EYE BANK ASSOCIATION of AMERICA

April 20, 2015

Division of Dockets Management (HFA–305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

In Re: Docket No. FDA-2015-D-0349-0002: Comments to the Draft Guidance Document Titled*: Investigation and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated Solely under Section 361 of the Public Health Service Act and 21 CFR Part 1271.* (February 2015)

Submitted electronically at www.regulations.gov

Dear Dockets Manager:

On behalf of the 85 U.S. member eye bank organizations, the Eye Bank Association of America [hereinafter referred to as the "EBAA" or the "Association"] submits these comments to the guidance document titled entitled *Investigating and Reporting Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Regulated Solely Under Section 361 of the Public Health Service Act and 21 CFR part 1271* dated February 2015. The draft guidance document is intended to provide manufacturers of human cells, tissues, and cellular and tissue-based products (HCT/Ps), with recommendations for complying with the requirements under Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271) for investigating and reporting adverse reactions involving communicable disease in recipients of these 361 HCT/Ps. The guidance provides updated information specific to reporting adverse reactions related to HCT/Ps to supplement the genral instructions accompanying the MedWatch mandatory reporting form, Form FDA 3500A.

The draft guidance, when finalized, is intended to supplement section XXII of FDA's guidance entitled "Guidance for Industry: Current Good Tissue Practice (CGTP) and Additional Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated December 2011 and supersede the guidance entitled "Guidance for Industry: MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" dated November 2005.

I. EBAA Background

Our U.S. member organizations provide close to 100% of all corneal tissue used for transplantation in the U.S. All EBAA eye bank members 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 eye tissue through the adoption and implementation of stringent medical standards, which are scientifically based, and specific to ocular tissue.

The EBAA is the world's oldest transplantation association, established in 1961 by the American Academy of Ophthalmology (AAO). The EBAA first established medical standards and an

accreditation program for inspection of eye banking organizations in 1980, and certification of technicians followed in the late 1980s. The Association's standards and procedures have been used as a model for adaptation by other organizations in the United States, and other countries. They are reviewed and revised twice a year by a board of renowned corneal surgeons and certified technicians with expertise and extensive experience in eye banking and then formally considered by the AAO, which has endorsed them each year since 1981. The EBAA standards representing "best practices" in eye banking, are based on science specific to ocular tissue, and enjoy widespread recognition and acceptance. The Medical Advisory Board is responsible for promulgating EBAA Medical Standards and a U.S. Food and Drug Administration (FDA) representative sits on the board.

The EBAA Accreditation Board, also established in 1980, conducts inspections of eye bank members on a regular three-year cycle or more often, as necessary. Eye banks which are accredited by the EBAA, follow EBAA medical standards, and employ EBAA procedures which closely parallel and often exceed those of the FDA Good Tissue Practice regulations.

The EBAA initiated an adverse reaction reporting system in 1990. EBAA Medical Standard M1.500 requires each distributing establishment to seek postoperative outcome information between three and six months after transplant. MS G1.000 requires the investigation and reporting of adverse reactions to the EBAA for review by the Medical Review Subcommittee of the Medical Advisory Board. Reporting of adverse reactions was redesigned in 2004 for online use, utilizing the EBAA Online Adverse Reaction Reporting System (OARRS). OARRS enables easy reporting of adverse reactions, surgery, microbiological results, tissue-mate status, tissue source, transportation and comments.

The EBAA strives to ensure the superior quality of banked human eyes through the adoption and implementation of stringent medical standards. On behalf of our member banks, we would like to offer these comments for consideration.

II. Comments to Specific Recommendations in the Guidance Document

Section III: Regulatory Requirements Regarding Investigating and Reporting Adverse Reactions

A. What is an Adverse Reaction under 21 CFR Part 1271?

An "adverse reaction" for 361 HCT/Ps is defined as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response (§ 1271.3(y)).

We recognize that whenever an HCT/P recipient experiences an unintended response, there may be multiple possible causes. Nevertheless, if one of the reasonable possibilities is that the HCT/P caused the response, then this would meet the definition of "adverse reaction." This would include situations in which the relationship between the response and the HCT/P is "unlikely" but nevertheless reasonably possible.

Request for Clarification:
We request increased clarity from the FDA regarding the statement "unlikely, but nonetheless reasonably possible".

Rationale:

The Eye Bank Association of America implemented an adverse reaction reporting system in 1990. In June 2013, we harmonized our adverse reporting categories with the European SOHO V&S (Vigilance and Surveillance of Substances of Human Origin) categories, recognized by the World Health Organization (WHO) Project NOTIFY. Eye banks are required to report an ocular infection to EBAA and FDA with an imputability level of "possible", "likely, probable", or "definite, certain".

A **"**Possible**"** graft-transmitted ocular infection is reported when the evidence is indeterminate:

- Surgeon reports an ocular infection believed to be due to donor tissue.
- No pre-implant donor culture was performed.
- No pre-existing or pre-disposing conditions, intraoperative complications, or possible sources of contamination are identified to exclude imputability.

The eye bank strongly considers the surgeon's impression about whether the recipient infection is tissue-related, since he/she has knowledge about potential intraoperative contributing factors, pre-existing infections, and patient noncompliance. In cases where there is evidence clearly in favor of attribution to alternative causes, we would determine the imputability to be "unlikely" and the eye bank would not report this infection to either EBAA or FDA.

However, any systemic infection due to a relevant communicable disease agent or disease (RCDAD) such as HIV, hepatitis, syphilis, West Nile Virus (WNV), or Creutzfeldt Jakob Disease (CJD) that develops in a recipient, whether or not it is suspected to be due to donor tissue, must be reported to both the EBAA and FDA.

Section III: Regulatory Requirements Regarding Investigating and Reporting Adverse Reactions

F. How Must I Submit Reports of Adverse Reactions Related to 361 HCT/Ps to FDA?

You must submit two copies of each adverse reaction report on a Form FDA 3500A (21 CFR 1271.350(a)(5)).3 Send these copies to:

U.S. Food and Drug Administration,
Center for Biologics Evaluation and Research, Document Control Center,
10903 New Hampshire Avenue, WO71, G112,
Silver Spring, MD 20993-0002.

You may obtain copies of Form FDA 3500A from CBER at the address listed above or electronically
at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf.

Recommendation:

The FDA should create an online MedWatch Mandatory reporting system for electronic submission of Form FDA 3500A, as they have done for HCT/P deviation reporting.

Section IV: Adverse Reaction Investigation

D. What Processing Information Should I Review in My Investigation of an Adverse Reaction?

Under § 1271.3(ff), "processing" means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as:

- *Testing for microorganisms;*
- *Preparation;*
- *Sterilization;*
- *Steps to inactivate or remove adventitious agents;*
- *Preservation for storage; and*
- *Removal from storage.*

Investigation of an adverse reaction related to a 361 HCT/P should include the review of processing records to determine whether there were any deviations or departures from your established procedures that may have resulted in contamination or cross- contamination of the HCT/P involved in the adverse reaction. The investigation should specifically include the following, as applicable:

- *The review of records related to the evaluation of the incoming bioburden, such as the results of recovery or procurement cultures, or findings on inspection of the HCT/P packaging or container for damage and contamination.*
- *The review of pre- and post-processing culture results, if applicable, and the determination as to whether any microorganisms present on those cultures were also present on recipient cultures. Although some microbiology laboratories do not routinely identify the species of certain microorganisms, speciation is desirable as it aids in the investigation of adverse reactions.*
- *The determination as to whether multiple cellular products were collected at different times from the same donor and combined to attain a certain therapeutic dose, and a review of the results of cultures performed on each separate product, if available.*
- *A verification that the process used for removal or inactivation of microorganisms was validated and performed as established in standard operating procedures.This verification should include a comparison of the list of representative challenge microorganisms that were used in your process validation to the type of microorganism(s) involved in the adverse reaction.*
- *The review of records of microbiological testing failures (e.g., sterility, pre-, or post-processing microbiological cultures) within the timeframe spanning at least 30 days before and after the suspect HCT/P was manufactured and a determination as to whether your establishment has experienced microbiological testing failures involving the same microorganism as identified in the recipient adverse reaction.*
- *A determination as to whether any HCT/Ps from the donor were discarded during or after processing because they did not meet your pre-established acceptance criteria related to communicable diseases (e.g., organism considered unacceptable, microbiological testing failure, contamination).*

Recommendation:

Change the language in the first bullet regarding what the investigation should include to:

The review of records related to the evaluation of the incoming bioburden, such as the results of recovery or procurement cultures, if applicable, or findings on inspection of the HCT/P packaging or container for damage and contamination.

Rationale:

Although conventional tissues may be cultured at the time of procurement, corneas are recovered in situ, and placed immediately into transport media that contains antibiotics. Cultures are not performed at the time of recovery or prior to processing, as these results would not be known prior to transplantation. Therefore this bullet point should include "if applicable," as does the bullet point regarding pre- and post-processing cultures.

Eye banks always inspect the container in which the cornea is placed to assure that it is intact and has not been compromised. Corneal media contains a pH indicator, and a color change could indicate contamination, in which case the tissue should not be used.

III. CONCLUSION

The EBAA thanks the FDA for the opportunity to comment on the draft guidance document. The Association understands and appreciates the FDA's efforts to help ensure the safety of human tissues for transplant and prevent the transmission of communicable disease by HCT/Ps.

We applaud your efforts to update and outline the requirements for investigating and reporting adverse reactions involving communicable disease in recipients of 361 HCT/Ps, which follow the expectations of the Current Good Tissue Practice (CGTP) Guidance. We appreciate the addition of Section V, which includes detailed instructions regarding completion of the Form FDA 3500A, including what information to include in the "Other Remarks" section on page 3 of the form.

The EBAA stands ready and willing to assist the FDA and our other transplant partners to develop appropriate regulatory scheme to ensure the safety of human tissues offered for transplant.

Sincerely,

Kevin P. Corcoran, CAE
President & CEO