (Table 5). If only the highest risk age groups (60 to 69 years) were screened and specificity were as high as 90%, tissue from approximately 21,580 donors would incorrectly be discarded over a period of 17.5 years to exclude one donor with symptomatic or diagnosed disease. The numbers of otherwise suitable donors not selected (per donor with disease appropriately excluded) would be much greater if screening were applied to a broader age range of donors or if the sensitivity of screening were less than

100%. Screening based on age alone would not be an attractive strategy either. If donors age 60 to 69 years were not selected, more than 19,000 donors (38,000 corneas) would be excluded for each additional case of symptomatic, diagnosed, or preclinical CJD eliminated from the donor pool. However, because the risk of disease among donors less than 40 years of age at the time of death is approximately 40 times lower than among older donors, efforts to maximize use of young donors would help to keep the overall level of risk of CJD transmission as low as possible.

There are sufficient donor corneas to meet current demand in the United States, but worldwide demand will far exceed supply for the foreseeable future. Consequently, loss of donor corneas due to more intensive screening would have a direct impact on the number of persons who could have their vision restored by cornea transplantation, and for others would likely lengthen the waiting time for surgical treatment. This view is supported by the recent initiation of a study sponsored by the National Eye Institute to evaluate outcomes following use of tissue from older cornea donors.¹⁸ If the results are favorable, the goal will be to increase the supply and acceptance of tissue from older donors. Also, concerns have been expressed that growth in the volume of refractive surgical procedures may constrain future availability of donor corneas. It is important, therefore, that consideration of new screening requirements take into account the likely impact on supply of donor corneas and that the supply not be limited unnecessarily.

In some states, the law allows for procurement of donor corneas by the medical examiner or coroner through a legislative consent process that does not require communication with the next of kin. Although current federal regulations require a "donor medical history interview," there is an exception for corneas obtained through legislative consent. The recently proposed rule drafted by the Food and Drug Administration would eliminate this exception.¹² If the donor's next of kin, acquaintances, or primary treating physician must be interviewed about symptoms suggestive of CJD, the number of donors obtained through legislative consent will be substantially reduced (possibly by as much as 90%)

because of the difficulty in locating appropriate individuals to interview during the short time available for procurement following the frequently sudden, unexpected, and traumatic deaths that are evaluated by medical examiners and coroners. At present, approximately 10% of all cornea donors in the United States are obtained through legislative consent. Data concerning the age distribution of those donors were collected from the Florida Lions Eye Bank, the Lions Eye Bank of Texas, and Tissue Banks International. It shows that in 1998 approximately 50% were age 40 years or less (as compared to 15% among all donors). Based on those data, we estimate that the overall risk of preclinical, symptomatic, and diagnosed CJD in this subgroup is about 40% less than the estimated preclinical risk alone among all other donors. This should more than compensate for any potential increase in risk due to less complete ascertainment of information concerning family medical history because only about 13% of patients with CJD have a family history of the disease.¹⁶ Consequently, the data support the view that more intensive screening of donors obtained through legislative consent might actually reduce the level of safety rather than enhance it because of the loss of a large proportion of those donors. It should be noted that ethical concerns have been expressed about the process of obtaining legislative consent, but those concerns do not center on the issue of risk due to CJD.

For several reasons, our estimate of the annual number of cornea donors with CJD (Table 4) is greater than the number of cornea recipients who might be expected to develop the disease. Data from the Eye Bank Association of America indicate that more than one third of donated tissue is either not suitable for transplant or is used for research or training purposes.¹⁷ Also, various biologic factors may influence the likelihood of transmission even if a recipient were to receive tissue from an affected donor. For example, genetic homozygosity for methionine at codon 129 (present in approximately 50% of the general population) is over-represented (80%) in patients with iatrogenic CJD.^{19,20} Additionally, attempts to transmit disease to experimental animals fail for 10% of patients with the most common form of CJD (sporadic disease).¹⁶

In the United States, more than 600,000 donor corneas have been transplanted without any additional reports of CJD transmission since 1974. This would require at least 300,000 donors (two corneas per donor). Using our overall estimated rate of CJD among donors, it can be calculated that 8.6 of those donors (99% CI, 8.3 – 9.0) would be expected to have had preclinical, symptomatic, or diagnosed CJD. Biologic and other factors probably account for the lower than expected rate of disease among recipients. For this reason, we believe the estimates of otherwise suitable donors that would be excluded by screening (Table 5) understate the numbers that would be excluded per case of CJD transmission prevented among cornea recipients.

In summary, the risk of disease transmission following cornea transplantation is remarkably low with use of current practices for excluding potential donors with a known diagnosis or family history of CJD. Our analyses indicate that screening based on signs and symptoms would likely lead to minimal additional improvement in safety, but would reduce the supply of suitable cornea donors, particularly young donors obtained through legislative consent, and result in many patients not receiving needed treatment in a timely manner. Consequently, we would not recommend such screening. It is possible that new variant CJD could be identified in the United States in the future and pose a new threat to cornea recipients. However, pre-emptive screening or restriction of the supply of young donors before the occurrence of sufficient cases to document a growing risk would likely not be beneficial because the incidence rate of disease is currently much lower among donors less than 40 years of age than among older donors.

ACKNOWLEDGMENTS

The authors wish to thank the following individuals for providing data concerning cornea donors:

Patricia Aiken-O'Neill, Esq, and Mr. Rusty Kelly at the Eye Bank Association of America; Mr. Richard Fuller at Tissue Banks International; Mary Anne Taylor, M.S., at the Florida Lions Eye Bank; Mary Beth Danneffel, RN, at the Lions Eye Bank of Texas, and Ellen Heck, MT, MA, at UT Southwestern Medical Center. Harout Armenian, MD, DrPH, George Bartley, MD, Dwight Cavanagh, MD, Robert Haley, MD, and Leonard Kurland, MD, DrPH, reviewed the manuscript and provided valuable suggestions; Donald McIntire, PhD, offered statistical assistance.

REFERENCES

1. Duffy P, Wolf J, Collins G, DeVoe AG, Streeten B, Cowen D. Possible person-to-person transmission of Creutzfeldt-Jakob disease. *N Engl J Med* 1974; 290:692-3.
2. Eye Bank Association of America, Medical Standards 1994:9.
3. Wilesmith JW, Wells GAH. Bovine spongiform encephalopathy. *Curr Topics Microbiol Immunol* 1991; 172:21-38.
4. Will RG, Ironside JW, Zeidler M, et al. A new variant of Creutzfeldt-Jakob disease in the UK. *Lancet* 1996; 347:921-5.
5. Collinge J, Sidle KCL, Heads J, et al. Molecular analysis of prion strain variation and the aetiology of "new variant" CJD. *Nature* 1996; 383:685-90.
6. Hill AF, Desbruslais M, Joiner S, et al. The same prion strain causes vCJD and BSE. *Nature* 1997; 389:448-50.
7. Brown P. The risk of bovine spongiform encephalopathy ("mad cow disease") to human health. *JAMA* 1997; 278:1008-11.
8. Pocchiari M. Early identification of variant Creutzfeldt-Jakob disease. [Editorial]. *Br Med J* 1998; 316:563-4.
9. Uchiyama K, Ishida C, Yago S, Kuramaya H, Kitmoto T. An autopsy case of Creutzfeldt-Jakob disease associated with corneal transplantation. *Dementia* 1994; 8:466-73.
10. Heckmann JG, Lang CJG, Petruch F, et al. Transmission of Creutzfeldt-Jakob disease via a corneal transplant. *J Neurol Neurosurg Psychiatry* 1997; 63:388-90.
11. Hogan RN, Brown P, Heck E, Cavanagh HD. Risk of prion disease transmission from ocular donor tissue transplantation. *Cornea* 1999; 18:2-11.
12. The Food and Drug Administration, Suitability Determination for Donors of Human Cellular and Tissue-Based Products, [Docket No. 97N-484S], 1999.

13. Holman RC, Khan AS, Belay ED, Schonberger LB. Creutzfeldt-Jakob disease in the United States, 1979-1994: using national mortality data to assess the possible occurrence of variant cases. *Emerg Infect Dis* 1996; 2:333-7.
14. National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999.
15. US Census Bureau. Population estimates for the US, regions, divisions, and states by 5-year age groups and sex, 1990-1998. Washington, DC, 1999.
16. Brown P, Gibbs CJ, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Ann Neurol* 1994; 35:513-29.
17. *1998 Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America, 1998.
18. Cornea Donor Study, Sponsored by the National Eye Institute, 1999.
19. Brown P, Cervenakova L, Goldfarb LG, et al. Iatrogenic Creutzfeldt-Jakob disease: an example of the interplay between ancient genes and modern medicine. *Neurology* 1994; 44:291-3.
20. Brown P, Preece M, Brandel JP, et al. Iatrogenic Creutzfeldt-Jakob disease at the Millennium. *Neurology* (in press).

Table 1 -- Creutzfeldt-Jakob Disease Deaths and Death Rates, and Deaths Due to All Causes in the United States, 1997

Age (years)	CJD Death Rate *	Expected CJD Deaths	All Cause Deaths **	CJD Deaths Per 1,000,000 All Cause Deaths
0-4	<0.01	0.2	33,546	6.0
5-9	0	0	3,645	0
10-14	0	0	4,416	0
15-19	0	0	14,272	0
20-24	<0.01	0.2	17,272	11.6
25-29	<0.01	0.2	19,272	10.4
30-34	0.04	0.8	26,266	30.5
35-39	0.08	1.8	38,172	47.2
40-44	0.16	3.4	51,236	66.4
45-49	0.45	8.3	65,090	127.5
50-54	0.99	15.0	79,792	188.0
55-59	2.14	25.2	98,130	256.8
60-64	3.55	35.7	133,863	266.7
65-69	5.03	49.2	194,776	252.6
70-74	5.75	50.3	269,498	186.6
75-79	5.60	39.7	325,799	121.9
80-84	3.94	18.4	344,731	53.4
<u>>85</u>	<u>2.42</u>	<u>9.5</u>	<u>594,068</u>	<u>16.0</u>
Total	-	257.9	2,314,245	111.4

Table 1 (cont) -- Creutzfeldt-Jakob Disease Deaths and Death Rates, and Deaths Due to All Causes
in the United States, 1997

- * Average annual deaths per 1,000,000 population, 1979 – 1994. Source: Holman RC, Khan AS, Belay ED, Schonberger LB: Creutzfeldt-Jakob disease in the United States, 1979 – 1994: using national mortality data to assess the possible occurrence of variant cases. *Emerg Infect Dis* 1996; 2:333-7.
- ** Source: National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999.

Table 2 -- Expected Annual Deaths Among Patients with Preclinical or Symptomatic Creutzfeldt-Jakob Disease in the United States

Age (years)	All Cause Death Rate *	Living Preclinical Patients **	Living Symptomatic Patients +	Expected Deaths	
				Preclinical Patients	Symptomatic Patients
0-4	358	1.0	0.1	0	0
5-9	185	0	0	0	0
10-14	232	0.6	0	0	0
15-19	748	1.6	0	0	0
20-24	986	3.8	0.1	0	0
25-29	1,021	9.8	0.1	0	0
30-34	1,266	20.8	0.4	0	0
35-39	1,687	45.5	0.9	0.1	0
40-44	2,397	93.3	1.7	0.2	0
45-49	3,524	167.2	4.2	0.6	0
50-54	5,262	263.1	7.5	1.4	0
55-59	8,346	376.5	12.6	3.1	0.1
60-64	13,312	468.3	17.9	6.2	0.2
65-69	19,951	469.0	24.6	9.4	0.5
70-74	30,849	354.3	25.2	10.9	0.8
75-79	46,125	199.9	19.9	9.2	0.9
80-84	74,259	112.8	9.2	8.4	0.7
≥85	<u>153,452</u>	<u>95.0</u>	<u>4.8</u>	<u>14.6</u>	<u>0.7</u>
Total	-	2,682.5	129.2	64.1	3.9

Table 2 (cont) - - Expected Annual Deaths Among Patients with Preclinical or Symptomatic
Creutzfeldt-Jakob Disease in the United States

- * Deaths per 1,000,000 population, 1997. Source: National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999.
- ** Estimated numbers of living preclinical patients at any point in time were derived from age-specific death rates of Creutzfeldt-Jakob disease, estimated duration of preclinical disease (10 years), and United States population estimates.
- + Estimated numbers of living symptomatic patients at any point in time were derived from age-specific death rates of Creutzfeldt-Jakob disease, estimated duration of the interval from onset of symptoms to diagnosis (6 months), and United States population estimates.

Table 3 - - Estimated Proportions of All Deaths that Yield Donor Corneas

Age (years)	Cornea Donors *	All Cause Deaths **	Cornea Donor Fraction +
0-10	635	37,191	0.017
11-20	1,890	18,688	0.101
21-40	4,390	100,982	0.044
41-60	13,095	294,248	0.045
61-70	12,234	328,639	0.037
>70	12,813	1,534,096	0.008
Unknown	<u>245</u>	<u>401</u>	<u>-</u>
Total	45,302	2,314,245	-

* Source: 1998 *Eye Banking Statistical Report*. Washington, DC: Eye Bank Association of America, 1998. The age groupings are those used by the Eye Bank Association of America.

** Source: National Vital Statistics Reports, Deaths: Final Data for 1997, Vol. 47, June 30, 1999. The age groupings used for this column are: 0-9, 10-19, 20-39, 40-59, 60-69, and ≥ 70 .

+ Calculated by dividing the numbers of cornea donors by the numbers of all cause deaths.

Table 4 - - Estimated Annual Numbers of Cornea Donors Who Died of Creutzfeldt-Jakob Disease or Who had Preclinical or Symptomatic Disease at the Time of Death *

Age (years)	Preclinical Disease	Symptomatic Disease	Died of CJD	Total
0-4	0	0	0	0
5-9	0	0	0	0
10-14	0	0	0	0
15-19	0	0	0	0
20-24	0	0	0	0
25-29	0	0	0	0
30-34	0.001	0	0	0.001
35-39	0.003	0	0.001	0.004
40-44	0.010	0	0.002	0.012
45-49	0.026	0	0.004	0.030
50-54	0.061	0	0.007	0.068
55-59	0.140	0.004	0.011	0.155
60-64	0.232	0.007	0.013	0.252
65-69	0.348	0.019	0.018	0.385
70-74	0.092	0.007	0.004	0.103
75-79	0.077	0.008	0.003	0.088
80-84	0.070	0.006	0.002	0.078
≥85	<u>0.122</u>	<u>0.006</u>	<u>0.001</u>	<u>0.129</u>
Total	1.182	0.057	0.066	1.305

Table 4 (cont) - - Estimated Annual Numbers of Cornea Donors Who Died of Creutzfeldt-Jakob Disease or Who had Preclinical or Symptomatic Disease at the Time of Death*

- * The estimates were derived by multiplying the expected numbers of preclinical and symptomatic deaths shown in Table 2 by the cornea donor fractions for the corresponding age groups from Table 3. Because most patients who die of Creutzfeldt-Jakob disease are excluded from becoming cornea donors by current donor screening criteria, one percent of the expected deaths from the disease in each age category shown in Table 1 were multiplied by the cornea donor fractions. Slight differences in the values shown in Table 4 from those derived by multiplying the numbers shown in Tables 1-3 are due to rounding in the underlying calculations.

Table 5 -- Estimated Numbers of Otherwise Suitable Donors Incorrectly Excluded by Screening for Symptoms Suggestive of Creutzfeldt-Jakob Disease Per Donor with Disease Correctly Excluded *

Age Range Screened	Proportion of All Donors Screened (%)	No. of Years Screening Required to Exclude One Case of CJD **	Donors Incorrectly Excluded By Specificity of Screening		
			95%	90%	80%
All	100	8.1	18,415	36,831	73,662
>50 years	72	8.6	13,976	27,952	55,904
60-69 years	27	17.5	10,790	21,580	43,160

* Donors with Creutzfeldt-Jakob disease correctly excluded by screening are defined as those that without screening based on symptoms would remain in the donor pool. The estimated annual numbers of such donors are shown in the "symptomatic disease" and "died of CJD" columns in Table 4. For these calculations, it is assumed that the sensitivity of screening would be 100% (i.e., all donors with "symptomatic disease" or "died of CJD" as estimated in Table 4 would be excluded by the screening process). The calculations are based on the volume and age distribution of cornea donors in the United States as reported by the Eye Bank Association of America for 1998.¹⁷

Table 5 (cont) - - Estimated Numbers of Otherwise Suitable Donors Incorrectly Excluded by
Screening for Symptoms suggestive of Creutzfeldt-Jakob Disease Per Donor with
Disease Correctly Excluded*

** The number of years of screening required to correctly exclude one donor with disease is the inverse of the sum of the estimated numbers of such donors as shown in the "symptomatic disease" and "died of CJD" columns in Table 4 for the age categories being screened. The numbers of years of screening were multiplied by the annual numbers of donors in the corresponding age categories. The indicated levels of specificity were applied to these figures to calculate the numbers of otherwise suitable donors that might incorrectly be excluded.

January 27, 2000

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

Re: Suitability Determination for Donors of Human Cellular and Tissue-Based Products,
[Docket No. 97N-484S]

Dear Sir/Madam:

The Eye Bank Association of America recently commissioned a committee to provide an independent report on the occurrence and transmissibility of Creutzfeldt-Jakob Disease (CJD) as it relates to cornea transplantation and to comment on the proposed rule concerning "Suitability Determination for Donors of Human Cellular and Tissue-Based Products." The committee includes members with expertise in prion disease, cornea transplantation, eye banking, neurology, and epidemiology. We have considered various approaches to minimize the risk of CJD development among cornea recipients and have reached the following conclusions:

1. Collection of information on signs and symptoms suggestive of CJD would not be a useful method of screening potential donors. At best, the possible reduction in risk of CJD transmission would likely be very small in relation to the associated costs, particularly due to decreased supply of useable tissue.
2. Current laboratory methods of testing for CJD are not adequate to screen potential donors within the short time before corneas must be used.
3. The death rates of CJD, though quite low, are highest in the older age groups. For purposes of minimizing the overall risk of CJD transmission, each Eye Bank should encourage policies and procedures that ensure maximum use of young donors even as the supply of older donors continues to expand.
4. The available medical information on potential donors should be reviewed for any evidence of a diagnosis or family history of CJD and for evidence that human pituitary-derived growth hormone had been received. Any with positive findings should be eliminated from further consideration for cornea donation. We are not aware of any Eye Bank in the United States that does not already adhere to this recommendation.

Collection of information on signs and symptoms suggestive of CJD: This issue was approached by evaluating epidemiological information on age-specific death rates of CJD, age-specific all cause death rates, the current age distribution of cornea donors, and estimates of the incubation period of CJD in humans. We estimated the levels of risk posed by potential donors who might have been symptomatic from CJD at the time of death (approximately 9% of total risk) as well as by those who might have been incubating CJD (assuming a 10-year incubation period) even though symptoms had not yet developed (approximately 91% of total risk). These estimates suggest that much of the potential risk could not be eliminated because donors with preclinical (not yet symptomatic) CJD could not be identified.

Among the annual total of approximately 45,000 cornea donors in the United States, we estimate that 1.3 donors might be expected to have either preclinical or symptomatic CJD. However, the

risk of CJD occurring in a cornea recipient is much lower than the estimate of the likelihood of CJD occurring in a cornea donor. In the United States, a single case was reported in 1974, before guidelines were used to specifically exclude potential donors with known CJD. No additional cases of CJD have been reported among recipients of the more than 500,000 donor corneas that have been transplanted in the United States since that time. Because of the low frequency of CJD among potential donors, any screening program would need to have very high specificity (i.e., correctly identify those who do not have CJD) in order to avoid significant losses of useable tissue. Several factors would limit the specificity of questioning about symptoms of CJD including: 1) the symptoms of CJD overlap with common age-related findings among the elderly (e.g., mental deterioration); and 2) the information would be obtained by technicians with limited medical training from family members and others who may have considerable difficulty in judging and agreeing on whether a potential donor had a particular symptom.

Our estimates indicate that because of the combination of low occurrence of symptomatic CJD at the time of death of cornea donors (approximately 1 case every 8 years) and limited specificity of questioning about signs and symptoms, screening would likely result in many thousands of otherwise useable corneas being discarded in order to exclude even a single donor who had symptomatic CJD. For example, if the specificity of screening were as high as 90% and screening were applied only to donors 50 to 69 years of age (the group at highest risk), more than 15,000 donors (30,000 corneas) would be excluded during the same eight-year period. Although sufficient donor corneas are available to meet current demand in the United States, worldwide demand will far exceed supply for the foreseeable future. Consequently, restriction of the supply of donor corneas would have a direct impact on the number of patients who could have their vision restored by cornea transplantation.

Laboratory testing of potential cornea donors for CJD: Potential screening tests would be limited to immunohistopathological examination of either brain or retina. Neither test satisfies criteria necessary for testing to be performed on a routine basis. The criteria would include: 1) reasonable cost in relation to expected improvements in safety; 2) high sensitivity and specificity; 3) completion of testing within the short period of time before a donor cornea must be used; and 4) accessibility and availability of tissue for testing. Screening of blood for the presence of diagnostic prion protein might meet these criteria, but no sufficiently sensitive methodology has yet been discovered (several laboratories are currently working on the problem, and a blood test may become available within the next two years).

Encourage maximum use of young donors: The risk of CJD among donors less than 40 years of age at the time of death is approximately 40 times lower than the already low risk among older donors. This suggests that efforts to maximize the supply of young donors would help to keep the overall level of risk of CJD transmission as low as possible. However, exclusion of potential donors because of older age would not be an appropriate screening strategy because even among older donors the risk of CJD occurrence is quite low, more than half of all cornea donors are older than 60 years, and demand for donor corneas exceeds the available supply. If donors age 60 to 69 years were not selected, more than 19,000 donors (38,000 corneas) would be excluded for each case of preclinical or symptomatic CJD eliminated from the donor pool.

New variant CJD: Although no cases of new variant CJD have been identified in the United States, the possibility exists that new variant CJD could occur in the future. We believe that any screening or restriction of the supply of younger donors before a first case of new variant CJD has

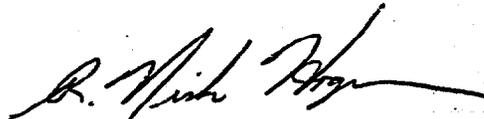
been reported would not be beneficial because the risk of CJD is currently far lower (about 40 times lower) among donors less than 40 years of age than among older donors.

The risk of developing CJD following cornea transplantation is remarkably low with use of current practices for screening potential donors. Our analyses indicate that screening based on signs and symptoms suggestive of CJD would likely lead to minimal additional improvement in safety, but would reduce the supply of donor corneas and result in many patients not receiving needed treatment. Consequently, we would not recommend such screening. If you so desire, we would be pleased to discuss our analyses and recommendations in greater detail. Thank you for your consideration of this information.

Sincerely,



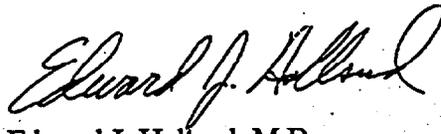
Robert H. Kennedy, M.D., Ph.D., M.B.A.
Chair, Committee on Prion Disease,
Commissioned by the Eye Bank Association of America
Associate Professor of Ophthalmology
UT Southwestern Medical Center
Dallas, TX



R. Nick Hogan, M.D., Ph.D.
Assistant Professor of Ophthalmology
UT Southwestern Medical Center
Dallas, TX



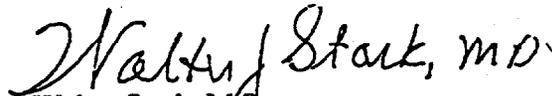
Paul Brown, M.D.
Senior Research Scientist
Laboratory of CNS Studies, NINDS
National Institutes of Health
Bethesda, MD



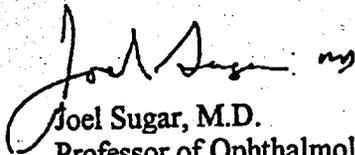
Edward J. Holland, M.D.
Chair, Medical Advisory Board,
Eye Bank Association of America
Professor of Ophthalmology
University of Minnesota
Minneapolis, MN



Richard Johnson, M.D.
Professor of Neurology
Johns Hopkins University
Baltimore, MD



Walter Stark, M.D.
Professor of Ophthalmology
Johns Hopkins University
Baltimore, MD



Joel Sugar, M.D.
Professor of Ophthalmology
University of Illinois
Chicago, IL

cc: Patricia Aiken-O'Neill
President/CEO
Eye Bank Association of America

February 2, 2000

By Hand Delivery

U.S. Department of Health and Human Services
Assistant Secretary for Planning and Evaluation
Attention: Privacy-P
Room G-322A
Hubert H. Humphrey Building
200 Independence Avenue, SW
Washington, D.C. 20201

**Re: Comments on the Proposed Standards for Privacy of Individually
Identifiable Health Information (RIN 0991-AB08)**

Dear Assistant Secretary:

On November 3, 1999, the Department of Health and Human Services ("HHS") published proposed regulations regarding "Standards for Privacy of Individually Identifiable Health Information." 64 Fed. Reg. 59918. The American Academy of Ophthalmology ("AAO") and the Eye Bank Association of America ("EBAA") welcome the opportunity to comment on these proposed regulations. While we support the goals of protecting privacy we are concerned that, unless modified, the regulations may unintentionally impede the ability of eye transplant agencies to facilitate transplant operations, research, and medical advancements. If the intent of the proposal is to protect current organ and tissue procurement activities, we applaud it. However, we seek further clarification as it relates to eye and eye tissue procurement activities. Important policy considerations support exempting *all* activities related to the procurement and distribution of eyes and eye tissue from the individual authorization requirement. Accordingly, the AAO and EBAA request that HHS clarify the proposed regulations by modifying the definitions of "health care" and "individual" so as to allow essential donor information to be gathered and exchanged by and between certain entities on an expedited basis, as necessitated by the nature of the donation process. We also suggest that HHS maintain (with clarification) the research exception that applies to the use or disclosure of deceased individuals' protected health information ("PHI").

I. The Eye Bank Community and the Donation Process

The American Academy of Ophthalmology is the world's largest ophthalmic educational and scientific non-profit organization. The Academy's mission is to

advance the lifelong learning and professional interests of ophthalmologists to ensure that the public can obtain the best possible eye care. The Academy represents nearly 20,000 eye physicians and surgeons.

Founded in 1961, the EBAA is a non-profit organization dedicated to the restoration of sight through the promotion and advancement of eye banking. EBAA's 108 member eye banks, located worldwide, make possible more than 46,000 sight restoring transplants annually. As the oldest transplantation organization in America, the EBAA has led the field with the establishment of medical standards for the procurement and distribution of eyes and comprehensive certification programs for technicians. These standards and certification programs have served as models for other transplant organizations, as well as state legislation in jurisdictions such as Florida and New York.

AAO member ophthalmologists rely upon EBAA member organizations to obtain the eyes and eye tissue necessary to perform surgery, conduct research, and improve medical education. EBAA provides grants to encourage research advancing the restoration of sight. Thus, the donation and distribution of eyes and eye tissue are integral to the functioning of each organization.

Last year more than 45,000 individuals donated their eyes for purposes of transplantation, research, medical education, and therapy. In 1998, over 47,000 individuals made donations to eye banks. Of these donations, 47,425 eyes were used for corneal grafts and 21,904 for research purposes. Donations are also used for medical education. *Time is the critical factor in procuring and distributing eyes.* The standard of practice among eye banks is to recover donor eyes *within the first six hours* after death to assure viability for transplantation and research. *Slowing down the process risks the loss of viable eye tissues.*

To facilitate donations from individuals who did not authorize donation before death, hospitals and eye banks typically use and/or disclose PHI (as defined at 42 C.F.R. § 164.504¹) without authorization to determine whether the donation is suitable. The process begins upon the imminent or actual death of an individual. At this stage, the hospital will typically contact a transplant organization or its agent to begin the screening process.² At this

¹ For purposes of these comments, we refer to the proposed regulatory provisions by their proposed Code of Federal Regulation designation.

² This system mirrors the Health Care Financing Administration's Condition of Participation regulations ("HCFA's COP regulations"), which require hospitals to notify Organ Procurement Organizations ("OPOs") of every death or imminent death. See 42 C.F.R. Pt. 482. Eye banks are not typically OPOs.

preliminary stage eye banks consider it inappropriate and insensitive to involve grieving families in what may prove to be a futile endeavor. The information needed typically includes: the name of the decedent, the patient identification number, the time and date of death, and a brief health history to evaluate the possibility of infectious diseases (such as HIV or hepatitis).

Thus, an initial determination of suitability is contingent upon access to, and analysis of, the potential donor's PHI provided to the transplant organization by the hospital. Following this determination, the decedent's (or individual facing imminent death's) next of kin is approached for consent to donate for corneal transplantation, eye research and medical education. This consent includes, among other things, an authorization for the release of the donor's medical history.

After obtaining this consent, the eye bank creates a comprehensive donor profile from a variety of sources and assigns a donor number. Based upon the above referenced consent, the eye bank makes the eyes or eye tissue available for transplant, research, or medical education using the assigned donor number. Current Food and Drug Administration regulation requires that eyes or eye tissue be labeled with some PHI for distribution purposes.

Due to the fact that eye banks rely upon the voluntary decisions of individuals and their next of kin to donate, confidentiality is a high priority to ensure public trust and confidence in the system. The EBAA has developed and widely circulated to its members medical and ethical standards that address the need to maintain donor and recipient confidentiality. [Attachment A]

DEFINITIONS

II. AAO and EBAA Are Concerned that the "Definitions" in the Proposed Regulations Inadvertently Hamper the Activities Necessary to Procure and Distribute Eyes and Eye Tissue.

AAO and EBAA are concerned that as currently defined, the definitions of "health care" and "individual" do not encompass all of the activities necessary to carry out the procurement and distribution of eyes and eye tissue.

A. "Health Care"

Under the proposed regulations, no authorization is required for the use or disclosure of PHI in connection with "treatment," "payment" or "health care operations." *See* 45 C.F.R. § 164.506(a)(1). The regulations define "treatment" as, among other things, "the provision of health care by, or the coordination of health care . . . among health care providers." *See id.* at § 164.504. "Health care" is defined to include any " . . . [p]rocurement or banking of blood,

sperm, organs, or any other tissue for administration to patients.” *See id.* at § 160.103. In addition, uses or disclosures of the PHI of a deceased individual for research purposes appear not to require an authorization. *See id.* at § 164.506(f). All other uses or disclosures of PHI must be pursuant to a valid authorization, except for the uses and disclosures enumerated as exceptions to the general authorization rule. *See id.* at §§ 508 & 510. One such exception is for uses or disclosures “otherwise required by law.” *See id.* at § 510(n). The regulations, however, create several ambiguities that, if left unchanged, could threaten the ability of eye banks to continue their work.

First, it is unclear whether eyes or eye tissue are within the definition of “health care.” In the transplant community, eyes and eye tissue have always been treated as distinct from vascularized organs and other tissues. Because these regulations do not include eyes or eye tissue in the list of biologicals that may be procured without an authorization, it is unclear whether eyes and eye tissue come within the definition. Therefore, HHS should clarify the definition of “health care” by expressly adding “eyes or eye tissues” to the list of biologicals in the definition.

Second, the use of the term “administration to patients” is problematic because it is unclear as to what activities HHS is referring. The definition does not explain this phrase, nor does the preamble. We are concerned that while the definition includes the term “procurement,” it does not appear to include the distribution and screening activities that are central to eye banks. Therefore, we suggest that HHS modify this definition to include these activities as part of “health care.” Accordingly, we suggest the following modification to the definition of “health care:”

Health care means the provision of care, services, or supplies to a patient and includes . . . (3) Procurement, processing, screening, distribution, or banking of blood, sperm, organs, eyes or eye tissue, and any other tissue.

B. “Individual”

The definition of “individual” is similarly vague and threatens the ability of eye banks to obtain authorization from a decedent’s next-of-kin for the use or disclosure of necessary PHI. The current provision defines “individual” to include “an executor, administrator, or other person authorized under applicable law to act on behalf of the decedent’s estate.” These designated persons clearly may authorize the use or disclosure of PHI of a deceased individual. *See id.* at § 164.504(1)(iii). It is less clear, however, whether the next-of-kin could authorize the use or disclosure of PHI, even if he or she is authorized to donate the eye or eye tissue under state law. Indeed, the definition as proposed suggests otherwise. Eye banks seeking to procure, screen, and distribute viable eyes and eye tissue must act quickly. They would lose valuable time trying to determine whether an individual is designated to act on the behalf of the decedent’s estate. In addition, eye banks are not

equipped to make such determinations. The proposed regulations add a level of complexity and complication that could seriously impede the recovery of viable eyes and eye tissue in a timely manner.

Therefore, we suggest that HHS modify the definition of "individual" in the following manner so as to permit the next-of-kin, if available, to authorize uses or disclosures of PHI related to the eye and eye tissue donation process:

***Individual* means the person who is the subject of the protected health information, except that: (1) "Individual" includes: . . . (iii) With respect to deceased persons, the next-of-kin (as defined under applicable law) or an executor, administrator, or other person authorized under applicable law to act on behalf of the decedent's estate.**

The eye bank community requests these modifications to the definitions to ensure that the proposed regulations do not impede the uses and disclosures that are a necessary part of the flow of information between entities engaged in the procurement and distribution of eyes and eye tissue.

DECEASED PERSONS

III. AAO and EBAA Strongly Support the Research Exception to the Two-Year Period of Confidentiality for the Use and Disclosure of a Deceased Individuals' PHI

The proposed regulations establish the general rule that an individual's PHI remains confidential for two years after that individual's death. The only exception appears to be that the PHI of a deceased individual may be used or disclosed for research purposes without an authorization after death. *See id.* at § 164.506(f). Thus, under this provision, PHI obtained from a deceased individual could be used or disclosed for research purposes without an authorization and without the approval of an Institutional Review Board ("IRB"). AAO and EBAA applaud HHS's recognition of the need for such an exception, but request confirmation that PHI obtained *during the donation process* of eyes and eye tissue can be used or disclosed for research purposes without an individual authorization and without the approval of an IRB.

Research is essential to improving the diagnosis and treatment of diseases and disorders of the eye. When eyes or eye tissue have been donated but are unsuitable for transplantation, the eye tissue is placed with academic teaching hospitals, research facilities and individual ophthalmologists to advance understanding of eye and vision disorders. When notified of a potential donation, an eye bank will use PHI to screen the donation. Requiring an authorization at the screening stage would add a cumbersome step to the

Assistant Secretary for Planning and Evaluation

February 2, 2000

Page 6

process since eye banks do not then know if eyes or eye tissue will be used for transplantation or research. Such a requirement would impede the efforts of eye banks to facilitate important research.

Secondly, subjecting these initial uses or disclosures of PHI for screening purposes to IRB approval, which can take several weeks, would similarly severely hamper the provision of eyes and eye tissue to the researchers. Unlike the researchers who eventually obtain the eyes or eye tissue, eye banks need to use and disclose the PHI during the initial procurement, processing, screening, and distribution process. As noted, this process is extremely time sensitive. In most cases, there are only six hours in which an eye bank can act and maintain the viability of the eyes or eye tissue.

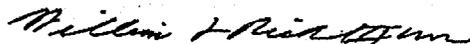
Therefore, AAO and EBAA suggest that HHS maintain the research exception for the use or disclosure of a deceased individual's PHI after death and clarify that this information may be used or disclosed to or by eye banks for research purposes.

IV. Conclusion

AAO and EBAA believe the definitions of "health care" and "individual" should be modified so as to include all activities directly related to the donation process. We also believe the proposed research exception to the post-death two-year period of confidentiality be maintained and clarified to ensure that eye banks can use this information during the donation process for research purposes. We place great importance on maintaining the confidentiality of patient information, but stress that the flow of PHI is absolutely essential for facilitating transplant operations, research, therapy, and the advancement of medical education.

We appreciate the opportunity to share our concerns with HHS.

Respectfully submitted,



William L. Rich III, MD
Secretary for Federal Affairs
American Academy of Ophthalmology
1101 Vermont Avenue, NW, Suite 700
Washington, DC 20005-3570
202-737-6662



Patricia Aiken-O'Neill, Esq.
President/CEO
The Eye Bank Association of America
1015 18th St., NW Suite 1010
Washington, DC 20036
202-775-4999

Attachment A



**EYE BANK
ASSOCIATION
of AMERICA**

Medical Standards

**These Standards have the approval of the Eye Banking Committee
of the American Academy of Ophthalmology**

November 1999

TABLE OF CONTENTS

A1.000 Introduction and Purpose.....	1
A1.100 Scope.....	1
B1.000 Accreditation.....	1
B1.100 Eye Bank Inspection.....	2
C1.000 Personnel and Governance.....	2
C1.100 Director.....	2
C1.200 Medical Director.....	3
C1.300 Technical Staff.....	4
C1.400 Change in Governance.....	4
C2.000 Training, Certification, and Continuing Education of Technical Personnel..	4
C3.000 Facilities.....	5
C3.100 Eye Bank Laboratory.....	5
C3.200 Equipment, Maintenance and Cleaning.....	5
C3.300 Instruments and Reagents.....	6
C3.400 Procedures Manual.....	6
C3.500 Satellite Laboratories.....	7
C3.600 Infection Control and Safety.....	7
C3.700 Waste Disposal.....	7
D1.000 Donor Screening.....	7
D1.100 Screening of Donors.....	8
D1.110 Tissue from donors with the following is potentially hazardous.....	8
D1.120 Contraindications.....	8
D1.200 Documentation of Donor Information.....	12
D1.300 Method of Consent.....	12
D1.400 Donor Age.....	12
D1.500 Interval Between Death, Enucleation, Excision, and Preservation.....	12
D1.600 Eye Maintenance Prior to Enucleation.....	13
D1.700 Living Donors.....	13
E1.000 Procurement and Preservation Procedures.....	13
E1.100 Enucleation Procedure.....	13
E1.200 In situ and Laboratory Removal of the Corneoscleral Rim.....	13
E1.300 Use of Short or Intermediate Term Preservation Medium.....	13

E1.400 Long Term Preservation.....	14
E1.500 Whole Globe Preservation.....	14
E1.600 Scleral Preservation.....	14
F1.000 Tissue Evaluation.....	14
F1.100 Gross Examination.....	14
F1.200 Slit-lamp Examination.....	14
F1.300 Specular Microscopy.....	15
G1.000 Quality Assurance.....	15
G1.100 Quality Control.....	15
G1.200 Testing.....	16
G1.210 Microbiologic Culturing.....	16
G1.220 Serologic Testing.....	16
G1.230 HIV Screening.....	17
G1.240 Hepatitis B Screening.....	17
G1.250 Hepatitis C Screening.....	17
G1.260 HTLV-I and HTLV-II Screening.....	17
G1.270 Syphilis Screening.....	17
G1.280 Non-Required Laboratory Results.....	17
G1.290 Discordant Test Results.....	18
H1.000 Non-Surgical Donor Tissue.....	18
I1.000 Storage.....	18
J1.000 Labeling.....	18
K1.000 Distribution of Tissue.....	19
K1.100 Review of Donor Medical History.....	19
K1.200 Receivers of Tissue.....	19
K1.300 Fair and Equitable System.....	19
K1.400 Returned Tissue.....	19
K1.500 Tissue Recall.....	19
L1.000 Documentation to Accompany Donor Tissue.....	19
L1.100 Tissue Report Form.....	19
L1.200 Package Insert Form.....	20
L2.000 Packaging, Sealing and Packing for Transport.....	21

M1.000 Eye Bank Records.....	21
M1.100 Length of Storage.....	21
M1.200 Confidentiality.....	21
M1.300 Donor Screening Forms.....	21
M1.400 Minimum Information to be Retained.....	21
M1.500 Recipient Follow-Up Information.....	22
N1.000 Amendments.....	23
Index	24

EBAA MEDICAL STANDARDS

A1.000 Introduction and Purpose

These standards have been developed to assure consistently acceptable levels of quality, proficiency, and ethics in dealing with eye tissue for transplantation and define the minimum standards of practice in the procurement, preservation, storage, and distribution of eye tissue for transplantation and research, as determined by the ophthalmological medical community.

A1.100 Scope

These standards are intended to apply to any and all aspects of eye banking, to include:

- Identification and screening of donors
- Procurement of eye and corneal tissue
- Laboratory processing of tissue, including preservation and biomicroscopic examination of tissue
- Storage of tissue
- Distribution of tissue for transplantation, research and teaching

These standards shall be reviewed at least annually and revised as necessary to incorporate current research findings and improved clinical practice.

B1.000 Accreditation

In order for an eye bank to become an accredited member of the Eye Bank Association of America, it must comply with the EBAA Bylaws and the following:

1. Demonstrate compliance with EBAA Medical Standards.
2. Pass the site inspection by the EBAA Medical Standards Committee.
3. Demonstrate proficiency in all aspects of eye banking by procuring, processing and distributing (within the geographic territory it defines as its service area) at least 25 surgical corneas for penetrating keratoplasty annually and provide documentation of their performance.
4. Certify compliance with applicable Federal and State regulations.

Eye Banks applying for EBAA membership must complete the Medical Advisory Board Questionnaire. Pending approval of the EBAA Board of Directors, the applicant may be accepted for provisional EBAA membership and will be subject to an on-site inspection within one year. A provisional member eye bank must complete the accreditation process within one year after obtaining provisional status in the EBAA. Any provisional member eye bank failing to complete the accreditation process after a site inspection will have until the time of the next meeting to correct deficiencies and satisfy accreditation

requirements. If, at the end of this period, the provisional member eye bank fails to meet accreditation standards, it may not proceed to full membership with voting rights.

Once accredited, an eye bank must be inspected and reaccredited at least every three years to maintain accreditation and voting membership in the EBAA.

B1.100 Eye Bank Inspection

The Accreditation Committee of the EBAA shall be responsible for inspecting member Eye Banks as outlined in the written procedures of the Committee.

Accreditation and reaccreditation site inspections shall be scheduled following written notification of the impending inspection. Unannounced inspections may be conducted should an allegation of violation of Medical Standards be made to the committee, or should the results of inspections by official agencies indicate violation of Medical Standards. A copy of the written report of the results of the inspection shall be sent to the Chair of the Accreditation Committee within ten (10) working days of the receipt. The Accreditation Committee shall be copied on all future correspondence relating to the inspection. Failure to permit an inspection will result in suspension or revocation of an eye bank's accreditation.

Demonstration of proficiency in any and all aspects of eye banking may be required during the site inspection and of any or all technical personnel.

C1.000 Personnel and Governance

C1.100 Director

All policies and procedures of each eye bank shall be under the supervision of a Director appointed by the eye bank's Board of Directors, Board of Regents or other governing body. The Director shall be responsible for all administrative operations including compliance with these standards.

The Director shall be the individual responsible for the day-to-day operation of the Eye Bank. It is this individual's responsibility to carry out policies of the Eye Bank's Board, to determine what tissues are to be collected, and to prescribe clinically acceptable means for their processing, quality control, storage and distribution.

The Director, if not a physician, shall consult with the Medical Director, as well as other medical and legal authorities, in carrying out prescribed responsibilities as necessary. These consultations shall be documented and made available for review during a site inspection.

The Director shall provide all staff members with adequate information to perform their duties safely and competently. Delegation of responsibility for the clinical work of the eye bank shall be as follows:

C1.200 Medical Director

The Eye Bank must have a Medical Director. When the Medical Director is not available, a back-up Medical Director shall be designated who is capable of fulfilling the responsibilities of the Medical Director on an interim basis.

The Medical Director must be an ophthalmologist who has completed a corneal fellowship or who has demonstrated expertise in external eye disease, corneal surgery, research or teaching in cornea and/or external disease. If the Medical Director has not served a corneal fellowship, then the eye bank must have and document a consulting relationship with an ophthalmologist who has.

Each Medical Director and co-directors of each member eye bank shall attend the Medical Directors' Symposium at the annual meeting of the EBAA at least once every three years and a Medical Advisory Board meeting once every three years. A newly appointed Medical Director shall attend a Medical Directors' Symposium within one year of appointment, unless a Co-Medical Director has fulfilled the requirement. The eye bank shall provide written documentation of such attendance at the time of the eye bank site inspection.

The Medical Director shall oversee and provide advice on all medical aspects of the Eye Bank operations. These include but are not limited to:

1. Formulation, approval, and implementation of medical policies and procedures.
2. Participation in training and oversight of technical staff with regard to tissue procurement, tissue preservation and tissue evaluation.
3. Participation in establishment and operation of a quality assurance program.
4. Responsibility for verification of competency for tissue procurement and preservation by personnel applying for CEBT certification.

The Medical Director may delegate responsibility for tissue procurement, preservation, and tissue evaluation to qualified eye bank personnel; however, the Medical Director shall ensure that the eye bank operates in compliance with the EBAA Medical Standards. Ultimate responsibility for the suitability of each tissue for the transplantation in patients rests with the transplanting eye surgeon.

An eye bank has three months to replace a Medical Director who has resigned.

C1.300 Technical Staff

The Director shall appoint technical staff and ensure that staff has the appropriate qualifications and training for the performance of their job responsibilities. The Director shall ensure that there are a sufficient number of qualified eye bank technicians and supportive technical staff to promptly and proficiently perform all eye bank laboratory tests and procedures.

Each eye bank must have at least one EBAA certified technician in a supervisory role. If the medical director fulfills this role, he or she must pass an EBAA Technician Certification exam and maintain that certification. For non-certified technicians, the eye bank Executive Director or Medical Director must designate in writing those nonphysician technicians who are qualified and authorized to perform eye bank laboratory procedures.

An eye bank has six months in which to replace the EBAA certified eye bank technician in a supervisory role. The EBAA office and the Chair of the Accreditation Committee shall be notified in writing of the lack of an EBAA certified technician in a supervisory position. If a six month deadline cannot be met, an extension can be granted under the following circumstances: a) the eye bank submits appropriate evidence of its intent to comply with this standard, b) a consulting relationship is established with the Technical Director (CEBT) of an accredited eye bank, and c) the non-CEBT technician in charge in the interim has demonstrated satisfactory proficiency to a member of the EBAA Practical Performance Committee.

C1.400 Change in Governance

An eye bank that undergoes a change in governance must notify the EBAA office and the Chair of the Accreditation Committee (in writing) within 30 days. Changes in governance include merger of eye banks, affiliation of two or more eye banks, affiliation of an eye bank with another non-eye bank organization (E.G. tissue banks, organ procurement organizations, hospitals, blood banks, etc.), a change in the name of the eye bank, or a change in required personnel, i.e. Director, Medical Director.

C2.000 Training, Certification, and Continuing Education of Technical Personnel

An eye bank must provide an orientation program for each new technician and the employee's participation must be documented.

An eye bank must provide educational opportunities such as in-service training programs, attendance at meetings, seminars, and workshops for all technical personnel, including laboratory supervisors, at a frequency that is defined and reasonable for the size and needs of the technical staff.

For an eye bank technician to receive EBAA Certification, he or she must pass the EBAA Technician Certification examination. To sit for the examination, the eye bank technician must be employed by a transplant organization and be recommended by the Executive Director or a physician meeting the requirements of a medical director, as outlined in Section C1.200. A passing grade in both the written and practical portions of the exam will result in EBAA certification, provided that the appropriate fees have been paid. An EBAA certified technician must renew his or her certification at least once every three years by documenting the specified minimum number of continuing education units (CEU's) which have been approved by the EBAA Technician Subcommittee. To maintain certification, a technician must attend an EBAA meeting at least once every three years.

All EBAA accredited eye banks must have one Certified Eye Bank Technician (CEBT) attend an EBAA sponsored skills workshop once every three years. Each eye bank shall institute and document an in-house technician skills review and training for all technical staff on an annual basis.

C3.000 Facilities

Each eye bank must have sufficient space, equipment and supplies to perform the volume of laboratory services with optimal accuracy, efficiency, sterility, timeliness and safety. The EBAA office and the Chair of the Accreditation Committee shall be notified of the relocation of an eye bank.

C3.100 Eye Bank Laboratory

The laboratory must be a separate area with limited access in which activities directly related to eye banking are carried out. The laboratory shall have a sink with a drain and running water. There must be adequate counter space for preparation of donor material. The room including walls, floor and sink must be kept clean at all times. Appropriate documentation of regular laboratory cleaning schedules must be maintained and kept on file for a minimum of three years.

Each eye bank laboratory must have an adequate stable electrical source and a sufficient number of grounded outlets for operating laboratory equipment.

C3.200 Equipment, Maintenance and Cleaning

Each eye bank laboratory shall have a refrigerator with a device, visible without opening the refrigerator, for recording temperature variations. Temperature variations must be recorded daily and remain within the range of 2 to 6° Celsius. These records must be kept for a minimum of three years. The refrigerator's continuous temperature recorder must be calibrated against an NIST standard thermometer at least once a year. The refrigerator shall be maintained for the

use of tissue and tissue storage media and must contain clearly defined and labeled areas for all tissue stored, i.e., quarantined tissue, surgical tissue awaiting distribution, and research tissue.

A laminar airflow cabinet or hood, is required for the preservation of any ocular tissue in the laboratory.

In the event of a power failure, there must be provision for immediate notification and action to be taken, which may include an emergency power supply to maintain essential refrigeration.

Appropriate maintenance and accreditation records must be maintained on each piece of equipment. These records must show dates of inspection, performance evaluations and any maintenance procedures or repairs performed. These records must be kept at least three years.

The eye bank must include in its procedures manual, the monitoring, inspection and cleaning procedures and schedules for each piece of equipment. Documented cleaning schedules for laboratory equipment must be kept on file for a minimum of three years.

C3.300 Instruments and Reagents

Adequate instrumentation must be available to provide for sterile removal of whole eyes and corneas. Instruments must be inspected frequently enough to assure that they function properly. An eye bank that uses autoclave to sterilize its instruments shall adhere to the maintenance procedures for autoclaves in the Procedures Manual, (Section C3.200) or if instruments are sterilized outside of the eye bank, the eye bank shall provide documentation of appropriate sterilization.

All sterilized instruments, supplies and reagents, such as corneal preservation medium, must contain sterilization dates, method or appropriate expiration dates that are current at all times if applicable.

C3.400 Procedures Manual

Each eye bank shall maintain its own procedures manual that details all aspects of its specific retrieval, processing, testing, storage, distribution, and quality assurance practices. Each procedure must be initially approved, signed, and dated by the Director and Medical Director. An annual review of each eye bank's procedure with signing and dating by the Director and Medical Director is required. Each eye bank must maintain copies of each procedure it uses and the length of time the procedure was in use.

C3.500 Satellite Laboratories

Satellite laboratories that either process or distribute tissue must have a certified technician and be supervised by and have access to a qualified Medical Director or his/her delegate. Such satellite laboratories must be inspected as part of the accreditation process of the parent bank.

C3.600 Infection Control and Safety

Written safety procedures for the eye bank operation shall be established in compliance with the Occupational Safety and Health Act (OSHA Act) of 1970 and the 1991 amendments to Part 1910 of title 29 of the Code of Federal Regulations, Subpart Z and/or applicable state statutes, which may supersede. All eye bank personnel must operate under the current Universal Precautions for health care workers issued by the Centers for Disease Control (CDC) of HHS.¹ These written procedures must be included in the eye bank's procedure manual.

C3.700 Waste Disposal

Human tissue and waste items shall be disposed of in such a manner as to minimize any hazard to Eye Bank personnel and the environment and to comply with state and federal regulations. Dignified and proper disposal procedures shall be used to obviate recognizable human remains and must be documented.

D1.000 Donor Screening

All donors must be identified by name. All prospective donors shall undergo a thorough physical examination as close as possible prior to donation with special attention to physical signs of HIV disease, infectious hepatitis, and injecting drug use. Each eye bank shall have a consistent policy for conducting and documenting this examination. Each eye bank shall also have a consistent policy for examination and documentation of the prospective donor's available medical record and death investigation. Review of all available records on each donor shall be performed by an individual who is qualified by profession, education, or training to do so, and who is familiar with the intended use of the tissue.

Medical and social history are important aspects of donor evaluation. Adequate donor evaluation includes:

- (1) serologic testing (see Section G1.200)
- (2) physical assessment of the donor (see above paragraph)
- (3) tissue evaluation (see F1.000)

¹ On December 6, 1991, the Occupational Safety and Health Administration (OSHA) of the U.S. Department of Labor (DOL) published its final rules regulating worker occupational exposure to bloodborne pathogens, including but not limited to hepatitis B virus (HBV) and human immunodeficiency virus (HIV). These regulations went into effect March 6, 1992, and make employers responsible for providing and ensuring safe working conditions in all work settings. See the December 6, 1991, *Federal Register*, Vol. 56, no. 235.

- (4) donor history evaluation: this must include the donor's name and donor information obtained from at least one of the following:
- a) pathologist or medical examiner physical assessment of death report
 - b) police investigation report (accompanied by a and/or c)
 - c) medical examiner's investigative report
 - d) family interview
 - e) medical record or hospital chart
 - f) treating physician interview
- (5) medical director oversight to review any donor information where questions arise in the above areas (C1.200). This shall be documented.
- (6) Information shall be sought for available sources to rule out the possibility of CJD and other related diseases, specifically evaluating (a) change in cognition, (b) Cerebellar dysfunction, (c) speech abnormalities, (d) upper motor neuron signs such as myoclonus. This standard shall not be implemented until further data is obtained from a newly formed subcommittee using outside experts in the field of Prion disease.

D1.100 Screening of Donors Must be Conducted for the Following:

D1.110 Tissue from donors with the following is potentially hazardous to eye bank personnel and requires special handling:

- Active Viral Hepatitis
- Acquired Immunodeficiency Syndrome (AIDS) or HIV seropositivity
- Active viral encephalitis or encephalitis of unknown origin
- Creutzfeldt-Jacob Disease
- Rabies

D1.120 Contraindications

Tissue from donors with the following are potentially health threatening for the recipient(s) or pose a risk to the success of the surgery and shall not be offered for surgical purposes:

A. Penetrating Keratoplasty

1. Death of unknown cause
2. Death with neurologic disease of unestablished diagnosis
3. Creutzfeldt-Jacob disease and family history of a blood relative with Creutzfeldt-Jacob disease
4. Subacute sclerosing panencephalitis
5. Progressive multifocal leukoencephalopathy
6. Congenital rubella
7. Reyes Syndrome

8. Active viral encephalitis or encephalitis of unknown origin or progressive encephalopathy
9. Active septicemia (bacteremia, fungemia, viremia)
10. Active bacterial or fungal endocarditis
11. Active viral hepatitis
12. Rabies
13. Intrinsic eye disease
 - a. Retinoblastoma
 - b. Malignant tumors of the anterior ocular segment or known adenocarcinoma in the eye of primary or metastatic origin
 - c. Active ocular or intraocular inflammation: conjunctivitis, scleritis, iritis, uveitis, vitreitis, choroiditis, retinitis
 - d. Congenital or acquired disorders of the eye that would preclude a successful outcome for the intended use, e.g., a central donor corneal scar for an intended penetrating keratoplasty, keratoconus, and keratoglobus
 - e. Pterygia or other superficial disorders of the conjunctiva or corneal surface involving the central optical area of the corneal button
14. Prior intraocular or anterior segment surgery
 - a. Refractive corneal procedures, e.g., radial keratotomy, lamellar inserts, etc.
 - b. Laser photoablation surgery
 - c. Corneas from patients with anterior segment (e.g., cataract, intraocular lens, glaucoma filtration surgery) may be used if screened by specular microscopy and meet the Eye Bank's endothelial standards.
 - d. Laser surgical procedures such as argon laser trabeculoplasty, retinal and panretinal photocoagulation do not necessarily preclude use for penetrating keratoplasty but should be cleared by the medical director.
15. Leukemias
16. Active disseminated lymphomas
17. Hepatitis B surface antigen positive donors (as specified in Section G1.230)

18. Recipients of human pituitary-derived growth hormone (pit-hGH) during the years from 1963-1985²
19. HTLV-I or HTLV-II infection
20. Recipient of Dura Mater graft
21. Hepatitis C Seropositive donors
22. HIV Seropositive donors (as specified in Section G1.220)
23. HIV or high risk for HIV: Persons meeting any of the following criteria should be excluded from donation:

Behavioral/History Exclusionary Criteria: (May, 1994 CDC Guidelines)

- a. Men who have sex with another man in the preceding 5 years.
- b. Persons who reported nonmedical intravenous, intramuscular, or subcutaneous injection of drugs in the preceding 5 years.
- c. Persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates.
- d. Men and women who have engaged in sex for money or drugs in the preceding 5 years.
- e. Persons who have had sex in the preceding 12 months with any person described in items a-d above or with a person known or suspected to have HIV infection.
- f. Persons who have been exposed in the preceding 12 months to known or suspected HIV-infected blood through percutaneous inoculation or through contact with an open wound, non-intact skin, or mucous membrane.
- g. Inmates of correctional systems. (This exclusion is to address issues such as difficulties with informed consent and increased prevalence of HIV in this population.)

Specific Exclusionary Criteria for Pediatric Doctors:

- h. Children meeting any of the exclusionary criteria listed above for adults should not be listed as donors.
- i. Children born to mothers with HIV infection or mothers who meet the behavioral or laboratory exclusionary criteria for adult donors (regardless of their HIV status) should not be accepted as donors unless HIV infection can be excluded in the child as follows:

² Potential donors who received pituitary-derived growth hormone (pit-hGH) during childhood at any time during the years from 1963-1985 should not be accepted as eye or corneal donors because of potential risk of transmitting Creutzfeldt-Jacob disease (CJD). Some 7,000 U.S. children received therapeutic pit-hGH through early 1985 and there are unknown numbers of persons who may have used this drug non-therapeutically, e.g., during rigorous physical training. All known recipients and their treating endocrinologists have been notified and a fact sheet is available, HHH Publication No. 88-2793, December 1987.

Children >18 months of age who are born to mothers with or at risk for HIV infection, who have not been breast fed within the last 12 months, and whose HIV antibody tests, physical examination, and review of medical records do not indicate evidence of infection can be accepted as donors.

- j. Children ≤18 months of age who are born to mothers with or at risk for HIV infection or children of mothers with or at risk of HIV infection who have been breast fed within the past 12 months should not be accepted as donors regardless of their HIV tests results.

Laboratory and Other Medical Exclusionary Criteria:

- k. Persons who cannot be tested for HIV infection because of refusal, inadequate blood samples (e.g. hemodilution that could result in false-negative tests), or any other reason.
- l. Persons with repeatedly reactive screening assay for HIV-1 or HIV-2 antibody regardless of the results of the supplemental assays.
- m. Persons whose history, physical examination, medical records, or autopsy reports reveal other evidence of HIV infection or high-risk behavior, such as a diagnosis of AIDS, unexplained weight loss, night sweats, blue or purple spots on the skin or mucous membranes typical of Kaposi's sarcoma, unexplained lymphadenopathy lasting >1 month, unexplained temperature >100.5 F (38.6 C) for >10 days, unexplained persistent diarrhea, male-to-male sexual contact, a history of syphilis or gonorrhea within the previous 12 months, or needle tracks or other signs of parenteral drug abuse.

B. Lamellar or Patch Grafts

Criteria are the same as listed for penetrating keratoplasty except that tissue with local eye disease affecting the corneal endothelium or previous ocular surgery that does not compromise the corneal stroma, e.g., aphakia, iritis, is acceptable for use.

C. Epikeratoplasty

Criteria are the same as listed for penetrating keratoplasty except that tissue with local eye disease affecting the corneal endothelium, e.g., aphakia, iritis, is acceptable for use. Death to preservation time may be extended.

D. Scleral Tissue

Criteria are the same as listed for penetrating keratoplasty except that tissue with local eye disease affecting the corneal endothelium, e.g., aphakia, iritis, is acceptable for use. Death to preservation time may be extended.

D1.200 Documentation on Donor Information

Donor screening forms and/or copies of medical charts, medical examiner or coroner review forms and gross autopsy results must be completed and retained on all donated eye tissue as part of the donor record. *See Section L1.000.*

A unique donor identifying number, i.e, medical examiner or coroner case number, hospital medical record number, social security or driver's license number, shall be obtained and recorded in the donor record.

D1.300 Method of Consent

Documentation of legal consent for enucleation or in situ excision is essential for medical-legal reasons. Consent procedures and forms must conform with state law and documentation for consent must be retained. In medical examiner's/coroner's cases, the eye bank shall adhere to the consent regulations specified by the medical examiner's or coroner's legislation in its state. In each case the consent designation and restrictions, if any, must be adhered to and cannot be altered without the witnessed resigning or redesignation of the legally appropriate consentor.

D1.400 Donor Age

Since no definite relationship has been established between the quality of donor tissue and age, the upper and lower age limit is left to the discretion of the Medical Director.

D1.500 Interval Between Death, Enucleation, Excision and Preservation

Acceptable time intervals from death, enucleation or excision to preservation may vary according to the circumstances of death and interim means of storage of the body. It is generally recommended that corneal preservation occur as soon as possible after death. All time intervals for each donor, i.e., the time of death to the time of enucleation and preservation and/or the time to corneal excision, shall be recorded. If the donor has been refrigerated prior to enucleation or in situ corneal excision, this information shall be noted.

D1.600 Eye Maintenance Prior to Enucleation

The prospective donor's corneal integrity should be maintained. Recommended procedures for eye maintenance shall be found in the procedures manual. Each individual eye bank's procedure is left to the discretion of the Medical Director and shall be clearly documented.

D1.700 Living Donors

Eye tissue that is removed and processed for surgical use from a living donor shall have the same standards applied as for all cadaveric tissue, e.g., the same donor medical history shall be obtained, the same records, serology, etc. No extended quarantine period, outside the usual 24-48 hours for serology results, shall be required for corneal tissue used for transplantation that is stored in short or immediate term culture medium.

E1.000 Procurement and Preservation Procedures

Specific procurement procedures can be found in the EBAA Procedures Manual. Variations of these procedures are at the discretion of the eye bank's Medical Director as long as they do not violate standard aseptic practice and are documented. This manual has been approved by the Medical Policy and the Technician's Subcommittees, and shall be periodically reviewed and modified as necessary.

The Medical Director and Director are responsible for assuring that eye bank personnel comply with all applicable procedures for the procurement and preservation of tissue.

E1.100 Enucleation Procedure

Ultimate responsibility for personnel to perform enucleation rests with the Director, the Medical Director and existing state law.

E1.200 In Situ and Laboratory Removal of Corneoscleral Rim

Removal of the corneoscleral rim shall be performed using sterile technique by individuals specifically trained in in situ retrieval and/or laboratory removal of the corneoscleral segment. Laboratory removal must be performed with a laminar air flow hood or cabinet which meets either Federal Standard 209(b) as a Class 100 Hood or National Sanitation Foundation (NSF) Standards as a Class II or Class III cabinet, or in an operating room. For in situ corneal removal, the eye shall be examined with the use of a penlight prior to excision.

E1.300 Use of Short or Immediate Term Preservation Medium

Eye Banks shall use an appropriate corneal storage medium that has been manufactured in accordance with FDA Good Manufacturing Practices. The

medium shall be used and stored according to the manufacturer's recommendations for temperature, date and other factors. The manufactured medium purchased and shipped to the eye bank shall be inspected for damage upon arrival. The lot number of medium used for each cornea shall be recorded on the tissue report containing the unique I.D. number of the tissue to allow tracking and recall.

E1.400 Long Term Preservation

Some eye banks employ long-term preservation of corneal tissue, such as organ culturing. While these methods are not in widespread use, an eye bank that uses long-term preservation shall carefully document the procedure in their procedures manual, and adhere to rigid aseptic technique.

E1.500 Whole Globe Preservation

Procedures for whole globe preservation may be found in the EBAA Procedures Manual. Eye banks that store whole eyes for lamellar or refractive keratoplasty shall employ aseptic practice using one of the preservation methods given in the procedures manual. The selected preservation method must be documented in the eye bank's own procedures manual.

E1.600 Scleral Preservation

Various methods of preserving sclera may be found in the EBAA Procedures Manual. Eye banks shall preserve sclera tissue aseptically, using one of these methods. The selected preservation method must be documented in the eye bank's own procedures manual. A preservation date for scleral tissue shall be indicated.

F1.000 Tissue Evaluation

The ultimate responsibility for determining the suitability of the tissue for transplantation rests with the transplanting surgeon.

F1.100 Gross Examination

The corneal-scleral segment shall be initially examined grossly for clarity, epithelial defects, foreign objects, contamination and scleral color, e.g., jaundice.

F1.200 Slit-lamp Examination

The cornea shall be examined for epithelial and stromal pathology and in particular endothelial disease. Enucleated whole globes shall be examined in the laboratory prior to distribution and/or corneal excision. If in situ corneal

excision is performed, examination of the donor eye anterior segment with a penlight or a portable slit lamp is required. After corneal excision, the corneal-scleral rim shall be evaluated by slit lamp biomicroscopy, even if the eye donor has been examined with the slit lamp prior to excision of the corneal-scleral rim, to insure that damage to the corneal endothelium or surgical detachment of Descemet's membrane did not occur.

The minimum information that must be documented with the slit lamp biomicroscopy is outlined in the EBAA Procedures Manual.

F1.300 Specular Microscopy

Specular microscopy may provide additional useful information in screening donor corneal tissue to determine suitability for transplantation. If the eye bank utilizes specular microscopy, it must have a written procedure that includes how information is used.

G1.000 Quality Assurance

Each eye bank shall have a formally established quality assurance program. This program shall include ongoing monitoring and evaluation of activities, identification of problems, and development of plans for corrective actions. These standards shall provide the basis for development of the QA program. Each eye bank shall document all aspects of its QA program and maintain records of all QA activities for a minimum of ten years. These include any corrective or remedial action taken for detected deficiencies. These records shall be available for review at the time of site inspection.

The eye bank's quality assurance program shall include a method for the receiving surgeon to report adverse reactions from the transplantation of corneal, scleral, or other ocular tissue to the source eye bank which in turn, must forward the adverse reaction information within a reasonable time to the EBAA office for review by the Medical Advisory Board. If systemic infectious disease such as HIV, hepatitis, or syphilis develops in a recipient, whether or not it is suspected to be due to donor tissue, this must be reported to the EBAA. An Adverse Reaction file shall be available for review by the site inspectors at the time of inspection and must be kept for a minimum of ten years. Serious adverse reactions shall be reported immediately to the EBAA office for review by the Medical Advisory Board. The Medical Director shall receive and review all adverse reaction reports, documenting any corrective actions he/she determines are indicated.

G1.100 Quality Control

The Director shall prescribe tests and procedures for measuring, assaying or monitoring properties of tissues essential to the evaluation of their safety for transplantation, e.g., hepatitis B surface antigen and human

immunodeficiency virus (HIV) antibody, and conform with federal requirements as well as individual state laws. Results of all such tests or procedures, together with evaluations based on these findings, shall become part of permanent record of all tissues processed.

G1.200 Testing

If an eye bank performs its own microbiologic or serologic testing, it must meet applicable accreditation requirements established under the Clinical Laboratories Improvement Act (CLIA). Verification of satisfactory compliance with a College of American Pathologists (CAP) Proficiency Testing Program, or other proficiency testing program approved by CLIA, shall be available at the time of the site inspection.

G1.210 Microbiologic Culturing

Culturing of Eye Bank donor eyes is advised despite the recognition by many that bacteriologic contamination of donor eyes does not necessarily lead to infection and that presurgical or surgical cultures may not correlate with postoperative infection if it should occur. Cultures may be performed either before and/or at the time of surgery.

A. Presurgical Cultures

Eye Banks may elect to perform corneal-scleral rim cultures at the time of corneal preservation in tissue culture medium. Positive culture reports shall be reported to the receiving surgeon or recipient eye bank.

B. Surgical Culturing

Each eye bank shall recommend culturing of the corneal-scleral rim for corneal transplantation, or a piece of sclera for scleral implantation at the time of surgery. Positive results in cases of postoperative infection shall be reported to the eye bank that procured the tissue as well as to the eye bank that distributed the tissue.

G1.220 Serologic Testing

Sections G1.230-G1.270 specify the EBAA required serologic tests which must be performed on each donor from which tissue is designated for surgical use.

Plasma Dilution Donor Evaluation: Each eye bank shall document on each transplant donor whether blood loss was known or suspected as determined by the Medical Director or qualified designee and whether the donor received any infusion/transfusion of crystalloids and/or colloids and blood. An algorithm meeting FDA regulations shall be used to record

infusion/transfusion volumes given to each donor within 48 hours prior to obtaining the blood sample for serologic testing on every donor with blood loss, and on every donor age 12 and under receiving any amount of infusion/transfusion preceding sampling. If the total volume infused/transfused is equal to or in excess of the donor's total blood volume or plasma volume, the sample is not suitable for testing.

Autologous blood and autologous blood product infusion is excluded from calculations.

G1.230 HIV Screening

All member eye banks must have operational an HIV-1/HIV-2 screening program using an FDA approved test for all donors of surgically designated tissue. To comply with FDA requirements, a negative screening test must be documented prior to release of tissue for transplantation.

G1.240 Hepatitis B Screening

All member eye banks must have an operational hepatitis B screening program using an FDA approved test for hepatitis B surface antigen for all donors of surgically designated tissue. To comply with FDA requirements, a negative screening test must be documented prior to the release of tissue for transplantation.³

G1.250 Hepatitis C Screening

All member eye banks must have an operational Hepatitis C screening program using an FDA approved test for all donors of surgically designated tissue. To comply with FDA requirements, a negative screening test must be documented prior to release of tissue transplantation.

G1.260 HTLV-I and HTLV-II Screening

Donor screening for HTLV-I and HTLV-II is not required.

G1.270 Syphilis Screening

Serologic screening for syphilis is not required.

G1.280 Non-Required Laboratory Results

If laboratory results of non-required tests for infectious disease are reported for tissue for transplantation to the eye bank, they must be taken into account and/or acted upon by the medical director.

³ The EBAA recognizes the use of neutralization assay or confirmatory tests as scientifically valid.
EBAA Medical Standards-November 1999

G1.290 Discordant Test Results

All member eye banks must report conflicting serologic test results. In addition, results of other serologic tests that are not required but may be indicative of risk for HIV or hepatitis must also be reported within 60 days.

H1.000 Non-Surgical Donor Tissue

If donor tissue is provided for purposes other than surgery, e.g., research, practice surgery, etc., and if that donor tissue is not screened for HIV or Hepatitis, a label stating that screening for HIV-antibody, Hepatitis B or Hepatitis C has not been carried out or stating "potentially hazardous biologic material" or some other designation acceptable under the guidelines of the CDC must be attached to the container used for the donor tissue storage and/or transport.

I1.000 Storage

All surgical tissue shall be stored in quarantine until results of HIV, HBsAg, HCV, and any other relevant donor screening tests have been recorded as non-reactive.

All tissue shall be stored aseptically at a temperature appropriate to the method of preservation used. Eye banks must precisely document their procedures for storage of corneal tissue, whether it is in the form of the whole eye or the cornea only in an appropriate medium.

J1.000 Labeling

Each corneal or scleral tissue container shall be clearly and indelibly labeled to include at least the information below.

1. Name of source eye bank.
2. Tissue identification number. *There must be a unique identification number for each ocular tissue or fraction thereof that is distributed for surgical use.*
3. Type of tissue.
4. Date and time of donor's death.
5. Date and time of corneal/scleral preservation.
6. Preservation date for scleral tissue and long-term preserved tissue.
7. A statement that the tissue is intended for single patient application only and that it is not to be considered sterile and that the FDA therefore recommends culturing or reculturing.
8. A statement that the tissue was procured from a donor who was non-reactive when tested for HIV antibody, hepatitis B surface antigen (HbsAg), and hepatitis C antibody (HCV).
9. Type of preservation medium.

K1.000 Distribution of Tissue

K1.100 Review of Donor Medical History

Prior to distribution of tissue for transplantation, the Medical Director or his/her designee shall review and document that the medical and laboratory information is in accordance with medical standards.

K1.200 Receivers of Tissue

Tissue shall be distributed to physicians, dentists, institutions and other eye banks.

All tissue sent from EBAA accredited eye banks to eye banks in this or other countries must comply with the standards defined by the EBAA Medical Advisory Board.

K1.300 Fair and Equitable System

Eye banks shall establish and document a system of distribution that is just, equitable and fair to all patients served by the eye bank. Documentation of distribution (time and date of requests for, offers of, and delivery of eye tissue) shall be available for inspection by the Accreditation Committee. Access to tissue shall be provided without regard to recipient sex, age, religion, race, creed, color or national origin.

K1.400 Returned Tissue

For corneas returned and redistributed, tissue transportation and storage information must be documented and made available to the eye bank and transplanting surgeon.

K1.500 Tissue Recall

Eye banks must have a policy and procedure for potential recall of tissue.

L1.000 Documentation to Accompany Donor Tissue

L1.100 Tissue Report Form

For special research studies, by recommendation of the Medical Advisory Board and approved by the EBAA Board of Directors, certain specific data may be masked on the tissue report form and label. A copy of the

tissue report form and/or donor screening form shall accompany the tissue.
The tissue report shall contain the following:

Name of (Source) Eye Bank

Location of Eye Bank

Telephone Number of Eye Bank

Eye Bank identification number unique to each tissue graft

Type of preservation medium

Age of donor

Cause of death

Death date and time

Preservation date and time

Name of technician who enucleated, excised, and evaluated the tissue

Slit lamp report/date

Specular microscopy report/date

EBAA Accreditation Status of Eye Bank

For a medical examiner tissue procured under legislative consent, a statement shall be added to advise the receiving surgeon that the tissue was determined to be suitable for transplantation in the absence of a donor medical history interview.

A summary of records reviewed regarding the suitability of tissue for transplant as described in the FDA Final rule 1270.33(d).

L1.200 Package Insert Form

A "Package Insert" form that meets the EBAA requirements defined below shall accompany the tissue for transplantation. This form shall include the following:

1. Recommended storage temperature for specific type of tissue (cornea; sclera; whole globe). Specific emphasis on DO NOT FREEZE for corneas.
2. That the surgeon should check for integrity of the seal and immediately report to the eye bank any evidence of possible tampering.
3. For corneas in Optisol. That color change per the manufacturer's guidelines may indicate a change in pH, in which case the tissue should not be used and a report made immediately to the eye bank.
4. Whether pre-surgical microbiologic cultures were performed by the eye bank, including the advisement that cultures of the donor rim and sclera should be performed at the time of surgery.
5. The form shall also advise the receiving surgeon that the tissues are delivered with no warranty as to merchantability or fitness for a particular purpose, and that the receiving surgeon is ultimately responsible for judging if the tissue is suitable for use.
6. Serologic tests were performed by a laboratory which was approved by CLIA or CAP.

7. The U.S. Food and Drug Administration (FDA) approved tests used for serology are approved for pre-mortem blood samples but have not been validated for cadaveric blood.

This information may be included on the eye bank's donor screening form as long as it is easily noticed; otherwise a separate package insert form is advised.

L2.000 Packaging, Sealing and Packing for Transport

Each tissue shall be individually packaged and sealed with a tamper-evident seal.

The tissue shall be packed in a water-proof container with wet ice, so as to maintain the temperature of the tissue at an acceptable level. Packing shall be done so that the package insert and tissue label do not become wet. Special instructions shall be included on a Package Insert. See *Section L1.200*.

M1.000 Eye Bank Records

M1.100 Length of Storage

All records shall be kept for a minimum of ten years from the date of transplantation/implantation, distribution or whichever is longer.

M1.200 Confidentiality

All eye bank records and communications between the eye bank and its donors and recipients shall be regarded as confidential and privileged.

M1.300 Donor Screening Forms

Donor screening forms shall contain information regarding the circumstances surrounding the death of a donor and adequate medical history so that the suitability of the tissue for transplantation may be judged.

M1.400 Minimum Information to be Retained

Forms for retaining donor and recipient information shall be established for permanent record and shall be readily accessible for inspection by the EBAA Accreditation Committee. Eye Bank records shall include the following minimum information:

See Section L1.000 for information to be included on the Tissue Report Form.

Eye bank identification number unique to each tissue graft

Name of eye bank
Type of preservation medium
Preservation media lot numbers
Unique donor identification number
Name of donor (or if import tissue, name of importing eye bank and their unique ID number)
Age of donor
Cause of death
Death date and time
Enucleation or in-situ excision date and time
Preservation date and time
Slit lamp report
Specular microscopy (if done)
Name of enucleator/evaluator/technician
Name of surgeon receiving tissue
Recipient identification readily traceable to each unique graft number
(See Section M1.500)
Date, time, method of transportation
Utilization of tissue: i.e., surgical, research, training
Printed results of all EBAA required serologic screening tests
Microbiologic screening results if performed
Microbiologic reports of positive donor rim cultures from the receiving surgeon if reported
Adverse reactions if reported

M1.500 Recipient Follow-Up Information

1. Each eye bank shall retain recipient information from each using surgeon on each surgically used tissue. This information shall be obtained and retained by the distributing eye bank.
2. This information shall include the following:

Patient's name

Unique identification according to the following order of preference:

Social security number

Driver's license number

Hospital information number

Alien identification

Passport number

Age

Date of Birth

Diagnosis

Name of surgeon receiving transplanting tissue

Date of surgery

Location of surgery

Post-operative complications (tissue related)

3. Scleral tissue may be stocked at an institution only if it is for single patient use; the distributing eye bank must be notified of the recipient information when tissue is used and must be able to track the tissue.
4. Each eye bank must seek recipient follow-up information concerning possible adverse reactions on all tissue distributed between three and twelve months postoperatively.

N1.000 Amendments

These standards may be amended as required.

The Medical Advisory Board shall be charged with proposing amendments to these standards as medical technology, techniques and information require. A comment period may be provided prior to the intended effective date.

INDEX

Accreditation.....	1,2,4-7,16,19-21
Adverse Reactions.....	15,22,23
Amendments.....	7,23
Anterior segment surgery.....	9
Aseptic practice.....	13,14
Bacteriologic contamination.....	16
Biomicroscopic examination.....	1
Blood volume.....	17
Cataract.....	9
CDC.....	7,10,18
Certified technician.....	4,5,7
Choroiditis.....	9
Clarity.....	14
Cleaning.....	5,6
CLIA.....	16,20
Colloids.....	16
Confidential.....	21
Congenital rubella.....	8
Conjunctivitis.....	9
Consent.....	10,12,20
Contraindications.....	8
Coroner.....	12
Creutzfeldt-Jacob.....	10
Crystalloids.....	16
Director.....	2-4,6,13,15
Dilution of the donor's blood.....	11
Disseminated lymphomas.....	9
Distribution.....	1,2,6,14,19,21
Documentation.....	1,3,5-7,12,19
Donor age.....	12,17
Donor information.....	8,12
Donor screening.....	1,9,12,17-19,21
Encephalitis.....	8,9
Endocarditis.....	9
Enucleation.....	12,13,22
Epikeratoplasty.....	11
Epithelial.....	14
Equipment.....	5,6
Ethics.....	1
Exclusionary criteria.....	10,11
Eye bank records.....	21
Eye maintenance.....	13
Facilities.....	5
FDA.....	13,16-18,20,21

Federal requirements.....	16
Federal Standard 209(b).....	13
Glaucoma filtration.....	9
Gross examination.....	14
HCV.....	18
Hepatitis.....	18
Hepatitis B.....	7,9,15,17,18
Hepatitis B surface antigen.....	9,15,17,18
Hepatitis C.....	10,17,18
Hepatitis C seropositive donors.....	10
High risk for HIV.....	10
HIV.....	7-12,15-18
HIV screening.....	17
HTLV-I.....	10,17
HTLV-II.....	10,17
Human pituitary-derived growth hormone.....	10
Human tissue.....	7
In situ.....	12-14
Infection.....	7,10,11,16
Infection control.....	7
Infusion.....	16,17
Inspection.....	1-3,6,15,16,19,21
Instruments and reagents.....	6
Intermediate term preservation medium.....	13
Intravenous.....	10
Intrinsic eye disease.....	9
Iritis.....	9,11,12
Jaundice.....	14
Karposi's Sarcoma.....	11
Keratoconus.....	9
Keratoglobus.....	9
Label.....	16,18,19,21
Labeling.....	18
Laboratory.....	1,4-6,10,11,13,14,17,19,20
Lamellar.....	9,11,14
Laser photoablation.....	9
Laser trabeculoplasty.....	9
Leukemias.....	9
Living donors.....	13
Maintenance.....	5,6,13
Malignant tumors.....	9
Medical Advisory Board.....	1,3,15,19,23
Medical Director.....	2-9,12,13,15-17,19
Medical examiner.....	8,12,20
Medical history.....	13,19-21
Medical policy.....	13

Medical record.....	7,8,11,12
Medical Standards Committee.....	1
Microbiologic testing.....	16
Monitoring.....	6,15
National Sanitation Foundation (NSF) Standards.....	13
Non-Required laboratory results.....	17
OSHA.....	7,17
Package insert.....	20,21
Packing.....	21
Penetrating keratoplasty.....	1,8,9,11,12
Personnel.....	2-4,7,8,13
pH.....	20
Plasma volume.....	17
Positive culture results.....	16
Preservation.....	1,3,6,11-14,16,18,20,22
Presurgical cultures.....	16
Procedures Manual.....	6,13-15
Procurement.....	1,3,4,13
Proficiency testing.....	16
Progressive multifocal leukoencephalopathy.....	8
Provisional member.....	1,2
Pterygia.....	9
Quality assurance.....	3,6,15
Quality control.....	2,15
Quarantined tissue.....	6
Rabies.....	8,9
Radial keratotomy.....	9
Refractive corneal procedures.....	9
Refrigerator.....	5
Retinitis.....	9
Retinoblastoma.....	9
Returned tissue.....	19
Reyes Syndrome.....	8
Safety.....	5,7,15
Satellite laboratories.....	7
Sclera.....	12-16,18,20,23
Scleritis.....	9
Sclerosing panencephalitis.....	8
Screening.....	1,7,8,11,12,15,17,18,20-22
Seal.....	20,21
Septicemia.....	9
Serologic tests.....	16,18,20
Serologic testing.....	7,16,17
Slit lamp.....	15,16,21,23
Specific Exclusionary Criteria.....	10
Specular microscopy.....	9,15,20,22

State laws.....	16
Stromal pathology.....	14
Surgical culturing.....	16
Syphilis.....	11,15,17
Technical staff.....	3-5
Technician subcommittees.....	5
Test results, non-required.....	17
Time intervals.....	12
Tissue Recall.....	19
Training.....	3-5,7,10,22
Transfusion.....	16,17
Transplantation.....	1,3,13-17,19-21
Transplanting surgeon.....	14,19
Transport.....	18,19,21,22
Universal Precautions.....	7
Uveitis.....	9
Warranty.....	20
Waste disposal.....	7

18th St. N.W.
1010
. DC 20036
775-4999

Dockets Management Branch (HEA-305)
Food and Drug Administration

5630 Fishers Ln. Rm 1061

Rockville, MD 20852

0179 L28

