February 23, 2015

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

In Re: Docket No. FDA-2014-D-1696-0001: Comments to the Draft Guidance Document Titled *Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff* (December 2014)

Submitted electronically at www.regulations.gov

Dear Madams and Sirs:

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to the guidance document titled *Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products: Draft Guidance for Industry and Food and Drug Administration Staff* (December 2014). The draft guidance document is intended to clarify the Food and Drug Administration's (FDA or Agency) approaches for determining whether a product or specific materials derived from the human body will be regulated as human cells, tissues, and cellular and tissue-based products (HCT/P) solely under section 361 of the Public Health Service Act (PHS Act) and the regulations codified at 21 C.F.R. Part 1271 (referred to as "361 HCT/Ps"), or as a drug, device, or biologic subject to premarket review and regulated under Section 351 of the PHS Act and/or the Federal Food, Drug and Cosmetic Act (FDCA). Additionally, this draft guidance document is intended to replace the current guidance document titled, *Guidance for Industry and FDA Staff: Minimal Manipulation of Structural Tissue Jurisdictional Update* (Jurisdictional Update), which the Agency published in final form in September 2006.

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 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. THE DRAFT GUIDANCE REPRESENTS A MAJOR DEPARTURE FROM PREVIOUS TISSUE REGULATION AND MUST BE ADVANCED THROUGH NOTICE AND COMMENT RULEMAKING.

The FDA provides two definitions of minimal manipulation in Section 1271.3(f).

(1) For structural tissue, minimal manipulation means that the processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement (21 CFR 1271.3(f)(1)).
(2) For cells or nonstructural tissues, minimal manipulation means that the processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues (21 CFR 1271.3(f)(2)).

In addition, as part of the final rule establishing the framework for the regulation of HCT/Ps, the FDA included the following examples of minimal manipulation as part of the preamble. Language in a preamble is binding on the agency unless subsequently repudiated by the agency or overruled by a court.

> "At this time, examples of HCT/P's that we consider to be minimally manipulated include those that have been subjected to the following procedures: Density gradient separation; selective removal of B-cells, T-cells, malignant cells, red blood cells, or platelets; centrifugation; cutting, grinding, or shaping; soaking in antibiotic solution; sterilization by ethylene oxide treatment or irradiation; cell separation; lyophilization; cryopreservation; or freezing."

The draft guidance fails to mention the processing of corneal or scleral tissue, which has always

been considered minimal manipulation. In our review of the guidance, pre-cutting or preparation of tissue for DMEK or DSAEK or ALK and laser shaping for ALK or PK would qualify as "minimal manipulation." For the PK and ALK cases, where the tissue has both structural and biologic functions, the cutting or shaping does not alter either the structural or biologic function. For EK cases, where the tissue has a biologic but not a structural function, the preparation or pre-cutting does not alter its biologic function. Sterilization by irradiation will not alter the structural function of corneas used for glaucoma tube shunt coverage and treating surface conditions including pterygium or trauma.

We are disappointed that the Agency opted not to re-iterate or expand upon a list of processing steps that would be considered minimal manipulation as well as not directly addressing the classification of products related to processing steps that improve safety or enhance the original relevant characteristics.

The draft guidance introduces the new concept of "main function", which is not introduced or defined as part of the regulatory framework under 21 CFR Part 1271. By characterizing each HCT/P as either "structural" or "non-structural", the FDA has failed to acknowledge that many HCT/Ps can have more than one function. The FDA does not provide the "main function" for all HCT/P types, and provides no definition of "main function" for any of the non-structural or cellular therapies.

The term "main function" shifts the focus from the function in the recipient to the function in the donor. Under current law, whether an HCT/P is considered to be more than "minimally manipulated" is determined by the tissue's function in the recipient. Thus, for structural tissue, the analysis is concerned with the effects that processing has on the "tissue's utility for reconstruction, repair, or replacement". The draft guidance, however, analyzes minimal manipulation in terms of the "main function" of the HCT/P. It focuses on "[t]he main function of the HCT/P, in the donor." This significant change in analysis—from utility in the recipient to function in the donor—is a significant rewrite of the Part 1271 regulations.

As such, it is likely that many HCT/Ps will be considered more than minimally manipulated and, thus, subject to regulation beyond section 361 of the PHS and 21 C.F.R. Part 1271, irrespective of how they are processed. This draft guidance document could render more HCT/Ps subject to regulation as drugs, devices, or biologics under Section 351 of the PHS Act, the FDCA, and the applicable regulations. These products would be subject to the more stringent regulatory requirements of these authorities, including premarket review requirements.

We share the concerns of our transplantation partners that if finalized in the current form, this guidance document establishes a binding norm because it imposes significant new obligations. By expanding the meaning of "minimal manipulation" to rely upon the "main function" to determine whether a tissue type is considered structural or non-structural, coupled with the interpretation that such designation applies across all products from the tissue type, FDA has imposed a new limitation on a right (and obligation) established under the HCT/P regulations, 21 C.F.R. Part 1271.

Therefore, we assert that notice-and-comment rulemaking is required. Rulemaking would require FDA to articulate the basis for and purpose of its regulatory approach. In addition, the rulemaking process would result in the Agency analyzing the impact on patient care, in addition to the economic impact, of any de facto regulatory reclassifications.

Recommendation: If the FDA opts to proceed with the broad expansion of the term minimal manipulation, then the Agency should do so via formal rulemaking and not through the guidance document process.

At minimum, we request that the FDA hold a public workshop on this draft guidance document.

Recommendation: In light of stated flaws of the new term "main function," we recommend that the Agency formally withdraw this guidance document. And, if the Agency opts to proceed with creating this new term, the FDA should do so via the formal rulemaking process. As part of that rulemaking process, we recommend that the FDA address the following:

- Provide the scientific basis for the various HCT/P types;
- Provide a scientific accounting of the functions or functions of all HCT/P types;
- Provide the scientific rationale for selecting one of the functions or functions as the main function for the HCT/P type;
- Provide the scientific rationale for shifting the focus of the utility of the tissue from its function in the recipient to the function in the donor;
- Provide the scientific rationale for "locking in" only one main function for an HCT/P type and not examining how it is utilized in the recipient; and
- Provide the distinction between the term "main function" and the term "homologous use."

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.

The EBAA is concerned that if FDA moves forward with this draft guidance document without additional public discussion, it will be detrimental to patients and veterans that are currently dependent upon HCT/Ps. 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