MEBTC

MIDWEST EYE-BANKS AND TRANSPLANTATION CENTER

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May 7, 2001

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

Ref: Docket No. 97N-484P
Current Good Tissue Practices for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule: 21 CFR Part 1271; Monday, January 8, 2001 Federal Register

Dear Commissioner Henney:

The Midwest Eye-Banks and Transplantation Center (MEBTC) is providing comments on Proposed 21 CFR Part 1271 for three FDA-registered eye banks: Illinois Eye-Bank, Chicago, IL (established 1947), BroMenn-Watson Gailey Eye-Bank, Normal, IL (established 1952) and Michigan Eye-Bank, Ann Arbor, MI (established 1957). MEBTC is the corporate entity for these eye banks that provide eye banking services to the northern two-thirds of Illinois, the entire state of Michigan and northwestern Ohio. Corporately, we provided 2760 corneas for transplant during calendar year 2000.

All three eye banks have received three-year accreditation status from the Eye Bank Association of America, the highest accreditation awarded. In addition, the Michigan Eye-Bank was inspected by the FDA in 1997 and in 2000 and both eye banks in Illinois were inspected by the FDA in 2000. No 483's were issued in any of the four inspections.

In addition to commenting on specific provisions of the Proposed Rule in the attached document, we would like to comment on some of the unique aspects of corneal tissue and eye banking when compared with tissue banks.

In many aspects of operations, eye banks are more similar to organ procurement organizations than to tissue banks. For example, corneas are living tissue whose viability can be maintained by immersion in nutrient medium at controlled temperatures for a limited period of time, just as with kidneys and other solid organs. Corneas are recovered and maintained, not processed, preserved, or stored—again like solid organs.

The determination of suitability for transplant through donor screening is similar for organs, corneas and tissues, but the evaluation of corneas for surgical suitability is distinct. That is, since corneas are living tissue that continue to undergo biologic changes, the structure and integrity of the cornea that can be visualized at any given time may change between evaluations. For this reason corneas are provided with the understanding

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BroMenn-Watson Gailey Eye-Bank
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that it is the surgeon's ultimate responsibility to determine whether any given cornea meets the needs of the intended recipient. Eye banks strongly recommend that surgeons examine corneas with a slit lamp microscope prior to surgery.

Unlike solid organs that have well-established tests of organ function (cardiac output, liver function tests, etc...), there are no tests of cornea function. The specular microscope provides information on the density and morphology of the endothelial cells, but does not indicate how well, if at all, these cells function. Without a functioning endothelial cell layer, corneal clarity cannot be maintained.

MEBTC's comments on specific sections of the proposed rule are attached. In addition, we present these comments with regard to the justification for rule-making expressed in the Supplementary Information:

FDA's cost-benefit analysis, if correct, indicates annualized costs of $1,221,798, compared with yearly benefits in the range of $61,292 to $1,365,936. We believe FDA has not clearly demonstrated any benefit due to reduced retransplantations, and that the cost figures, though detailed, are low. In eye banking, even using FDA's figures, the juice is clearly not worth the squeeze.

FDA's justification for regulation of function and integrity is extraordinarily weak. The entire argument for FDA regulation of function and integrity is based on increased risk of communicable disease transmission from repeat transplants. By FDA's numbers, total primary graft failures range from 7 to 156 per year. FDA assumes that all of these primary graft failures will be prevented by the proposed regulation, but gives no evidence to support any reduction in retransplants required. Given the current disease transmission rate of zero per 50,000 transplants annually, the amount of potential disease that can be attributed to preventable regrafts is, at most, vanishingly small.

We ask FDA to consider carefully what would constitute an appropriate regulatory model for eye banks, to use the existing EBAA regulatory structure where possible, and to lumping industries together for regulatory convenience. The public interest has been well-served by MEBTC and other EBAA eye banks. Careful oversight by FDA can (at least theoretically) improve the safety of corneal transplants, but the proposed rule, painting with an awkwardly broad brush, does not.

We would be happy to respond to any questions you may have regarding this letter or the attached comments.

Sincerely,

Florence M. Johnston
President & Chief Executive Officer

cc: Senior Staff
MEBTC Board of Directors

Part 1271
Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products

Inspection and Enforcement; Proposed Rule

1271.3 Definitions

Adverse reaction: noxious and unintended response to any human cellular and tissue-based product (HCT/P) for which there is a reasonable possibility that the response may have been caused by the product (i.e., relationship can't be ruled out).

Complaint: any written, oral or electronic communication alleging:
- HCT/P has or may have transmitted communicable disease
- function or integrity of HCT/P may have been impaired
- any other problem with HCT/P that could result from failure to comply with current good tissue practice (CGTP)

Product deviation: an event that represents a deviation from CGTP, applicable standards or established specifications; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease agent or disease from an HCT/P to a recipient, or may lead to product contamination, or may adversely affect the function or integrity of the product.

Processing: any activity other than recovery, donor screening, donor testing, storage, labeling, packaging or distribution performed on a HCT/P, including but not limited to preparation, sterilization, steps to inactivate adventitious agents, preservation for storage and removal from storage.

MEBTC comments:

- Corneas are living tissue that are recovered and evaluated, not manufactured. Since there are no nationally accepted scientific standards for what constitutes a "good" cornea, eye banks cannot guarantee their function. There are no set specifications for corneas as noted in the definition of product deviation. We have proxy indicators, i.e., cell counts and cell morphology, that can be taken into account when evaluating tissue, but the outcome may be dependent upon factors beyond the eye bank's control, such as graft/host interaction, surgical factors, recipient compliance with medications and physical instructions and other unknown, uncontrollable issues. MEBTC requests that further information be sought from physicians and scientists in the field.
- MEBTC requests that the definition of adverse reaction found in Eye Bank Association of America (EBAA) Medical Standards be used for corneas. A reportable adverse reaction is defined as any communicable or other disease transmitted by and attributable to transplantation of donor eye tissue, including infection (as manifested by endophthalmitis, keratitis or systemic viral disease) and biologic dysfunction (such as immediate endothelial failure or donor corneal dystrophy). 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.
- EBAA Medical Standard F1.000 *Tissue Evaluation,* states that ultimate responsibility for determining the suitability of the tissue for transplantation rests with the transplanting surgeon. EBAA Medical Standard L1.200 *Package Insert Form* requires the following statement accompany tissue: "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".

Subpart D-Current Good Tissue Practice

1271.150 General

MEBTC comments:

- MEBTC objects to the terms "manufacturer" and "product". Human tissues are generously donated by grieving families and should not be referred to in terms that suggest they are commodities. We request that you consider the term "Tissue Procurement Organization" to replace "manufacturer" for eye banks because human eye tissue is recovered and evaluated, not processed as is bone, veins, heart valves, etc. In this way, the FDA could distinguish between procurement and processing organizations. Additionally, MEBTC requests that the FDA consider "material" or "human cellular and tissue-based material" (HCT/M) to replace product and human cellular and tissue-based product.
- MEBTC requests definition of function and integrity as noted in complaint and product deviation definitions.
- EBAA Medical Standard G1.200 *Testing,* requires infectious disease testing be performed by a lab accredited under CLIA. We feel that the proposed rule is unduly burdensome in requiring eye banks to be responsible for ensuring subcontractor's compliance with these regulations. We recommend that compliance can be met by obtaining copies of applicable certifications, accreditations and credentials and by a letter from the subcontractor stating they are responsible for meeting the requirements of the rule applicable to their function.
- MEBTC agrees with the FDA that ultimate responsibility for providing suitable tissue should be assigned to the establishment making it available for distribution regardless of whether they actually distribute the tissue or not.

1271.155 Exemptions and alternatives

Provides details regarding requests for exemptions and alternatives to requirements.

MEBTC comments

MEBTC has no comments on this section.

1271.160 Establishment and maintenance of a quality program

MEBTC comments

- MEBTC requests clarification on "quality audit" which is defined as a documented, independent inspection and review of the establishment's activities to verify degree of compliance. Can the audit be conducted internally and/or would the EBAA accreditation process, although not performed annually, constitute an independent review?
- EBAA Medical Standard G1.000 *Quality Assurance* requires a formally established quality program including receiving and reporting adverse reactions. All records of quality assurance and adverse reactions must be retained for a minimum of ten years.

1271.170 Organization and personnel

MEBTC comments

- MEBTC has no comments on this section.

1271.180 Procedures

MEBTC comments

- EBAA Medical Standard C3.400 *Procedure Manual,* requires eye banks to annually review and maintain copies of each procedure it uses and the length of time the procedure was in use. The standard also requires eye bank Director and Medical Director approval of procedures prior to implementation or revision of existing procedures.

1271.190 Facilities

MEBTC comments

- EBAA Medical Standard C3.000 *Facilities,* requires sufficient space, equipment and supplies to perform the volume of laboratory services with optimal accuracy, efficiency, sterility, timeliness and safety.
- EBAA Medical Standard C3.100 *Eye Bank Laboratory,* requires separate lab areas with limited access and sets physical requirements of the lab.

1271.195 Environmental control and monitoring

MEBTC comments

- Once final placement of corneas in storage media occurs, they remain in the closed, sealed vial until the time of surgery or disposal.
- Cleaning may be performed by the facility housing the eye bank or contracted out to a cleaning service.
- Consequently the section on control and monitoring of ventilation and air filtration would not apply.
- EBAA Medical Standard C3.200 *Equipment, Maintenance and Cleaning,* sets requirements for calibration and certification of lab equipment, maintenance and cleaning and requires records of such to be kept for a minimum of three years. The standard requires eye banks to include procedures for monitoring, inspection and cleaning procedures and schedules for each piece of equipment.

1271.200 Equipment

MEBTC comments

- MEBTC feels this requirement is overly broad and requests the regulation to allow the establishment to write and maintain procedures for use of equipment, cleaning, calibration, etc. that prevent circumstances that increase the risk of introduction, transmission and spread of communicable disease. Furthermore, eye banks are a single material tissue bank; many only deal with one product. This simplifies the process and establishes a more controlled environment.
- Request records not be maintained at each piece of equipment as long as they're readily available.
- MEBTC requests that letters of certification, maintenance and/or contractor/vendor calibration/validation be sufficient to comply with this section.

- EBAA Medical Standard C3.200 *Equipment, Maintenance and Cleaning* (see above).

1271.210 Supplies and reagents

MEBTC comments

- MEBTC requests clarification regarding procedures for receipt of supplies. Does this requirement pertain to all supplies used solely in the recovery of human tissues?
- Is verification from each vendor for each supply used a requirement for all supplies or only those that come in contact with the donor or tissue recovered?
- MEBTC feels that this requirement is overly broad and requests that FDA allow the establishment to write and maintain procedures for use of supplies and reagents that prevent circumstances that increase the risk of introduction, transmission and spread of communicable disease. Furthermore, eye banks are a single material tissue bank; many only deal with one product. This simplifies the process and establishes a more controlled environment.
- EBAA Medical Standard C3.300 *Instruments and Reagents,* requires adequate instrumentation for sterile removal of eyes and corneas. The standard requires inspection of instrumentation to assure proper functioning, documentation of appropriate sterilization and that 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.

1271.220 Process controls

MEBTC comments

- MEBTC requests clarification on use of the terms "process" and "processing". We specifically request clarification on the use of the term "manufacturing process".
- There are no specifications set for corneas, criteria are determined by local Medical Directors in conjunction with EBAA Medical Standards.
- MEBTC requests clarification on what constitutes "in-process monitoring".
- MEBTC requests exemption for eye banks from this section. Corneas are not processed per the FDA's definition, therefore this section does not apply. MEBTC suggests that other parts of the manufacturing process are better addressed through the quality program.
- MEBTC requests clarification on the term "preservation for storage". Corneas are stored in media to maintain viability but are not preserved for long-term storage.
- MEBTC requests clarification on the term "removal from storage".
- MEBTC requests clarification on the term "preparation".

1271.225 Process changes

MEBTC comments

- MEBTC requests clarification on use of the terms "process" and "processing". We specifically request clarification on the use of the term "manufacturing process".
- EBAA Medical Standard C3.400 *Procedures Manual,* requires each eye bank to maintain its own procedures manual detailing all aspects of screening, retrieval, processing, testing, storage, distribution and quality assurance practices. The standard requires initial approval, signature and date of eye bank Director and Medical Director review. Subsequent annual reviews with sign off are required. Requires eye bank Director and Medical Director approval

of procedures prior to implementation or revision of existing procedures. Each eye bank must maintain copies of each procedure it uses and the length of time the procedure was in use.

1271.230 Process validation

MEBTC comments

- MEBTC requests clarification on the requirement for monitoring and control of validated processes. Is the quality review sufficient to ensure that specific processes continue to be met?
- Per the FDA's definition of processing, this section does not apply to eye banks. MEBTC requests clarification on use of the terms "process" and "processing". We specifically request clarification on the use of the term "manufacturing process".
- EBAA Medical Standards J1.000 *Labeling,* L1.000 *Documentation to Accompany Donor Tissue,* L1.100 *Tissue Report Form* and L1.200 *Package Insert Form* set requirements for labeling and information that accompanies tissue.

1271.250 Labeling controls

MEBTC comments

- EBAA Medical Standard J1.000 *Labeling,* sets requirements for labeling tissue which meet the proposed rule.
- EBAA Medical Standard L1.100 *Tissue Report Form* states requirements for information which accompanies distributed tissue and requires suitability determination.

1271.260 Storage

MEBTC comments

- EBAA Medical Standard I1.000 *Storage,* sets requirements for storage of surgical tissue and documentation of procedures for storage of corneal tissue and requires temperatures appropriate to the method of preservation.
- EBAA Medical Standard C3.200 *Equipment, Maintenance and Cleaning,* states requirements for temperature monitoring.
- EBAA Medical Standard E1.300 *Use of Short or Intermediate Term Preservation Medium,* states requirements for use of corneal storage medium, tracking and recall.

1271.265 Receipt and distribution

MEBTC comments

- MEBTC requests that verification/testing from the vendor be sufficient to meet the requirements for package validation in this section.
- MEBTC requests that package validation could be handled more appropriately by verification.
- EBAA Medical Standard K1.400 *Returned Tissue,* requires that corneas returned and redistributed have tissue transplantation and storage information documented and made available to the eye bank and transplanting surgeon.

- EBAA Medical Standards K1.000 *Distribution of Tissue,* requires sign off of tissue prior to distribution for transplantation by the eye bank Medical Director or designee and sets requirements for distribution.

1271.270 Records

MEBTC comments

- In response to FDA's requests for comments on whether there were specific types of records that may be exempt from the ten-year retention, MEBTC suggests that all records be retained for a period of ten years.
- EBAA Medical Standard M1.000 *Eye Bank Records*, requires records be kept for a minimum of ten years from the date of transplantation/implantation, distribution or whichever is longer. Also requires that all records and communications be regarded as confidential and privileged.

1271.290 Tracking

MEBTC comments

- MEBTC requests definition of consignee. Is the surgeon accepting the tissue considered the consignee or the hospital/facility receiving it?
- Domestic/International distribution through an eye bank should be considered. It is difficult to obtain recipient information for corneas that are provided for humanitarian purposes internationally through eye bank programs or medical projects. MEBTC requests exemption from this section for those instances and that recipient tracking be left under the jurisdiction of those countries.
- EBAA Medical Standard M1.500 *Recipient Follow-Up Information,* requires retention of recipient information and seeking possible adverse reaction information.
- EBAA Medical Standard D1.200 *Documentation of Donor Information,* requires a unique donor identifying number be obtained and recorded in the donor record.
- EBAA Medical Standards J1.000 *Labeling* and L1.100 *Tissue Report Form,* requires an eye bank identification number unique to each tissue graft.

1271.320 Complaint file

MEBTC comments

- MEBTC suggests narrowing definition of "complaint" to relate to communicable disease transmission or graft failure.
- MEBTC requests clarification of "promptly".
- EBAA Medical Standard G1.000 *Quality Assurance,* requires reporting adverse reactions from the transplantation of corneal, scleral or other ocular tissue. EBAA considers a reportable adverse reaction to be any communicable or other disease transmitted by and attributable to transplantation of donor eye tissue, including infection and biologic dysfunction. 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.

- EBAA Medical Standard M1.500 *Recipient Follow-Up Information,* requires each eye bank to seek recipient follow-up information concerning possible adverse reaction on all tissue distributed between three and twelve months postoperatively.

Subpart E- Additional requirements for Establishments described in 1271.10

1271.350 Reporting

MEBTC comments

- MEBTC requests extending report time to 30 days of initial reporting to allow time for investigation and follow-up.
- MEBTC requests reporting requirements to be consistent with EBAA Medical Standards. Since EBAA Medical Standards already require reporting, this section is unnecessarily burdensome in requiring dual reporting. Therefore, MEBTC requests "deemed status" for EBAA similar to that accorded to other agencies, e.g., JCAHO.

1271.370 Labeling and Claims

MEBTC comments
MEBTC has no comments on this section.

Subpart F-Inspection and Enforcement of Establishments Described in 1271.10

1271.390 Applicability

MEBTC comments
MEBTC has no comments on this section.

1271.400 Inspections

MEBTC comments

- MEBTC requests that the eye bank representative be the Executive Director or person functioning in that position at the time of the inspection.
- Question copying, photographing and videotaping of any records required to be kept under this part particularly records of quality assurance activities.

1271.420 HCT/P offered for import

MEBTC comments

MEBTC has no comments on this section.

1271.440 Orders of retention, recall, destruction and cessation of manufacturing

MEBTC comments
MEBTC requests clarification of recall and suggests that "notification" may be a more appropriate term especially in cases where the tissue has already been transplanted.

Place Labels in This Space

Options: 1 UPS Tracking Label and your address label
2 UPS Air Shipping Document
3 UPS Worldwide Waybill

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(Docket No. 97N-484P)

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