

# MEBTC

MIDWESTEYE-BANKSANDTRANSPLANTATIONCENTER

11/24 '99 08:29 10:05

December 28, 1999

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

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

Dear Commissioner Henney:

The Midwest Eye-Banks & Transplantation Center (MEBTC) appreciates the opportunity to comment on the Food and Drug Administration's (FDA) proposed rule: **Suitability Determination for Donors of Human and Tissue Based Products**. MEBTC is a 501 (c)(3) not-for-profit organization whose mission is to procure and provide donated human eye tissue of the highest quality for sight restoring transplantation procedures. MEBTC is comprised of the Michigan Eye-Bank, the Illinois Eye-Bank and the BroMenn Watson Gailey Eye-Bank. These three banks provide over 2,500 corneas each year for transplant.

MEBTC banks are founding members of the Eye Bank Association of America (EBAA) and participate at all levels of the Association. We actively support the Association's programs in the establishment of Medical Standards, the accreditation of eye banks and the education programs for eye bank technicians, ophthalmologists and researchers.

MEBTC worked closely with the EBAA in the development of the Association's comments on the proposed rule. We strongly support the Association's position as stated in the attached documents.

Sincerely,



Florence M. Johnston  
President & Chief Executive Officer

Jls: 122899CommentsFDA.ADM.Reg

Enclosure

By UPS Overnight

cc: MEBTC Board of Directors

**97N 484S**  
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ASSOCIATION  
of AMERICA**

*Dedicated to the Restoration Of Sight since 1961*

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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.

EBAA Annual Meeting, Washington, DC, June 21-24, 2000  
EBAA Education Conference, Orlando, FL, October 21-23, 1999  
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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 I3** 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 **8 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-a-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 **safe-guard** 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.**

**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)**

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

*These terms are found through& 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 (**Macsai, Norris, Cornea, 1995; 14:595-600**). It has also been demonstrated (**Goldberg, Laycock, Kinard, Wang, Repose, 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**.

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### **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.

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### **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, eyebanking** 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

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Nicholas Hogan, **MD**, **PhD**  
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**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 w&k 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.

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### **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**.

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### **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 (1) (i)*

Section 127.1.55 (1) (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** 099 1-**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 and 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 law 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. Sugar<sup>1</sup> 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 al<sup>2</sup> 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 al<sup>3</sup> 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 1997. 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 Cavanagh<sup>4</sup> 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:

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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.

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