



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of the Ombudsman
5600 Fishers Lane
Room 14B-03, HF-7
Rockville, MD 20857

Food and Drug Administration
Rockville MD 20857

November 26, 2001

[]
Regulatory Counsel
[]
1301 K Street, N.W.
Washington, D.C. 20005

Re: Request for Designation
Bio-Tissue, Inc.
Amniotic Membrane for Ocular Surface Reconstruction
Our file: 2001.016

Dear []

We have completed our review of the request for designation (RFD) for Bio-Tissue's amniotic membrane product for ocular surface reconstruction, filed by this office on June 28, 2001. The RFD sought confirmation that Bio-Tissue's amniotic membrane product is a medical device that would be reviewed and regulated by the Center for Devices and Radiological Health. On July 30, 2001, representatives of the Food and Drug Administration and Bio-Tissue held a meeting to discuss the RFD. On September 12, 2001, Bio-Tissue supplemented the RFD with additional information, and agreed to extend the RFD response deadline to give FDA an opportunity to review the new information.

Amniotic membrane is the innermost layer of the fetal membrane. It consists of an epithelial layer, a basement membrane, and an avascular stroma. Amniotic membrane encloses the fetus, and serves as a physical barrier separating the fetus from the surrounding maternal environment. Bio-Tissue submitted information demonstrating that amniotic membrane has four other properties that protect the fetus: an anti-scarring function; and anti-inflammatory function; an anti-angiogenic function; []

Bio-Tissue gathers amniotic membrane from women undergoing elective Cesarean section procedures, preserves it with [], and freezes it at []¹. No cells, such as corneal limbal cells, are seeded or cultured on the amniotic membrane product described in the RFD. Surgeons use the product to reconstruct the ocular surface when the cornea or conjunctiva is damaged. Like amniotic membrane,

¹ According to Bio-Tissue, this method of preservation has been shown to devitalize cells. On July 25, 2001, Bio-Tissue sent FDA a copy of an article concluding that amniotic membrane is no longer viable after processing. Cryopreserved human amniotic membrane for ocular surface reconstruction; Graefe's Arch Clin Exp Ophthalmol (2000), 238:68-75.

the ocular surface consists of an epithelial layer, a basement membrane, and an avascular stroma. The RFD stated that Bio-Tissue's amniotic membrane product

According to the RFD, the effects of amniotic membrane transplantation include

Bio-Tissue submitted the RFD seeking confirmation that its amniotic membrane product is a medical device to be reviewed and regulated by CDRH because of its understanding that the product would not be eligible for regulation solely under section 361 of the PHS Act. This understanding was based on prior FDA statements that the amniotic membrane intended for use in the eye would require premarket approval of a marketing application.² However, when FDA reviewed the information contained in the RFD, the agency began to reconsider whether the amniotic membrane product described therein is suitable for regulation as a tissue product rather than as a medical device or biologic. As described below, we have now concluded that Bio-Tissue's amniotic membrane product for ocular surface reconstruction meets all the requirements for regulation as a tissue product solely under section 361 of the Public Health Service Act (PHS Act).

Under recently adopted regulations,³ a tissue may be regulated solely under section 361 of the PHS Act if it meets all the following criteria:

- the product must be minimally manipulated;
- the product must be intended for homologous use;
- the product must not be combined with a drug or device, except for a sterilizing, preserving or storage agent; and
- the product must not have a systemic effect and is not dependent on the metabolic activity of living cells for its primary function. 21 CFR 1271.10(a).

FDA's prior position that premarket approval of a marketing application would be required was based on the conclusion that use of amniotic membrane in the eye was not a homologous use. Homologous use means the replacement or supplementation of a recipient's cells or tissues with a human cell, tissue, or cellular or tissue based product that performs the same basic function or functions in the recipient as in the donor. 21 CFR 1271.3(c). A tissue's basic function is what it does from a biological/physiological point of view, or is capable of doing when in its native state. The use of a tissue product may be homologous even when it does not occur in the same location as it occurred in the donor.

² See the Proposed Approach to Regulation of Cellular and Tissue-Based Products, February 28, 1997, page 17. See also the preamble to the final rule "Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing," published in the Federal Register of January 19, 2001 (66 FR 5447, 5458).

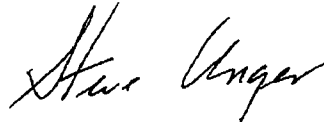
³ 21 CFR 1271; Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing, published in the Federal Register of January 19, 2001, 66 FR 5447.

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Bio-Tissue's RFD contained new detailed information about the ways in which its amniotic membrane product performs its protective function in utero, and how it performs when transplanted to the ocular surface. We conclude that amniotic membrane acts as a physical barrier against the external environment both in utero and on the ocular surface. In addition, Bio-Tissue presented persuasive information that both in utero and on the ocular surface, the amniotic membrane product described in the RFD acts as anti-scarring agent, an anti-inflammatory agent, and an anti-angiogenic agent, and

After considering this new information, and consulting with appropriate officials in the Center for Devices and Radiological Health and the Center for Biologics Evaluation and Research, FDA now concludes that Bio-Tissue's amniotic membrane product for ocular surface reconstruction, as described in RFD 2001.016, meets the criteria contained in 21 CFR 1271.10(a), including homologous use. Accordingly, the product is suitable for regulation solely under section 361 of the Public Health Service Act and the regulations promulgated thereunder at 21 CFR Parts 1270 and 1271.

Sincerely yours,



Steven H. Unger
Ombudsman