Regeneration™
TECHNOLOGIES

Regeneration
Technologies, Inc.
One Innovation Drive
Alachua, Florida 32615 USA
Phone: 904.418.8888
Fax: 904.418.0342

7 May, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Docket No. 97N-484P, "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement" (66 Fed. Reg. 1508, January 8, 2001)

Dear Sir or Madam;

RTI is the nation's largest processor and distributor of precision-tooled allografts (human-donor tissues that are processed or shaped to precise specifications for use with standard surgical instruments). RTI is based in Alachua, Florida, and distributes its allografts in all 50 states. In 2000, RTI distributed over 150,000 allografts. Surgeons use RTI-processed allografts in a wide variety of procedures to improve patients' lives. Those procedures include spinal vertebrae repair, musculoskeletal reconstruction, repair, supplementation, fracture and periodontal repair and others. Surgeons throughout the United States have used RTI allograft tissues for patients, from pediatric to geriatric, to improve the quality of their lives.

Since its founding in 1998, RTI has worked closely with donor agencies to increase donations. RTI's efforts have been met with success. Tissue recovery rates have increased tenfold since 1999 in areas where RTI's tissue recovery network has been active. Organ donations have increased significantly in those areas as well.

RTI's precision-tooling innovations not only reduce the shaping work of the surgeon and, correspondingly, the time the patient is anesthetized, but eliminate the additional surgery required when the patient's own tissue is used. Many of RTI's precision-tooled allografts reflect the ways that surgeons have cut, shaped, and used allograft tissue in the operating room for decades. By processing allografts under aseptic, clean-room conditions and in accordance with both FDA donor screening and testing requirements and individual state requirements, RTI strives to make it easier for surgeons to use allograft tissue to benefit patients. RTI has received no reports of adverse reactions or other safety concerns regarding RTI's BioCleanse™ processed allografts.

RTI utilizes state-of-the-art tissue donor screening and tissue testing methods that meet and even exceed FDA requirements. For example, RTI has developed and uses the BioCleanse™ process. The BioCleanse™ process is a patent-pending, pharmaceutical grade, computer-controlled, validated, multi-step tissue sterilization procedure that eliminates microbial contaminants, HIV, hepatitis A, B, and C and other viruses (porcine parvovirus, bovine viral diarrhea virus, pseudorabies), syphilis, and bacillus stearothermophilis, as well as blood, fat and cellular debris.

97N-484P C15

RTI supports appropriate FDA efforts to regulate the tissue industry. RTI filed comments on FDA's 1998 proposed regulation titled "Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products" (63 Fed. Reg. 26744, May 14, 1998), was gratified to see that its comments were reflected in the final regulation (66 Fed. Reg. 5447, January 19, 2001), and appreciates the opportunity to submit these comments.

Major Comments

RTI offers the following comments on matters in FDA's proposed "Current Good Tissue Practice" regulations that are of particular importance to RTI:

Clearly FDA has drafted its proposed "current good tissue practice" regulations with reference to its "current good manufacturing practice" (CGMP) regulations. The CGMPs are, of course, titled after Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act, which requires that drugs be manufactured in accordance with "current good manufacturing practice." 21 U.S.C. 351(a)(2)(B). As FDA is aware, Section 501(a)(2)(B) conjoins the words "current" and "good" for a purpose. That purpose is to ensure that FDA regulations not merely prescribe what FDA regards as "good" practice but reflect or at least give due regard to what is "current" practice, i.e., what is reasonably attainable under current technology. Indeed, FDA notes in the preamble:

> The word 'current' is included in the term 'current good tissue practice' because the agency recognizes that appropriate practices may change over time, as research is conducted and new manufacturing methods are developed. These regulations are not intended to require that practices considered current at the time of issuance of the final regulations be maintained indefinitely; instead, the obligation on an establishment is to maintain up-to-date practices over time. 66 Fed. Reg. 1511 (January 8, 2001).

FDA has inspected RTI's facilities, has reviewed RTI's BioCleanse™ process, and concluded that RTI has adequately validated the process to prevent cross-contamination during processing. The New York State Department of Health has also inspected RTI's facilities and has found the BioCleanse™ process adequate for that purpose as well. New York State is, of course, one of only two states that both license and inspect tissue processors such as RTI. Accordingly, RTI maintains that the BioCleanse™ process has been established as a process that is not only "current" but "good" and therefore one that comports with "current good tissue practice."

Proposed Section 1271.220 Process Controls

Suggested Changes

RTI urges FDA to delete proposed Section 1271.220 (c), which reads:

> Sec. 1271.220 Process controls.

* * *

(c) Pooling. Human cells or tissue from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

Rationale

RTI strongly supports FDA's efforts to eliminate cross-contamination. Proposed section 1271.220 (c) as written, however, arguably fails to recognize as "current good tissue practice" the use of validated, innovative sterilization processes such as RTI's BioCleanse™ process – processes which, when combined with FDA's donor and testing criteria would further decrease the possibility of disease transmission and provide the public with safer allograft tissue. As FDA is aware, RTI supports FDA's donor screening and testing requirements.

As noted earlier, RTI's BioCleanse™ process removes microbial contaminants, HIV, hepatitis A, B, and C and other viruses (porcine parvovirus, bovine viral diarrhea virus, pseudorabies), syphilis, and bacillus stearothermophilis, as well as blood, fat and cellular debris. As also noted, both FDA and the New York State Department of Health have reviewed RTI's innovative – and validated – BioCleanse™ process.

Given the availability of the BioCleanse™ process, the availability of perhaps other validated sterilization processes, and certainly the prospects for development of additional sterilization processes that would prevent cross-contamination, RTI believes proposed section 1271.220(c) is inappropriately restrictive and could freeze the state of the art. RTI believes the proposed subsection is also unnecessary in light of proposed section 1271.220(a), which itself would require the use of manufacturing processes that protect against cross-contamination. Proposed section 1271.220(a) states:

> "Sec. 1271.220 Process controls.
>
> (a) General. Each establishment engaged in the processing of human cellular or 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**." 66 Fed. Reg. 1555 (January 8, 2001). (Emphasis added).

That part of the preamble that discusses proposed section 1271.220(c) discusses only the potential adverse consequences of lot processing or batch processing (or, as the proposal describes it, "pooling") of tissue, stating:

> "Section 1271.220(c) would prohibit the pooling of human cells or tissue from two or more donors during manufacturing. Pooling refers to placing products in physical contact with each other or mixing them in a single receptacle. Such commingling of cells or tissues from a single

infected donor with cells or tissues from other donors can contaminate the entire pooled quantity, greatly increasing the risk to recipients of the pooled materials of exposure to infectious agents. The proposed regulation is consistent with recommendations made by FDA's Transmissible Spongiform Encephalopathy Advisory Committee, at their meeting on October 6, 1997, with respect to the pooling of dura mater." 66 Fed. Reg. 1516 (January 8, 2001).

RTI would emphasize that lot or batch processing ("pooling") has public health benefits as well, as FDA Director, Center for Biologics Evaluation and Research Kathryn C. Zoon, Ph.D., observed in 1997 in testimony on blood products before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight. There Dr. Zoon stated:

> "Human plasma proteins for therapeutic use have been manufactured from large pools of plasma for over 50 years. In order to manufacture plasma derived products, most domestic manufacturing facilities have been designed to work at large scales, using large plasma pools to permit manufacturing of sufficient quantities of products. These plasma pools are derived by combining units from individual donations. The number of units combined into a common mixture for processing is known as 'pool size.' Typically, plasma pool sizes will range from thousands to hundreds of thousands of individual units. **For certain products, the use of large pools of plasma (or the pooling of multiple manufacturing batches into larger lots) may contribute to product consistency and efficacy. For example, the production of Immune Globulin (Human), used to treat Hepatitis A, is mandated by FDA regulation at or above a minimum scale of 1,000 donors to ensure the inclusion of a broad spectrum of antibodies** (see 21 C.F.R. 640.102(d))." Statement of FDA's Kathryn C. Zoon, Ph.D., Director, Center for Biologics Evaluation and Research, before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, July 31, 1997, at 3. (Emphasis added).

Dr. Zoon went on in her testimony to weigh the potential consequences, both beneficial and adverse, of limiting blood product pool size, stating as to the latter:

> "In setting upper limits on [blood product] pool size, potential adverse consequences also must be considered. **Decreasing pool size may decrease the number of vials available from a batch. With small size batches, quality monitoring and release testing could consume a large portion of the batch. Decreasing batch size in existing plants may result in sub-optimal processing. Decreasing batch size in existing plants might decrease overall product availability.**
>
> **It should be noted, also, that reducing pool size necessarily would require the production of a larger number of lots of any given product to be produced in order to maintain the supply of that product at a constant level.** Therefore, for the full benefit of the smaller pools to be realized by the recipients of these products, measures also must be taken to insure that the recipients are not exposed to more lots of product and, thereby, to more pools.

It may be that there are other approaches to reduce risk, including additional and more sensitive testing methods, improved donor screening processes, improved viral clearance procedures, and improved plasma management practices. FDA is committed to examining all of these possibilities." Statement of FDA's Kathryn C. Zoon, Ph.D., Director, Center for Biologics Evaluation and Research, before the Subcommittee on Human Resources and Intergovernmental Relations, Committee on Government Reform and Oversight, July 31, 1997, at 6. (Emphasis added).

RTI would note that technology is available that has been shown to virtually eliminate HIV, HBV, and HCV transmission, as demonstrated in the blood industry by a wide variety of products including Plas+® SD, a virally inactivated pooled plasma product available internationally from American Red Cross since 1991.

RTI's BioCleanse™ tissue sterilization system is one such technology. The BioCleanse™ process has been reviewed by the New York State Department of Health, as well as by FDA under 21 CFR 1270 and found to be adequately validated to prevent cross-contamination during processing.

As noted, RTI's BioCleanse™ process sterilizes tissue and removes unnecessary blood elements, such as leukocytes. The process thus adds an additional layer of safety to allografts produced in conventional aseptic processing. More than 53,000 allografts having been implanted after being distributed using the BioCleanse™ process. RTI has received no reports adverse reactions or other safety concerns regarding its products, which further supports the safety and efficacy of the BioCleanse™ system.

Lot or batch processing ("pooling") allograft tissue also offers advantages to the recipient and surgeon. For example, allograft osteoinductivity (the ability of the tissue to induce new bone growth) is known to be propagated by the synergistic activity of more than a dozen different bone growth factors. Each individual donor, however, has only a select few of these distinct types. The blending of growth factors from different donors ensures that the grafting material has uniform representation of these necessary biomolecules, resulting in faster healing for the patient and significantly improved clinical outcomes.

This concept has been proposed by the American Red Cross for tissue and is standard practice in the biologics industry. Tissue forms other than blood products also require the combination of several types of tissues for proper graft function. This is the case for RTI's mechanically engineered assembled allografts, which are currently under development. These graft types will have dimensional specification and weight-bearing capacities significantly greater than what is possible from a non-assembled graft. These attributes are necessary to treat certain spinal conditions safely. Without the ability to combine tissue types safely, such as with the BioCleanse™ sterilization process, these optimal treatment options would not be available. Given the technological trend in the plasma, biologics, and tissue industries, it is reasonable and prudent that any "current good tissue practice" regulations make provision for validated processes such as the BioCleanse™ process.

That part of the preamble quoted above which discusses "pooling" states that "[proposed Section 1271.220(c)] is consistent with the recommendations made by FDA's Transmissible Spongiform Encephalopathy Advisory Committee, at their meeting on October 6, 1997, with respect to the pooling of dura mater." 66 Fed. Reg. 1516 (January 8, 2001). Although that may be true, the preamble offers no reasons that RTI can address in these comments as to why the proposed "current good tissue practice" regulations should be consistent with FDA's treatment of dura mater. RTI respectfully requests the opportunity to address any such reasons if FDA were to raise them. RTI would note in this connection, as FDA itself has noted, that pooling is a longstanding, common, and accepted practice in the blood products industry. RTI would also note that FDA regulates dura mater as a medical device, not as tissue, and therefore that FDA's comparison between tissue generally and dura mater is not necessarily apposite.

Proposed Section 1271.290 Tracking

Proposed Section 1271.290(b)(1) -- Suggested Revision

RTI urges FDA to amend proposed Section 1271.290(b)(1) to read as follows (proposed language in bold; language suggested for deletion bracketed):

"Sec. 1271.290 Tracking.

* * *

(b) Method of product tracking. (1) Each establishment shall establish and maintain a method of product tracking that enables the tracking of all human cellular and tissue-based products from [:

(i) The donor to the recipient or final disposition; and

(ii) The recipient or final disposition to the donor] **the donor or the production lot to the distributor, transplant facility, or transplanting surgeon, as appropriate.**"

RTI also proposes that FDA define "production lot" as a discrete group of products manufactured in the same processing episode that are traceable to a discrete group of donors. This definition need apply only to lot-processed or batch-processed products manufactured using a validated sterilization method as outlined in the above comments on proposed Section 1271.220(c).

Proposed Revision to Section 1271.290(1)(b) – Rationale

Currently most if not all tissue banks have a mechanism in place to trace grafts from the donors to the distributors, hospitals, or physicians. Establishments commonly use a prepaid post card enclosed with each product, which the hospitals and/or physicians are to fill out with the recipient information and return to the tissue bank. Neither tissue banks or the agency has the authority to mandate hospital or physician compliance with the tissue banks request to complete the recipient information. This is reflected in the return rate of these cards being less than 100%. RTI therefore encourages FDA, as noted above, to change the wording of the rule from "from the donor to the recipient" to "from the donor or production lot to the distributor, transplant facility, or transplanting physician." As above, RTI suggests that FDA define a "production lot" as a discrete group of products manufactured in the same processing episode that are traceable to a discrete group of donors. The definition need apply

only to pooled products manufactured using a validated sterilization method as outlined in the above comments to §1271.220(c).

Proposed Section 1271.290(c) -- Suggested Revision

RTI urges FDA to amend proposed Section 1271.290(c) to read as follows (proposed language in bold; language suggested for deletion bracketed):

"Sec. 1271.290 Tracking.

* * *

(c) Distinct identification code. As part of its tracking method, an establishment shall ensure that each human cellular and tissue-based product that it manufactures is assigned and labeled with a distinct identification code, e.g., alphanumeric, that relates the product to the donor **or the production lot, as appropriate,** and to all records pertaining to the product. Except in the case of autologous or directed donations, such a code must be created specifically for tracking and may not include an individual's name, social security or medical record number. An establishment may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process, or may assign a new code. An establishment that assigns a new code to a product shall establish and maintain procedures for relating the new code to the old code."

Proposed Revision to Section 1271.290(c) – Rationale

As noted, RTI believes FDA should recognize the appropriateness of lot-processing or batch-processing ("pooling") in conjunction with a sterilization system that has been validated to eliminate the risk of cross-contamination during the pooling process. Tissue banks that meet this exclusion should have a unique identification number that would relate the product to the donor pool and to all records pertaining to the pool. Such a procedure would satisfy the intent of the proposed regulations by facilitating recall of potentially adulterated products. RTI restates its belief that this will encourage industry to find innovative, safer processing methods to inactivate viruses, bacteria, and other microorganisms which, when combined with FDA's donor screening and testing criteria, will decrease the possibility of disease transmission, providing the public with a safer product.

Proposed Section 1271.290(d) -- Suggested Revision

RTI urges FDA to amend proposed Section 1271.290(d) to read as follows (proposed language in bold; language suggested for deletion bracketed):

"Sec. 1271.290 Tracking.

* * *

(d) Product information. As part of its tracking method, an establishment shall ensure that the identifier and type of each human cellular or tissue-based product that is implanted, transplanted, infused, or transferred into a recipient is recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor **or the production lot, as appropriate**."

Proposed Revision to Section 1271.290(d) – Rationale

Tissue establishments do not have the authority to mandate hospital compliance as outlined in RTI's comments to §1271.290(b). Nor do tissue banks have the ability to assure that hospital personnel record the tissue information in the recipients' medical records. Such would require an auditing of hospital records and patient charts, the resources for which will be difficult for tissue establishments to procure. Compliance may be better enforced by those entities charged with promulgating hospital regulations. Therefore, RTI suggests that FDA consider eliminating this section from the proposed regulations altogether .

Other Comments

RTI offers the following additional comments on matters in FDA's proposed "Current Good Tissue Practice" regulations:

Tissue with Drug or Device Excipients.

RTI urges FDA not to classify a tissue as a drug, biologic or medical device merely because it contains a drug, biologic or device as, e.g., an excipient. RTI believes such an approach could result in arbitrary and unnecessary regulation of tissue and cellular products as drugs, biologics or devices and prevent the delivery to patients of optimal tissue products. Many substances regulated by FDA may not affect the safety or viability of a cellular or tissue-based product or make a significant contribution to its function. RTI urges FDA not to regulate a cellular or tissue-based product as a drug or device unless the product carries new or additional risks that affect the safety of the tissue.

(1) **Proposed Section 1271.150 Current good tissue practice: general.** RTI is concerned that the statement ". . . and that the function and integrity of the products are not impaired through improper manufacturing" in proposed Section 1271.150(a) could be interpreted to mean the manufacturer is responsible for testing function and integrity of each product during and at the end of production. RTI believes it is not the intention of FDA to have the manufacturer test each product for function and integrity, but rather to inspect each product for relevant physical characteristics. RTI believes FDA should clarify the terms "function" and "integrity" for their use with respect to tissue and not how they are used with respect to devices. Many conventional tissues that have been used in surgery for many years have no known test for functionality. An example is cortical cancellous chips, which are used as bone void filler to replace missing bone. There is no known functionality test for these chips.

Proposed Section 1271.160
Establishment and maintenance of a quality program. RTI believes FDA has been misinformed regarding the availability of validated over the counter software, which could be used by tissue banks. RTI believes the use of validated software is essential for those tissue banks where software-generated data is used for decision making, but should not be a requirement for those establishments that use software which does not generate primary data on which quality decisions are made, i.e. where humans make critical decisions based upon hard copies of original data used to support and track all tissues and

who use readily available, over the counter software for convenience. Therefore, we suggest that §1271.160(e) be amended to reflect that software shall be validated only if it is relied upon as the sole data source for the decision making processes of the quality system.

RTI also believes FDA was not given accurate figures for its economic impact calculations, including on the availability of validated over the counter (OTC) software for use by tissue banks. Although software vendors validate their software, it remains the tissue facility's responsibility to validate the software as configured for its intended use. Most OTC software is highly configurable and therefore would require significant resources not only to configure but to validate. If the proposed requirement is implemented without regard to the criticality of the software, RTI believes the financial impact for small recovery agencies, small processors, and small distributors would be beyond the means of many and could force them out of business.

(2) **Proposed Section 1271.350 Reporting.** RTI urges FDA to amend proposed Section 220.350(a)(1) to read as follows (proposed language in bold; language suggested for deletion bracketed):

> "Sec. 1271.350 Reporting.
>
> (a) Adverse reaction reports. (1) Any establishment that receives information about an adverse reaction, regardless of source, shall review the information to determine whether the adverse reaction is required to be reported. The establishment shall report any adverse reaction involving the transmission of a communicable disease **directly related to the product**, product contamination, or failure of the product's function or integrity if the adverse reaction:
> (i) Is fatal;
> (ii) Is life-threatening;
> (iii) Results in permanent impairment of a body function or permanent damage to body structure; or
> (iv) Necessitates medical or surgical intervention. Each report shall be submitted on an FDA Form-3500A to the address in paragraph (a)(4) of this section within 15 calendar days of initial receipt of the information."

RTI is concerned that proposed §1271.350(a)(1) as written is too general and that "transmission of a communicable disease" should be restated as "transmission of a communicable disease determined to be directly related to the product" to reflect that a human cellular or tissue-based product establishment is not responsible for reporting communicable disease transmission from other sources, i.e. blood products administered during the surgery or other nosocomial routes of transmission. RTI would note that its suggested revision appears to be consistent with the wording of proposed Section 1271.220(a).

(3) Proposed Section 1271.400 Inspections

Proposed § 1271.400 sets out FDA's inspectional powers under this regulation. We are concerned by the unprecedented breadth of FDA's inspectional authority under this proposed regulation. For example, FDA says that it can take photographs or videotapes of the facility. The PHS Act mentions neither photographs nor videotapes. Nor, for that matter, does the FDC Act or any other FDA

regulations. FDA's proposal regarding taking photographs or videotapes raises questions about trade secret protection, accuracy of the depictions selected by the investigator, and FDA's statutory authority to use these tools. We believe FDA should delete this portion of the proposal, particularly since it is unnecessary in light of FDA's extensive authority to review paper records.

In addition, proposed § 1271.400 would give the FDA investigator unfettered discretion to question any employee. Historically, FDA has allowed companies to designate spokespeople, and maintained communication through designated individuals. We believe this system has served both FDA and industry well; the preamble gives no reason to depart from past practice. Conversely, giving investigators the discretion to identify any number of employees and demand that they be produced for questioning will be unduly disruptive. FDA's proposal also lacks any statutory foundation. RTI believes FDA should delete this position of the proposal, thereby treating tissue-product inspections the same as inspections of other products regulated by FDA.

RTI thanks the agency for this opportunity to comment on the proposed Current Good Tissue Practices, and for its consideration of our views.

RTI appreciates the opportunity to comment on the proposed "current good tissue practice" regulations and FDA's consideration of RTI's views.

Respectfully submitted,

Jamie M. Grooms

From: MICHAEL ROBERTS (904)418-8888
REGENERATION TECHNOLOGIES INC
2 INNOVATION DRIVE

ALACHUA, FL, 32615

SHIPPER'S FEDEX ACCOUNT #

FedEx.

To: Dockets Management Branch (HFA-305) (877)343-1853
Food and Drug Administration
5630 Fishers Lane, Rm. 1061

Rockville,, MD, 20852

SHIP DATE: 07MAY01
WEIGHT: 1 LBS

Ref:

DELIVERY ADDRESS
TRK # 7900 4492 3929 FORM 0201

PRIORITY OVERNIGHT

TUE
AA
Deliver by:
08MAY01

20852-MD-US

IAD
XA GAIA