



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

C. Randal Mills, Ph.D.  
cmills@rtitechnology.com

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Dockets Management Branch (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane  
Room 1061  
Rockville, MD 20852

RE: Docket No. 00N-1380; Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair

Dear Sir or Madam:

Representatives of Regeneration Technologies, Inc. (RTI) joined numerous representatives from the tissue banking industry and from the healthcare community, including surgeons, patients, and donor families in attending and participating in FDA's open public meeting, "Human Bone Allograft: Manipulation and Homologous Use in Spine and Other Orthopedic Reconstruction and Repair" held on August 2, 2000. The purpose of the meeting was to solicit input on the following questions posed by FDA in the meeting announcement:

- Which processing procedures applied to human bone allograft fall within, or outside of, FDA's proposed definition for minimal manipulation?
- Which uses of human bone allograft fall within, or outside of, FDA's proposed definition for homologous use?
- What risks to health have been identified and characterized for human bone allograft products?
- What controls have been identified to adequately address the risks to health of use of human bone allograft products?
- What industry standards for bone allograft products are available, and what standards will be needed in the future?

During this meeting, RTI proposed certain modifications to the proposed regulatory scheme and stated that we would submit a more detailed written description following the meeting. These comments present RTI's views on the questions asked by FDA as well as a written description of our alternative proposal. They also address ancillary concerns that have been engendered by the issue of increased FDA oversight of the tissue industry, including the justification for and potential adverse consequences of the promulgation of the proposed regulations. We hope that FDA will take these comments into consideration when deciding on the direction of any future regulation of this critical area of health care.

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### ***Minimal Manipulation and Homologous Use***

The language of FDA's proposed regulations discussing the "minimal manipulation" and "homologous use" criteria is open to various interpretations. Minimal manipulation of structural musculoskeletal tissue consists of processing that does not alter the "original relevant characteristics" of the tissue relating to its "utility for reconstruction, repair, or replacement." Under this definition, only processing that would artificially enhance or inhibit the reconstruction, repair, or replacement capabilities (incorporation) of structural tissue would be considered "more-than-minimal" manipulation. The strictest (yet still valid) *interpretation* of "more-than-minimal" manipulation would encompass any processing at all, including, for example, cleaning, cutting, and shaping processes that decrease or increase the tissue's ability to incorporate into that of the recipient. FDA has stipulated however, that these processing methods are not more than minimal manipulation. The agency's interpretation thus is one of degree rather than kind. This is the major source of the ambiguity in the proposed definition. If FDA decides to pursue this approach, the agency should provide a definition that more clearly addresses what degree of manipulation constitutes an alteration of original relevant characteristics. This may also require a more detailed definition of "original relevant characteristics."

From the industry point of view, there is very little that current processing techniques do to affect the original, relevant characteristics of bone grafts. A long history of clinical application and extensive laboratory research have revealed that processes such as irradiation, certain chemical treatments, and combination with other substances can have some structural effects. These include changes, to some degree, in structural integrity as detected by mechanical testing (modulus of elasticity, tensile strength, etc...). However, we do not believe that processing techniques, when employed as part of a validated operation by modern tissue banks, result in clinically relevant adverse effects. As described later in these comments, the processing techniques utilized by RTI have been thoroughly tested to ensure that allografts retain their natural healing characteristics.

The language used by FDA to define "homologous use" is equally ambiguous. "Homologous use" for structural tissue means "the tissue is used for the same basic function that it fulfills in its native state, in a location where such structural function normally occurs." Given that the primary function of the vertebrate skeleton in its natural state is structural support, there is no current application of allograft bone of which RTI is aware that would not fall within the definition. Therefore it would be difficult to regard the use of any structural bone allograft as being "non-homologous." The definition *becomes* ambiguous when certain grafts are singled out because of varying interpretations. For example, threaded cortical bone dowels are used in the spine for structural support only, just as the bone tissue from which they are processed supplied structural support to the femur in its native state. FDA seems to be taking the position that spinal interbody fusion introduces bone into a space where it does not normally occur. We do not concur. Interbody fusion *does* occur naturally to provide structural support when a vertebral disk degenerates. Using the same logic that FDA appears to be following with respect to bone dowels, bone would not occur normally where a large bone tumor is resected. Thus using allograft to fill the void left by surgery to achieve structural reconstruction would be a "non-homologous" use. Applications such as these are the reasons we have allografts. It is RTI's position that bone grafts used to augment or support the recipient's skeletal system are all



homologous in use. Accordingly we submit that no bone allografts fall outside of a reasonable interpretation of homologous use.

Of more critical significance to this issue is the justification for the proposed regulatory scheme. RTI is unaware of any established causal correlation between "more-than-minimal" manipulation and "non-homologous use" to the degree of risk posed by an allograft. We are therefore concerned that use of these criteria to determine the level of regulation to be applied may not fulfill the intent of the proposed regulation – to mitigate risk without stifling innovation or imposing undue regulatory burdens. We do, however, believe that the approach can be transformed into workable regulation that does accomplish these objectives.

To begin with, RTI offers the following definitions to establish the scope of what articles should be regulated as human tissue for transplantation under Section 361 of the Public Health Services Act.

RTI proposes that human tissue be defined as,

*any material containing human cells and/or associated intracellular substances, which may or may not contain excipients, and are intended for clinical use in a human recipient.*

An excipient should be defined as,

*a material of non-human origin incorporated into human tissue during allograft production that is not removed in subsequent processing steps. The excipient must not have a systemic effect as used with the graft. The excipient also must not provide the primary function of the graft.*

Based upon these definitions it would be determined if a graft should be regulated under the current tissue scheme. If a graft falls outside of these definitions, an appropriate, product specific risk analysis should be performed to determine if additional regulatory controls are necessary to ensure recipient safety. If it is found that significant new risks may exist, additional regulation may be required.

We believe this approach would accommodate those tissues that may be processed in a way that would render them "more than minimally manipulated" under the proposed approach, yet carry no additional risk. In addition, this type of risk based approach would allow the processor to employ the most meaningful controls to ensure safety.

### ***Identification, Characterization, and Control of Risks***

In the design and development of our allografts and processing techniques, RTI conducts formal risk analyses to identify those characteristics of allografts that require additional control. A survey of risk assessments of bone allografts and published literature on the subject identifies some common concerns requiring appropriate measures to mitigate potential hazards. The most commonly identified sources of potential risk are disease transmission, mechanical strength, osteoinductivity, and biocompatibility. These four areas are reviewed in more detail below. We have also included a description of the types of controls that RTI has found to be appropriate for addressing such risks.



## **Disease Transmission**

The risk of disease transmission through human allograft is a well studied topic. Although viral transmission through tissue has occurred in the past, it is very rare. Even so, FDA has promulgated regulations to address and mitigate this risk in a responsible, relevant manner. 21 CFR Part 1270, FDA's final rule for "Human Tissue Intended for Transplantation," as well as FDA's Proposed Rule on "Suitability Determination for Donors of Human Cellular and Tissue-Based Products" require medical history screening and donor blood testing for various known pathogens. These regulations have proven sufficient to mitigate this risk based upon the absence of viral transmission through allograft since their implementation. These are supplemental to voluntary measures taken by tissue banks such as additional donor testing and tissue disinfection processes. Currently, RTI employs the following disease screening practices for its allografts.

### **Serological testing:**

- HIV 1 and 2 antibody;
- HIV Proviral DNA by PCR;
- HTLV 1 and 2 antibody;
- Hepatitis B core antibody;
- Hepatitis B surface antigen;
- Hepatitis C antibody;
- Syphilis by Rapid Plasma Reagin (RPR); and
- Hemodilution determination.

### **Donor screening:**

- Medical and social history interviews;
- Post mortem physical examination; and
- Review of complete medical records by licensed physician.

### **Processing controls:**

- Controlled processing rooms (cleanroom processing);
- Environmental monitoring;
- Graft disinfection/sterilization
- Aseptic technique; and
- 14 day aerobic and anaerobic USP sterility cultures.

Tissue processing as a supplemental safety system is currently the subject of intense research and development in the industry. For example, RTI has developed the BioCleanse™ process to treat tissue as an added safety measure, further decreasing the possibility of donor-to-recipient disease transmission. This automated system has been validated to inactivate both enveloped and nonenveloped viruses, relevant bacterial contaminants, and highly resistant bacterial spores. RTI believes that this process provides surgeons and their patients with the safest tissue currently available.



## **Mechanical Strength**

The strength of cortical bone is affected by many factors, including preservation method, sterilization technique, storage duration, direction of mechanical loading and donor to donor variability. For this reason, only those preservation methods and sterilization techniques that have been tested and approved are used in allograft processing. Shelf life studies have been conducted to determine how long a graft can maintain its viability after processing. Surgeons are educated on allograft performance characteristics and literature documenting the functional load bearing capacity in different areas of the body is available. Surgeons can therefore assess functional requirements for their patients and select the appropriate graft for the particular surgical application.

Guidelines from the American Association of Tissue Banks (AATB) state that the tissue bank's medical director shall determine age limits for bone donors. The mechanical requirements for bone allografts, however, are application dependent, not age dependent. RTI makes use of tissue donations from adult donors of all ages. We feel it is inappropriate to rule out tissue based solely on age without consideration of its intended use or the results of material properties evaluations. There are many different types of allograft tissues used in a variety of applications at the discretion of the surgeon. An arbitrary age restriction on donors would unnecessarily limit the supply of tissues. RTI's solution is to use scientifically based, validated procedures for evaluating the mechanical properties of finished allografts.

At RTI, allografts are individually evaluated based on donor characteristics, physical characterization (mass and dimensional measurements), and visual inspection. Extensive research on the correlation of mechanical strength to donor demographics has given RTI an understanding of the factors that can affect tissue composition and thus mechanical strength. Based on this research we have established and validated formulae for determining which grafts can and cannot withstand both the surgical procedure and the transplant environment. Instead of setting arbitrary age limits on donor tissue, RTI has established quality standards which are applied to our finished allografts. RTI believes that this type of nondestructive evaluation is the most reliable way available of ensuring that surgeons are consistently provided with tissues that meet their expectations for mechanical performance.

## **Osteoinductivity**

It is commonly believed that the ability of demineralized bone matrix (DBM) to induce new bone growth is dependent upon several identifiable donor-dependent factors such as age, health, or activity level. However, the results of scientific analysis have not borne this out. In fact, osteoinductivity between donors is variable and not correlated to demographic characteristics. For this reason, RTI tests DBM from each tissue donor who is a candidate for use in grafts where osteoinductivity is a desired characteristic. Specifically, RTI ensures that only DBM that has been shown to be osteoinductive in an *in vivo* athymic nude rat model is made available for transplantation. In this model, DBM is implanted into a rat and after a period of time, the implantation site is histologically evaluated for evidence of new bone growth. We believe that *in vivo* testing of every lot of DBM is the best method currently available to ensure that medical practitioners receive allografts that meet their expectations for osteoinductivity.



### **Biocompatibility & Efficacy**

Graft rejection after transplantation is a key concern for patient safety and successful surgical outcome. This is an area where allograft tissue has enjoyed a long history of clinical success. Human bone is naturally biocompatible. Additionally, the standard chemicals commonly used to treat human bone tissue have been shown not to alter this biocompatibility. RTI has performed biocompatibility testing following FDA and ISO guidelines on tissue treated using our BioCleanse process. Controlled implantation studies have shown that tissue biocompatibility is not altered by the BioCleanse cleaning methods.

Allografts have also achieved clinical success as is evidenced by their high demand in surgical procedures. For spinal fusion surgeries, allograft bone is often the only option that surgeons will consider for their patients based on this history of success. Time under anesthesia as well as healing time are reduced with allografts as compared to autografts, further attesting to their clinical benefit.

### ***Existing Standards and Proposed Regulations***

RTI supports any additional regulation that is necessary to mitigate a real risk to public health. However, we do not believe that the tissues currently available to surgeons carry a risk that requires further regulation. RTI recognizes that in the future tissue-based technologies may pose new or different risks for which no suitable regulatory framework exists. Under these circumstances additional regulation may be warranted. However, additional regulation should reflect and be implemented to mitigate identified risks associated with these new technologies. The imposition of regulation beyond that for which legitimate risks exist has historically had adverse affects on health care, as was demonstrated by FDA requiring premarket review of heart valve allografts.

### **Current Regulatory Environment**

In addition to existing FDA regulatory standards, RTI currently follows both voluntary and mandatory standards of several other regulatory agencies and organizations. RTI is an ISO 9001/EN46001 certified manufacturing facility. This certification is an internationally recognized standard of quality assurance in product design, development, and production. In addition, RTI's Biomedical Laboratory is certified under the Clinical Laboratory Improvements Act (CLIA), which is intended to ensure the quality and reliability of clinical laboratories in the United States. CLIA standards apply to the areas of personnel qualification, administration, participation in proficiency testing, patient test management, quality control, quality assurance, and inspections. Our Biomechanical Laboratory performs testing in accordance with the guidelines promulgated by American Society for Testing and Materials (ASTM). ASTM develops voluntary standard test methods, specifications, practices, guides, classifications, and terminology in 130 areas covering subjects such as metals, paints, plastics, textiles, petroleum, construction, energy, the environment, consumer products, medical services and devices, computerized systems, electronics, and many others. Currently, RTI's biomechanical testing of human tissue is accomplished through appropriate adaptation of ASTM tests for synthetic materials to allograft, but RTI is aware ASTM is actively working on standards specific to tissue grafts.



RTI is also licensed as a tissue bank by the States of New York, Florida, California, and Maryland which enforce comprehensive regulations in the areas of donor recovery, screening, testing, storage, processing, and distribution. These regulations provide ample guidance for the tissue bank industry to adequately assure the safety of the tissue supply, and in some cases exceed the requirements mandated by FDA. For example, current FDA regulation does not require the reporting of adverse events. Adverse event reporting is mandated by the States of New York and Florida.

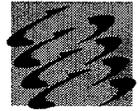
RTI is aware of and follows all scientifically applicable voluntary standards published by the American Association of Tissue Banks. In addition, RTI has many employees who are members of the AATB and have passed the AATB certification process for tissue bank specialists. RTI also participates in the exchange of scientific data with AATB and other tissue organizations by presenting at and participating in AATB's yearly meetings.

The AATB is to be commended for taking the lead in developing voluntary standards for tissue banking. However, many of these standards lack scientific justification and have not been validated. RTI has developed significant proprietary technologies that fall outside of the boundaries of these standards, yet have been fully validated using accepted scientific practice.

Because of our advanced processing methodologies, RTI would need to be granted deviations from several published standards to become AATB accredited. The procedure for the issuance of a deviation involves submitting the technology to the AATB standards committee, a committee comprised of members of various tissue banks, for review. Although RTI is confident that its technologies would easily withstand the scrutiny of this type of review, we cannot divulge our most proprietary technologies to a committee of our competitors. Furthermore, we do not think that the review process, as it now stands, allows for impartial assessment by the most qualified body of experts available. RTI feels strongly that decisions regarding the scientific validity of new technologies that may ultimately affect patient safety be made by qualified, independent experts exclusively.

RTI has been discussing with AATB alternate methods of demonstrating compliance to their standards and receiving accreditation. Most promising would be the use of third party review. This model would ensure that the review was independent of external influence and was conducted by a group of relevant experts. RTI believes that the adoption of this type of system would not only protect the proprietary materials of its members, but would also give more credibility to the accreditation process.

In summary, a wide variety of standards currently exist to regulate all aspects of human tissue processing. These measures provide ample control for the industry governing everything from obtaining informed consent to materials testing to allograft labeling. We do not believe that further standards need to be developed by FDA, however, we do believe that harmonization of existing standards into the federal regulatory framework would be in the best interest of the public health. As with all regulation, this framework should be based upon risk to public health and the most current scientific knowledge that has been amassed through decades of clinical success and from rigorous research leading to validated principles of allograft-based technologies.



## **Registration and Listing**

RTI supports FDA's proposal to require providers of tissue-based products to register with the agency and list their products. Establishing a unified registration program for tissue banks is vital to the continued growth and success of the industry because compliance with FDA regulations will be required and enforced for every registered concern. RTI understands that at present, FDA is not aware of the number of tissue banks in the United States making verification of industry-wide compliance impossible. Effective regulation must be applied universally, but first that universe must be defined.

RTI proposes that listing products be by type of tissue processed (such as bone, cartilage, tendon, fascia, cornea, skin, heart valves, etc...) rather than by individual product. Listing by individual product is impracticable for tissue banks, as the allografts are not labeled for specific uses, unlike medical devices. This type of listing would enable FDA to relay a health alert or possible new testing criteria or availability to appropriate entities and to effectively and efficiently identify industry members covering a wide range of allografts. Administration of listing in this manner would be clarified for the industry while enforcement would be simplified for the agency.

## **Future Regulations**

RTI supports FDA's efforts to draft and implement Good Tissue Practices as industry standards. Good Manufacturing, Laboratory, and Clinical Practices have shaped the regulatory environments for the medical device, pharmaceutical, and biological industries. These regulatory standards have improved the quality of traditional manufacturing industries and we believe they will do the same for tissue banking. To be successful, however, future tissue regulations should be built around the existing regulatory framework with the additional feature of allowing scientific advances to pave the way for future regulatory development. These regulations should be outcome based in that they should not dictate the specific methods that are to be used to achieve their goals. Instead reasonable standards for product safety should be established with the responsibility for demonstrating compliance to those standards residing with the individual tissue banks. This would allow for industry-wide uniformity with respect to tissue safety, while providing tissue establishments the flexibility necessary for continued process improvement.

New regulations should be constructed in such a way as to not stagnate or limit the innovation and creativity that have been the hallmark of tissue banking since its inception. Regulation that will allow these efforts to continue while providing scientifically justified guidance will result in improving the industry's methods for demonstrating compliance, thereby providing a reliable measure of the safety of human tissue for transplantation.

## **Conclusions**

RTI appreciates the opportunity to work with FDA in establishing a reasonable regulatory framework for human tissue. We believe that human tissue allografts currently available for transplantation within the United States are safe. This position was recently supported by Donna Shalala, U.S. Secretary of Health and Human Services in her August 8, 2000 progress report to Senator Richard J. Durbin. For this reason, and because of concerns raised by the ambiguity of the terms "minimal manipulation" and "homologous use", we do not believe that the proposed

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approach as presently formulated should be used to make decisions regarding which allografts will be regulated as tissue and which allografts will be regulated as medical devices, biologics, and/or drugs. Instead, RTI believes that its alternative approach described above can more appropriately address FDA's concerns regarding more complex tissue-based technologies of the future, while at the same time fostering innovation and avoiding unnecessary regulatory burden.

We hope that FDA will give our comments serious consideration and we look forward to a continuing, cooperative dialogue between the agency and the industry on these issues.

Sincerely,

C. Randal Mills, Ph.D.  
Director of Regulatory Affairs

CM/mr

From: MICHAEL ROBERTS (904)418-8888

1 INNOVATION DRIVE

ALACHUA, FL, 32615

To: Dockets Management Branch (HFA-305) (904)418-8888

Food and Drug Administration

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Room 1061

Rockville, MD, 20852

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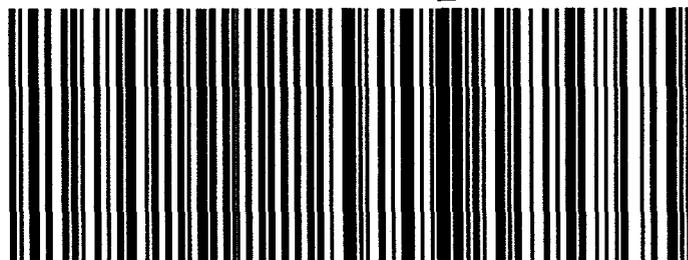
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