EYE BANK ASSOCIATION of AMERICA

Dedicated to the Restoration of Sight since 1961
Celebrating EBAA's 40th Anniversary

May 8, 2001

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

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

Dear Commissioner Henney:

On behalf of our more than 96 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 proposed rule that calls for the establishment of "good tissue practices," which includes methods used in, and the facilities and controls used for, the manufacture of human cellular and tissue-based products; record keeping; and the establishment of a quality program. The agency also proposes new regulations pertaining to labeling, reporting, inspections, and enforcement. This action is intended to improve the protection of the public health.

EBAA Background

The 96 U.S. eye banks, which are members of the EBAA, represent 99% of the entire U.S. eye banking community and provide 97% of all corneal tissue for transplantation. This count is based on an accreditation list that separates out each facility that is inspected even if it belongs to an umbrella entity. For statistical purposes, however, many eye banks count all of their facilities that distribute from a centralized area under one legal entity. This accounts for different totals reported in various materials. 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 EBAA strives to ensure the superior quality of banked human eyes through the adoption and implementation of stringent medical standards.

The eye banking community is proud of its history. 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. This eye banking model was successfully replicated in other communities across the United States. To date, there has been no evidence of fraud, no evidence of financial irregularity, no issues concerning the accessibility of corneal tissue, and no case of transmission of systemic-infectious disease for the last 14 consecutive years in the eye banking system. Eye banks lead the transplantation field with an accreditation program and medical standards that provide a model of success in the transplant community. The present system works extremely well, as demonstrated by our outcome success rate, and is currently able to provide sufficient amounts of tissue to those in need of sight restoring transplants. We have a positive story to tell and are willing to work with the FDA to define appropriate "good tissue practices" for all involved with banked human eye tissue.

FDA Proposal/EBAA Comment

The FDA is proposing this rule as one part of a comprehensive new system for regulating human and cellular tissue based products "to prevent the introduction, transmission, or spread of communicable diseases." The EBAA previously provided comment on the other parts of the new system, those of "registration" and "suitability determination." Each part of the new system has and will result in various changes in policies and procedures for eye banks and will require significant new expenditures to meet various FDA requirements. The sum total of the regulatory burden remains unknown.

It is the EBAA's intention to work with the FDA to develop the best possible "good tissue practices" that are appropriate for the eye bank community Our role is to represent our membership, to ensure the appropriate practice in the acquisition of human eye tissue and its subsequent transplantation, and at the same time, also ensure that cost does not impair access to the service. Balance must be achieved in drafting regulation and the significant differences between the processing of eye tissue and the processing of other types of cellular and tissue-based products must be recognized. The EBAA believes the highest quality standards and a strict "chain of custody" must be placed on human tissue and is supportive of the FDA's goal to this end. Accordingly, we ask the FDA to understand eye banking practices and to accommodate other approaches that reach the same goal accepted by eye banking.

As we examine each section of this proposed rule, we will comment on the policy as it impacts the eye banking community and in some cases offer refinements to the proposed rule to complement eye bank standards and procedures. Again, we appeal to the FDA to make modifications to the rule in certain sections to more accurately

reflect customary and acceptable state-of-the art practices; we believe the modifications will achieve FDA safety objectives, save unnecessary costs, and will allow a thriving community to continue to serve the public need.

Cost Data

The FDA performed a cost analysis of the financial impact on the eye banking community as it applied to the provisions proposed in this rule. All eye banks are classified as small businesses as defined by the U.S. Small Business Administration. We are also all 501 (c)(3) charitable organizations, operating on limited and carefully planned budgets that are supplemented in many communities from philanthropic organizations such as the Lions Clubs, the United Way, and other organizations.

Cost is an extremely important factor when discussing the impact of this proposed rule. Eye banks may, by law, only be reimbursed for the provision of transplantable eye tissue and may sometimes recover a nominal payment for non-transplantable tissue used for ophthalmic research or education. Access to sight restoring transplantation procedures will be threatened if fees become too high as costs escalate to cover operations under new government rules. Staff reductions are not possible given all the new tasks required in this proposed rule; additionally, the cost of our sanitizing and preservative agents, storage media and equipment used in evaluating eye tissue will increase in expense due to the requirements under the proposed rule.

There is great variability in size and complexity of eye bank operations depending on local access to concentrated population centers. Access is necessary, as corneas cannot be "stored" long-term or inventoried and must be provided to the surgeon in a timely fashion in order to preserve the integrity of the corneal cell structure and to ensure a cornea safe for transplant. 26 member banks provide up to 300 corneal tissues annually for transplant; of these, 8 provide fewer than 100 corneas (per bank) for transplant. Some of these banks are in areas designated as rural; these areas would otherwise not be served without a local eye bank. These banks will be challenged by a requirement which in effect, forces them to hire additional staff. Another 36 banks provide from 300-999 corneas for transplant annually. 15 banks offer over 1000 corneas for transplant (Source: 2000 Eye Banking Statistical Report, 80 U.S. eye banks reporting)

The EBAA conducted a preliminary survey of our membership to determine the potential operational complexity and the cost of implementing the provisions of the proposed rule. Costs varied greatly due to each bank's interpretation of the proposed rule's requirements. The median cost for start-up compliance was $41,533 and the mean was $50,566; both cost estimates are higher than the FDA's cost estimate of roughly $35,000. Not only does our rough survey show that the FDA's cost estimates are low, but the following facts would suggest problems with FDA's cost data: 1) the FDA used 1996 labor statistics to derive tissue bank employee wages; 2) the FDA identified the laboratory director and medical director as the same individual (these are generally two separate jobs with separate salaries); 3) the FDA did not add clerical expense for the

revision of minor policies and procedures; 4) the cost of preparing new operating procedures and revising existing procedures is bundled with training costs; and 5) several sections in the proposed rule lack cost estimates because no basis for predicting such costs exists.

The FDA estimates that when implemented, the proposed rule could save $1,365,936 in lost wages and health care costs as noted in the Wilhelmus (Arch Ophthalmology. 1995; 113:1497-1502) article on primary graft failure. EBAA believes the FDA hasmisinterpreted the results of the article and its cost estimates cannot be ascribed solely to eye bank practices and procedures. The Wilhelmus article cites cost data from nearly a decade ago at which time corneal transplants were primarily performed as in-patient procedures. Today, the vast majority of corneal transplants are performed in ambulatory surgical centers or as hospital out-patient procedures, dramatically altering the estimated costs. Patients undergoing cornea transplants are no longer admitted to a hospital, but instead are day patients whose surgeries take place under local anesthesia with subsequent out-patient follow-up. Diagnostic-related group (DRG) codes for cornea transplant include four months of post-operative follow-up by the surgeon, further reducing the quoted estimated costs. Further, the regulation fails to acknowledge the author's conclusion, that "no clearly defined donor or eye banking factor accounted for most cases of primary graft failure, although prolonged storage and advanced donor age may increase its risk."

In another study reported in the Cornea Journal, in 1994, on primary graft failure, the authors conclude, "primary graft failure fortunately is a rare but nevertheless major complication of penetrating keratoplasty... Eye bank-related factors were not incriminated in our case control study despite our initial suspicions and hypothesis." (Mead, et al, Cornea Journal; 13(4):310-316, 1994)

Thus, "primary graft failure" may be related to a variety of factors unrelated to eye bank processing, e.g. surgical technique, patient compliance, or patient health. In summary, the costs savings estimate is greatly exaggerated and the potential for problems related to "primary graft failure" as a result of the handling of tissue from donor to surgery center is minimal.

Also troubling is the 1994 Agency for Health Care Policy and Research (AHCPR), data referenced by the FDA, leading the reader of the proposed rule to believe that only 7,443 corneal transplants were performed that year when the actual number of corneal transplants reported to the EBAA for that year were 35,022. The reader is left with the impression that primary graft failure is much more likely to occur than it actually is because of a skewed denomination.

Given the lack of solid cost data and the resulting impact of even minimal increased expense on eye bank operating budgets, we ask that the FDA : 1) take into account the present safety and outcome success rate of individual tissue communities; 2) ensure that cost does not impair access to the service; 3) appreciate the time sensitivity of certain tissues; and 4) understand that the eye bank community relies solely on the

human gift of donation and that to secure such precious gifts is a labor intensive process.

Regulatory Terms: Manufacturers and Products

The proposed rule defines organizations that recover, screen, test, process, store, label, package, or distribute human cellular or tissue-based products 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 facilitate the transfer, not manufacture, of compassionately donated human eye tissue to give another the gift of sight. Instead of "manufacture", the FDA could consider the term: **"Tissue Service Organizations (TSOs) as the noun, and "handling" as the verb.**

The proposed rule refers generally to all human cells and tissues as "products." The term "product" connotes something that can be manufactured, although the Webster definition provides great latitude. The FDA could consider the term: **"material"**. The EBAA's recommended terms for "manufacturers" and "products" are appropriate to describing those involved with human tissue and will help maintain the public's appreciation of the spirit of donation.

SECTION BY SECTION REVIEW AND COMMENT

*Accompanying EBAA comments are cites of sections from EBAA's Medical Standards and Procedures Manual, enclosed as tabs B and C. In several areas, the EBAA may have to modify its Medical Standards and Procedures Manual to meet FDA's final requirements. Most of the proposed requirements are not difficult to meet, but require additional steps and documentation, resulting in time and labor. Such areas are not discussed in these comments; the EBAA will continue to share amended standards with the FDA and intends to incorporate final requirements into the EBAA Medical Standards, where they are not already addressed. Primarily discussed are major areas of concern with various proposed provisions and EBAA recommendations for change or elaboration in the preamble to the final rule.

Section 1271.150 Current Good Tissue Practice:General

FDA Proposed Rule -- 1271.150 (a) General. In summary, 1271.150 (a) of the the proposed rule broadly outlines "current good tissue practices (CGTP)" requirements and the goals the agency intends to accomplish through the implementation of such requirements.

EBAA Comment: The EBAA has developed scientifically-based and established Medical Standards and Procedures for our members that encompass "good tissue practices" for human eye tissue. We share the FDA's intention, through the

implementation of our standards, accreditation process, and certification for eye bank technicians (CEBT), to prevent the introduction, transmission, and spread of communicable disease through the use of human eye tissue. Our standards ensure that human eye tissue does not contain communicable disease agents, that human eye tissue does not become contaminated, and that the function and integrity of human eye tissue is not impaired through improper handling. [See EBAA Medical Standards A1.000, Introduction and Purpose and A1.100, Scope]

FDA Proposed Rule -- 1271.150 (b) Compliance with applicable requirements. The language herein requires "that an establishment that engages another establishment under a contract or agreement, or other arrangement, to perform any step in the manufacturing process, is responsible for ensuring that the work is performed in compliance with the requirements in this subpart and subpart C of this part."

EBAA Comment: The EBAA is concerned with the regulatory language included in 1271.150 (b). First, the language is unnecessarily broad, providing room for several different interpretations as to the level of oversight and involvement eye banks must have with their subcontractors. Second, the FDA must understand that work is subcontracted because the eye banks themselves do not have the expertise, personnel, or resources to perform contracted functions. Eye banks are simply not qualified, nor do they have the resources, to be responsible for "ensuring" compliance by subcontractors with meeting the requirements of the rule as they pertain to each tissue.

EBAA Recommendation: The EBAA recommends that compliance by subcontractors, i.e. medical laboratories, medical examiner offices, etc,. be deemed met by a letter of intent from the subcontractor stating that they (the subcontractor) are responsible for meeting requirements of the rule applicable to the subcontracted function. Contractor agreements would be renewed annually and the eye bank would be required to retain such letters and agreements on file. Problems with the subcontracted service would have to reported, documented, and a corrective action plan would have to be implemented.

Section 1271.155 Exemptions and Alternatives

FDA Proposed Rule -- 1271.155 Exemptions or alternatives. This Section outlines a process by which establishments may request an exemption or alternative from any requirements in Subpart C or D of this part regarding a human cellular and tissue-based product.

EBAA Comment: This Section contains no timeframe under which a decision shall be made for an exemption or alternative, yet the section clearly does not allow an establishment to begin operating under the terms of an exemption or alternative until it has been granted in writing. A maximum time period for a decision should be

established.

EBAA Recommendation: A new paragraph should be inserted between Subsections (d) and (e), stating: "Timeframe. The Director shall provide a written statement approving or disapproving the proposed exemption or alternative within 30 working days of his or her receipt of an oral, written or electronically filed request."

Additionally, the EBAA recommends that the final rule provide for a staggered implementation with this section of the rule to be implemented first and the remaining provisions be effective two years from the date of publication of the final rule in the Federal Register.

FDA Proposed Rule -- 1271.155 (c) Criteria for granting exemption or alternative. This paragraph states that "the Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of preventing the introduction, transmission, and spread of communicable disease and that:...."

EBAA Comment: The exemption or alternative language is too narrow and does not afford entities an exemption or alternative approach to a particular requirement of the rule not relevant to the tissue in question.

EBAA Recommendation: Modify 1271.155 (c) to state: "the Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of preventing the introduction, transmission, and spread of communicable disease or that such goals are not impaired by an exemption or alternative, and that:"...

Section 1271.160 Establishment and Maintenance of A Quality Program

FDA Proposed Rule -- 1271.160 Establishment and maintenance of a quality program. Under this Section of the proposed rule, the FDA outlines a comprehensive "quality program" for those involved in the manufacture of human cellular and tissue-based products.

EBAA Comment: The EBAA presently complies with a number of steps outlined in the proposed rule. However, we suggest some modifications to comply with EBAA practice and will modify our own Medical Standards to meet certain audit and report requirements, if kept in the final rule. 100% of our eye bank membership will have to increase quality control efforts as outlined in the proposed rule, and most will have to hire a separate "quality control" employee to track each provision of the program. This requirement will be time consuming and invariably expensive as noted even under FDA's assumptions. [Medical Standards G1.000 Quality Assurance; and Procedures Manual G1.000 Quality Assurance and G1.100 Testing]

FDA Proposed Rule -- 1271.160 (e) Computers. Paragraph (e) requires an establishment that uses computers or automated data processing systems for maintaining data or records related to the manufacture or tracking of human cellular or tissue-based products, to validate computer software for its intended use according to an established protocol.

EBAA Comment: This is the most troublesome requirement of this Section. The majority of eye banks, if not all, utilize computer systems for storage of data -- not 10%, as estimated by the FDA. As far as the Association can determine, no eye bank uses a computer system to make decisions about tissue suitability. Eye bank practice in this regard differs dramatically from blood bank practice, where computer systems make decisions about blood suitability and final disposition -- in such cases, software validation would be appropriate.

Eye banks maintain a paper chart on each donor tissue, including hard copies of a donor's medical chart. The information is entered by an operator into the computer for purposes of obtaining a summary of the information contained in said chart. Essentially, the paper chart is replicated with a computer record. A computer print-out of the tissue record will accompany the tissue to the transplant facility for legible, accurate identification and tracking.

Eye banks do not use computer software and hardware as decision making instruments. Computers in use at eye banks are solely for information storage and retrieval, word processing, and form printing.

EBAA Recommendation: The EBAA believes the appropriate "validation" requirement for eye banks would entail the following: 1) that the computer system be routinely backed-up so that data is not lost; 2) that the final computer print out be physically checked against the paper chart to ensure that data is consistent and that no operator error occurred; and (3) that a final supervisor, or his or her designee, sign-off be required prior to tissue release.

We ask the FDA to provide further guidance on this matter in the preamble to the final rule.

Section 1271.170 Organization and Personnel

FDA Proposed Rule 1271.170 Organization and Personnel. This Section of the proposed rule broadly outlines organization and personnel requirements.

EBAA Comment: EBAA is supportive of Section 1271.170 as proposed. EBAA Medical Standards and Procedures meet FDA requirements. [See Medical Standards C1.000 Personnel and Governance, and C2.000 Training, Certification, and Continuing Education of Technical Personnel; Procedures Manual C2.000 Training, Certification, and Continuing Education of Technical Personnel]

Section 1271.180 Procedures

FDA Proposed Rule 1271.180 Procedures. This Section of the proposed rule requires establishments to establish and maintain procedures for all significant steps performed in the manufacture of human cellular and tissue-based products. The procedures are to be designed to prevent circumstances that increase the risk of the introduction, transmission, and spread of communicable disease ...

EBAA Comment: EBAA is supportive of this Section as proposed. [See Medical Standards C3.400 Standard Operations, Procedures Manual and E1.000, References EBAA Procedures Manual]

Section 1271.190 Facilities

FDA Proposed Rule 1271.190 (a) General: This paragraph of the proposed rule outlines requirements for the physical plant of entities involved in the manufacture of human cellular and tissue-based products. The provision states: "The facility shall be maintained in a good state of repair. Adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities shall be provided."

EBAA Comment: Some eye banks are housed in university teaching hospitals or other hospital settings. Accordingly, much of the maintenance responsibility for the physical plant is performed by the hospital or university. This is also true of several other eye banks where the eye bank is a tenant in a building and not a freestanding facility. In these instances, the eye bank would have to work through building management for structural upkeep and repair. While the EBAA agrees that the facility must be maintained in a good state of repair, *a standard of reasonableness must be employed during the inspection process.* It should be acceptable for the facility to show that a certain problem has been brought to the attention of the building management and that a reasonable period of time for response is allowed.

Additionally, some eye banks, such as those in a teaching hospital or in a tenant situation, do not have toilet facilities on the premises, but have access to such facilities, e.g. down the hall. It is not essential to have toilet facilities in an eye bank; it is essential to have a sink with a drain and running water -- which all eye banks have. [See Medical Standards C3.000 Facilities General, C3.100 Eye Bank Laboratory, and C3.200 Equipment Maintenance and Cleaning; Procedures Manual C3.000 Facilities, C3.100 Eye Bank Laboratory, and C3.200 Equipment Maintenance and Cleaning]

EBAA Recommendation: The EBAA respectfully seeks modification to paragraph 1271.190 (a); deletion of the requirement for toilet facilities, and seek guidance in the preamble for those eye banks that are housed in teaching hospitals or other tenant situations.

Section 1271.195 Environmental Control and Monitoring

FDA Proposed Rule -- 1271.195 Environmental Control and Monitoring: This Section of the rule outlines procedures, "where appropriate," to control and monitor environmental conditions to provide proper conditions for operations.

EBAA Comment: Eye banks perform the majority of work on eye tissue, eg. the preservation of the corneal tissue, under the laminar airflow cabinet. We agree that it is critical to monitor the environment under the laminar airflow cabinet through inspection and periodic maintenance to ensure careful environmental control.

However, the impact of the overall air quality of the eye bank has a negligible effect on human eye tissue. If eye bank practices are followed properly, eye tissue would be minimally exposed to the overall environment. The impact would not effect the structure or integrity of the eye tissue. Most certainly, communicable disease could not be transmitted. To call for the installation of major environmental control systems would be cost prohibitive for most eye banks, and is not necessary or appropriate. [See Medical Standards C3.200 Environmental Monitoring the Laminar Flow Hood and C3.600 Infection Control and Safety]

EBAA Recommendation: EBAA believes that appropriate environmental controls should pertain to the laminar airflow cabinet; we have developed such standards and they are employed by our member banks. Standards for overall air filtration and ventilation control or other environmental monitoring are not necessary if appropriate procedures are followed. Such systems would be cost prohibitive for eye banks and add nothing to the quality of human ocular tissue offered for transplant. The EBAA requests that FDA acknowledge the requirements for the laminar airflow cabinet as sufficient to meet this section of the proposed rule and that an exemption from overall environmental controls be noted.

Section 1271.200 Equipment

FDA Proposed Rule -- 1271.200 (a) general. This paragraph stipulates that "any automated, mechanical, electronic, computer or other equipment used for inspection, measuring and testing shall be capable of producing valid results."

EBAA Comment: Manufacturers and those who service the equipment are best suited to analyze equipment function. [See Medical Standards C3.200 Equipment Maintenance and Cleaning and C3.300 Instruments and Reagents; and Procedures Manual 3.200 Equipment Maintenance and Cleaning]

EBAA Recommendation: The EBAA appeals to the FDA to accept vendor validation

and maintenance records and clarify the rule accordingly.

FDA Proposed Rule -- 1271.200 (c) Calibration of equipment. Paragraph (c) requires that "all automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be routinely calibrated according to established procedures and schedules."

EBAA Comment: Calibration of slit lamps is not practical. A slit lamp is similar to a lighted magnifying glass and is used to visually inspect corneal tissue. There can be no validation, as the procedure is operator dependent. [See Medical Standards C3.200 Equipment Maintenance and Cleaning]

EBAA Recommendation: Modify 1271.200 (c) accordingly: "all automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing shall be routinely calibrated, if said equipment produces valid results, according to established procedures and schedules."

Section 1271.210 Supplies and Reagents

FDA Proposed Rule -- 1271.210 Supplies and Reagents. This Section of the rule outlines several new steps for establishments relating to supplies and reagents used in manufacturing human cellular or tissue-based products. Specific requirements are outlined pertaining to records of receipt of each supply or reagent, verification of each supply or reagent, and use of each supply or reagent.

EBAA Action: EBAA is supportive of this Section of the proposed rule. This is a costly section for eye banks as it will require lab coordinator and technician time to receive, record, and verify all supplies and reagents, and then to track according to use on each particular tissue. [See Medical Standards C3.300 Instruments and Reagents].

Section 1271.220 Process Controls

FDA Proposed Rule -- 1271.220 Process Controls. This Section of the proposed rule requires that tissue "establishments engaged in the processing of human cellular and tissue-based products shall develop, conduct, control, and monitor its manufacturing processes to ensure that each human cellular or tissue-based product conforms to specifications, is not contaminated, maintains its function and integrity, and is manufactured so as to prevent transmission of communicable disease by the product."

EBAA Comment: Eye banks do not engage in the "processing" of human cellular and tissue-based products pursuant to the definition included in the proposed rule Section 1271.3 (mm). Eye banks do not "pool" eye tissue and do not "process" product as the term "processing" is defined by the proposed rule. Eye banks do not process (e.g. drill, shape, grind, form, or press) corneal donor tissue from a raw material

into a finished product. Corneal tissue cannot be sterilized and still maintain viability for transplantation. Between the time of recovery and transplantation, corneal tissue is kept refrigerated in a corneal storage medium. During such time, the eye bank determines the suitability of tissue for use following a review of the donor's relevant medical records, infectious disease testing, and microscopic tissue evaluation. If corneal tissue fails to qualify for transplantation, it is appropriately discarded, or is provided for non-transplant (e.g. research or education) use.

Once corneal tissue is removed from the donor it is not manipulated, altered, added to, or otherwise made into a product. Corneal tissue is provided for use without altering its integrity, form or function; it performs the same function in the recipient as it performed in the donor.

Eye banks are required by EBAA's Medical Standards to have in place a quality assurance program to evaluate the medical criteria used to determine a donor's suitability for use, staff training and continuing education, records management, distribution of tissue, and other aspects of handling corneal tissue. Such standards are specifically designed to address the nature of corneal physiology and post-mortem viability for transplant. Evaluation of corneal tissue does not occur with automated equipment. Each tissue is individually evaluated by eye bank personnel. No aspect of corneal tissue evaluation involves the introduction of reagents, binding agents, adhesives, or other material that can damage corneal tissue or which would require some type of in-process monitoring.

Accordingly, this section is inapplicable to eye banks and eye banks should not be required to assume responsibility for complying with implementation of this Section.

Section 1271.225 Process Changes

FDA Proposed Rule -- Subsection 1271.225 (a) Procedures. Paragraph (a) would require that procedures be established and maintained for making changes to a process. Any such change shall be verified or validated, to ensure that the change does not create an adverse impact elsewhere in the operation, and shall be approved before implementation by a responsible person with appropriate knowledge and background.

EBAA Comment: The proposed regulation would require establishments to institute "process" change procedures to govern modifications to established "processing" operations. Since eye banks are not involved with "processing" product, we believe it is inappropriate to implement change procedures for "processing" operations that do not exist. Accordingly, this section is inapplicable to eye banks and eye banks should not be required to assume responsibility for complying with implementation of this Section.

Section 1271.230 Process Validation

FDA Proposed Rule -- 1271.230 Process Validation, 1271.230 (a) and 1271.230 (d). The overall Section of the proposed rule applies to "validation of process" for human tissue. Paragraph (a) General, states that "where the results of a process cannot be fully verified by subsequent inspection and tests, the process shall be validated and approved according to established procedures. The validation activities and results.....shall be documented." Paragraph (d) Procedures, requires that procedures be established and maintained for monitoring and that requirements continue to be met.

EBAA Comment: Each eye tissue acquired by an eye bank is individually examined, evaluated, and tested. Even tissue from the same donor is examined separately. Since every tissue is subjected to its own verification of suitability based upon medical standards and criteria, "process validation" is not relevant to eye bank activities. Accordingly, this section is inapplicable to eye banks and eye banks should not be required to assume responsibility for complying with implementation of this Section.

Section 1271.250 Labeling Controls

FDA Proposed Rule -- 1271.250 Labeling Controls. This Section of the proposed rule call for procedures for the labeling of human cellular and tissue-based products. The procedures are to be designed to prevent mix-ups...

EBAA Comment: The EBAA is supportive of this Section as proposed. [See Medical Standards J1.000, Labeling, L1.000 Documentation, and K1.200 Receivers of Tissue and K1.200; Procedures Manual J1.000, Labeling, L1.000 Documentation]

Section 1271.260 Storage

FDA Proposed Rule -- 1271.260 Storage. This Section of the proposed rule broadly outlines requirements relative to storage areas.

EBAA Comment: The EBAA is supportive of this Section as proposed. [See Medical Standards C2.300, Equipment Maintenance and Cleaning and I1.000 Storage; Procedures Manual C2.300, Equipment Maintenance and Cleaning, E1.300 Use of Preservation Media, and 1.000 Storage]

Section 1271.265 Receipt and Distribution

FDA Proposed Rule -- 1271.265 Receipt and Distribution, 1271.265(a), 1271.265 (b), and 1271.265 (c). The above referenced Section and its paragraphs apply to defining receipt and distribution activities related to human tissue.

EBAA Comment: Please note that several new steps will be required of eye bank personnel under this Section of the rule; this will be costly in terms of time and expense. However, the EBAA believes that following these steps will enhance efforts to maintain a strict "chain of custody" on the tissue and that expending the effort is worthwhile. [See Medical Standards D1.000 Donor Screening, L2.000 Packaging, M1.000 Eye Bank Records, M1.100 Confidentiality, M1.200 Donor Screening Forms, M1.300 Information to be Retained, M1.400 Recipient and Follow-up Information, and M1.500 Disposition of Surgical Tissue; and Procedures Manual D1.000 Donor Screening, K1.000 Distribution of Tissue, K1.400 Returned Tissue Procedure]

FDA Proposed Rule -- 1271.265 (d) Packaging. Paragraph (d) requires "packaging and shipping containers to be designed, validated and constructed to ensure product function and integrity and protect the product from damage ..."

EBAA Comment: The EBAA is concerned with paragraph (d). The Association asserts that validation from the manufacturer of packaging and shipping containers should serve to meet the intention of this requirement. Eye bank personnel are not trained to validate the design and construction of shipping containers and packaging materials. [See Medical Standards L2.000 Packaging, Sealing, and Packing for Transport]

EBAA Recommendation: The EBAA requests that the FDA accept validation of packaging and shipping material from the manufacturer and that a letter or packaging insert from the manufacturer be kept on file with the eye bank. Additionally, eye bank personnel could be required to visually examine the shipping and packing material for any obvious damage, being held to a "reasonable lay person" standard. If damaged, the problem would be documented and reviewed with the manufacturer of the shipping and packing material. Further, the provisions in the proposed rule outlining "A Complaint File" (Section 1271.320) could be used to monitor problems with packaging failure. It is in the eye banks' interest to immediately correct package failure problems. We believe this serves as an appropriate check and balance.

Section 1271.270 Records

FDA Proposed Rule -- 1271.270 Records. This Section of the proposed rule outlines a number of provisions regarding records of tissue. Records are to be maintained concurrently with the performance of each significant step required in this subpart and subpart C of this part. Subsections of this Section require the establishment of a records management system, the keeping of several specific records, and the retention of all records for at least 10 years.

EBAA Comment: The purpose of this Section of the rule is to provide an electronic data or paper chain of custody on the disposition of all human tissue received by a tissue entity. Should a problem occur, the electronic data or paper chain of custody would allow one to review the handling of a particular tissue. The EBAA supports the goal of this provision. At present, eye banks are able to trace tissue back through the system, from donor to transplant facility and vice versa. As noted by the FDA, this Section will be expensive for eye banks to undertake. Most banks will have to expand their capacity to store all the data required under the proposed rule for a minimum of 10 years as spelled out in paragraph 1271.270 (e). [See Medical Standards M1.100 Records, Length of Storage, M1.400, Minimum Information to be Retained, D1.200 Documentation of Donor Information, M1.000 Eye Bank Records; Procedures Manual M1.050, Eye Bank Record Entry and Correction Procedure]

Section 1271.290 Tracking

FDA Proposed Rule -- 1271.290 Tracking. This Section of the rule outlines several specific "tracking" requirements for establishments that perform any step in the manufacture of human cellular or tissue-based products. Section paragraphs require that a method of product tracking be established to track all human cellular and tissue-based products from the donor to the recipient or final disposition, or vice-versa. As well, the Section's paragraphs require the adoption and use of a distinct identification code system that relates the product to the donor and to all records pertaining to the product; product information; donor information; and information from consignees.

EBAA Comment: We support the intended goal of this Section of the proposed rule, but have concerns relative to paragraphs 1271.290 (e) Recipient information and (f) consignees. Some corneas procured in the United States are exported to other countries where a desperate need for eye tissue exists for sight restoration procedures. Eye banks are able to track the tissue to the consignees which ship tissue abroad, but are not always able to track the tissue to the actual patient/recipient. [See Medical Standards, Minimum Information to be Retained, D1.200 Documentation of Donor Information, M 1.500 Recipient Follow-up Information, J1.000 Labeling; Procedures Manual J1.000 Labeling, and K1.000 Distribution of Tissue]

EBAA Recommendation: We ask that an exception be made for eye tissue that

is exported outside the U.S., and that signature and intended disposition from the consignees be acceptable for purposes of tracking. Providers of tissue for export would be responsible for educating entities that distribute abroad regarding the intention of the final rule. Voluntary participation is the only practicable method to continue the provision of eye tissue to countries outside the United States.

Section 1271.320 Complaint File

FDA Proposed Rule -- 1271.320 Complaint File. This Section of the proposed rule outlines requirements related to the handling of "complaints."

EBAA Comment. All eye banks would have to add a procedure to handle complaints pursuant to the proposed rule or revise an existing procedure. FDA estimates two complaints per year. This estimate is too low, particularly as it applies to larger volume eye banks. These matters are taken very seriously, and much time is spent investigating reported problems. [See Medical Standards G1.000 Quality Assurance; Procedures Manual G1.000 Quality Assurance, and G1.1000 Quality Control]

Section 1271.350 Reporting

FDA Proposed Rule -- 1271.320 (a) Reporting. Paragraph (a) of the proposed rule defines "adverse reactions" and requires a report to the FDA regarding such "adverse reactions" within 15 calendar days of the initial receipt of such information. The paragraph further requires an establishment to investigate all adverse reactions that are subject to the 15-day reports and to submit follow-up reports within 15 calendar days of the receipt of new information or as requested by the FDA.

EBAA Comment: The EBAA supports adverse reaction reporting, but seeks two changes to 1271.320 (a). First, the Association seeks to narrow the definition of "adverse reaction" from the broader definition used in the rule. The focus of the rule is on the safety and efficacy of the product to be transplanted. The definition utilized by the FDA considers situations that involve the impact of the surgical procedure, including the conditions surrounding the surgical procedure, and the practice of medicine in a surgical setting as "reportable". For example, the FDA requires reporting "failure of the product's function or integrity if the adverse reaction is "fatal." In such case, there is obvious failure of the product; the reason may be due to the patient's death from an adverse response to the administration of anesthesia. To report such incidence would provide false data on graft function and integrity, and lead to the unnecessary expenditure of investigation time.

Secondly, the follow-up reporting time-frame is inadequate to provide thorough information. In some cases, tissue is shipped great distances to transplant entities. To investigate "adverse reactions," tissue establishments have to work with the

cooperation of the transplant surgeons, transplant facilities, and patients over great distances. Fifteen days does not allow for adequate response time for information sent by mail. To provide better quality in reported information, the 15-day period should be extended to 30 calendar days [Medical Standards G1.000 Quality Assurance, M1.400 Minimum Information to be Retained, M1.500 Recipient Follow-up; Procedures Manual M1.550, Adverse Reaction Reporting]

EBAA Recommendation: The EBAA suggests the following definition for reporting an "adverse reaction:" "The establishment shall report any adverse reaction involving the transmission of a communicable disease or other disease transmitted by and attributable to transplantation of donor tissue, including infection and biologic dysfunction. Further, any systemic infectious disease such as HIV, hepatitis, or syphilis that develops in a recipient, whether or not it is suspected to be due to donor tissue, must be reported."

Subsection 1271.350 (a) (2) requires follow-up reports within **15** calendar days. EBAA asks that **30** calendar days be provided to allow for more thorough follow-up.

Section 1271.370 Labeling and Claims

FDA Proposed Rule -- 1271.370 Labeling and Claims. This Section of the proposed rule addresses label information and accompanying materials and claims.

EBAA Comment: This section is presently met by EBAA Medical Standards J1.000 Labelling and L1.000 Documentation; Procedures Manual J1.000 Labelling and L1.000 Documentation. Additionally, eye banks do not make therapeutic, or related claims for their tissue material.

Section 1271.400 Inspections

FDA Proposed Rule -- 1271.400 Inspections. This Section of the proposed rule outlines FDA inspection activity with respect to establishments involved in the manufacturing of cellular and tissue-based products. Paragraph (a) discusses notification policy for inspections. Paragraph (b) discusses frequency of inspections. Paragraph (c) identifies who the agency may call on during the time of the inspection. Paragraph (d) discusses FDA's right to review and copy records, take photographs and videotapes. Paragraph (e) discusses the FDA's disclosure policy.

EBAA Comment: Paragraph 1271.400 (a) "allows for an authorized representative of the FDA to make an inspection of the establishment at any reasonable time and in a reasonable manner ... Such inspection may be made with or without notice and will ordinarily be made during regular business hours." Most of our eye bank members are small facilities. Personnel of the eye bank also have many responsibilities, some of which require time outside of the facility, for example, in educating the public on donation, working with possible donor families, and procuring

tissue from donors. In smaller banks, the door may not always be open.

EBAA Recommendation: EBAA seeks appropriate notice on behalf of our members. We ask that at least **5 working days be given for routine inspections and 24 hour notice be given for inspections for cause**. This will serve to benefit the entire inspection process.

EBAA Comment: Paragraph 2171.400 (c) allows FDA's representative to call upon the most responsible person available at the time of the inspection. Again, this is problematic because eye bank facilities are usually small, and key staff are out of the bank performing other duties. It is critical to have personnel with the appropriate level of training and responsibility available during an inspection process.

EBAA Recommendation: The EBAA seeks a change to paragraph (c) that would require the **"FDA's representative to call on the Executive Director of the facility, or person serving in this capacity, and that such individual be present during an inspection process."**

EBAA Comment: Paragraph 1271.400 (d) allows for copying, videotaping, and photographing of any records required under this part of the rule. As written, this liberal definition gives FDA inspectors overly broad authority, including wide latitude to copy personnel training records, employee reviews, etc. The EBAA believes it is appropriate to limit reproduction to data that would relate to possible communicable disease transmission and/or biologic dysfunction of tissue. Additionally, little "due process" is afforded entities under inspection. The facility under inspection must be apprised of basic rights and must be advised as to what material is reproduced and why it is the subject of reproduction. The facility should be afforded a right of denial.

EBAA Recommendation: The EBAA seeks a change in paragraph 1271.400 (d) that narrows the definition of material that can be subject to reproduction, such as **"material can only be copied, videotaped and photographed that relates to possible communicable disease transmission or other disease transmitted by and attributable to transplantation of donor tissue, including infection and biologic dysfunction." Further, the facility must be apprised of the rationale for the taking or reproduction of material and be advised as to exactly what was taken. The facility must be also be granted the right to deny the taking of such material without an appropriate notice for cause.**

[See Medical Standards B1.100 Inspection; and Procedures Manual B1.100 EBAA Membership and Accreditation]

Section 1271.420 Human Cellular and Tissue-Based Products Offered for Import

FDA Proposed Rule -- 1271.440 Human Cellular and Tissue-Based Products Offered for Import. This Section of the rule outlines requirements related to tissue

offered for import within the United States.

EBAA Comment: Eye banks do not import tissue from outside the United States.

Section 1271.440 Orders of Retention, Recall, Destruction, and Cessation of Manufacturing

FDA Proposed Rule -- 1271.440 Orders of Retention, Recall, Destruction, and Cessation of Manufacturing. This Section of the proposed rule allows the agency to take certain action if it finds that a human cellular and tissue-based product or an establishment is in violation of the regulations in this part. The agency may order a recall or destruction of any violative products, may take possession of such product itself, or may order an establishment to temporarily cease manufacturing.

EBAA Comment: Paragraph 1271.440 (a) allows the FDA to take action upon a "finding" that a product or establishment is in violation of these regulations. This authority is overly broad. It would permit the agency to issue a recall notice if the establishment failed to perform clerical requirements that in no way directly relate to the safety or efficacy of the product, such as, for example inadvertent misplacement of training records for personnel.

EBAA Recommendation: The EBAA seeks a change in proposed paragraph 1271.440 (a) to narrow the scope of findings that must be made to trigger agency action, such as: "upon an agency finding that a human cellular and tissue-based product or establishment is in violation of the regulations in this part, and such violation relates to the possible transmission of communicable disease or other disease transmitted or attributable to transplantation of donor tissue, including infection or biologic dysfunction."

EBAA Comment: Paragraph 1271.440 (c)(1) states that an order will "ordinarily" provide for recall or destruction within 5 working days from receipt of the order. Subsection (c)(2) provides an alternative scenario in an agreement between the FDA and the person receiving the order as to the response to be taken. Whether this alternative path is chosen is entirely up to the discretion of the FDA. In many cases, however, particularly where extensive records are involved, 5 days is an inadequate amount of time for an establishment to take the steps necessary to obtain control over the material in question.

EBAA Recommendation: Rather than establishing a presumption of 5 days, from which the establishment may have to appeal pursuant to paragraph 1271.440 (e), the EBAA recommends that in all cases, the time period and response be determined by the FDA and the establishment, as set out in 1271.440 (c)(2).

EBAA Comment: Issuance of a recall or destruction order creates a potential for raising public alarm, with possible detrimental effects on the ability of eye banks to procure future donations. It is essential that public fear not be unnecessarily raised, and that FDA provide follow-up investigation of its initial finding to confirm the reasonableness and necessity of taking action.

EBAA Recommendation: The EBAA recommends that language, similar to the following, be added as paragraph 1271.440(f): "Upon the taking of any action pursuant to Section 1271.440 of these regulations, the FDA shall, within a reasonable time, conduct a follow-up investigation to determine the reasonableness and necessity of its initial findings. The results of such investigation shall be provided , in writing, to the persons or establishments in receipt of the order, all persons, facilities, or establishments which were contacted, notified or in any way involved in the execution of the order, including recipients of affected materials, and if such order was unduly disseminated, the public."

New Section: Deemed Status

In the preamble to the proposed rule, the agency invites comments on possible alternative inspection and enforcement provisions that would leverage agency resources, be cost-effective, and achieve the public health goals of the proposed rule. The EBAA offers two different approaches for your consideration.

(1) FDA could grant "deemed status" to private, not-for-profit organizations or State provided programs to administer the FDA inspection program. A "deemed" organization would be responsible for inspecting facilities to ensure that facilities are meeting the standards promulgated in the final rule. Final inspection reports of each facility would be kept on file by the "deemed" organization and available to the FDA for its review. Facilities that require Section 1271.440 actions would be reported directly to the FDA following the inspection of the facility for appropriate federal enforcement action.

(2) Amend Section 1271.400 to require that FDA inspectors be appropriately trained to examine establishments that manufacture cellular and tissue-based products according to the type of tissue manufactured by the facility. In other words, FDA inspectors that are to inspect eye banks, be trained and knowledgeable about eye bank practices. The FDA would be mandated to work with private "not for profit" organizations to develop appropriate training programs for inspectors.

EBAA Comment: The EBAA has developed a uniform inspection process. Our Medical Standards are specific to ensure the safety and quality of banked human eye tissue. Accordingly, our inspectors are trained and receive continuing education and feedback on how to conduct an inspection. Our safety history is a testament to the effectiveness of our medical standards and review process. The EBAA also has a policy of public reporting. The EBAA accreditation list is posted on its website for public

view.

The goal of the Department of Health and Human Services is to increase organ and tissue donation. The inspection process can and should be used as an opportunity to meet this goal by improving and upgrading the quality in all entities involved with the handling of cellular and tissue-based products.

Closing Comments:

We appreciate the opportunity to work with the FDA to ensure the highest quality standards for the procurement and distribution of human eye tissue.

While we agree with the agency's public health goals, we had difficulty providing appropriate comment on this proposed rule given the terminology of "manufacture," "manufacturing, "process," "processing," "processing material", "validation," and "verification." The terminology does not correlate with eye bank practices, thus making it difficult to determine what sections apply to eye banking. The agency utilizes a single framework to regulate tissue that is minimally handled to tissue that is "processed" into product. Further clarification will have to made in the preamble to the final rule.

Other than the major issues addressed in this proposed rule, most of the proposed requirements are not difficult to meet, but require additional steps and documentation, resulting in time and labor. Given that many eye banks are small entities, and are all 501(c)(3) organizations, we appeal to the agency to provide for a two year implementation period from the date of publication of the final rule in the Federal Register.

Please continue to use us as a resource in developing a response to the final rule.

Sincerely,

Patricia Aiken O'Neill

Patricia Aiken O'Neill
President and CEO, EBAA

Enclosure

EYE BANK ASSOCIATION of AMERICA

Dedicated to the Restoration of Sight since 1961
Celebrating EBAA's 40th Anniversary

EBAA Comments To FDA May 8, 2001

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