



American Academy of
Orthopaedic Surgeons®

AAOS

American Association of
Orthopaedic Surgeons®

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March 5, 2002

Kathryn C. Zoon, PhD
Director, Center for Biologics Evaluation and Research
Food and Drug Administration
141 Rockville Pike
Rockville, MD 20852-1448
Mail Stop: HFM-1

Re: Docket No. 97N-484R

Dear Dr. Zoon:

The American Academy of Orthopaedic Surgeons (AAOS), representing over 18,000 Board certified orthopaedic surgeons, is pleased to offer comments on Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing {Final Rule published in the Federal Register on January 19, 2001. [Docket No. 97N-484R]}. The Academy advocates revising the Final Rule in order to clarify the definition of the term "minimal manipulation."

The complexity of the issues and the imprecision of the term "minimal manipulation" as defined in 21 CFR §1271.10 of the Final Rule provide little guidance to orthopaedic surgeons and other users of cell- and tissue- based products:

Minimal manipulation is defined as: (1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement; and (2) For cells and nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

The vagueness of this definition presents challenges to FDA and orthopaedic surgeons alike in their dealings with the classification of tissue products. The Academy hopes to assist FDA in this matter by providing education and the opinions of orthopaedic surgeons, frequent users of allografts and tissue products, in the form of a categorization system for processed cell and tissue product.

The AAOS shares the concerns of the FDA to ensure patient safety in the use of allograft bone and tissue products. These concerns were served to an extent with the FDA's formation of a Tissue Reference Group (TRG) to review and define categories of human tissue. There have, however, been specific cases of problematic categorization of tissues by the TRG. Bone dowels serve as one example of the uncertainty and irregularity encountered in the categorization process. Bone dowels are conventionally processed to achieve specific surgically useful sizes, shapes and contours. Sizing, shaping and contouring operations can either be performed by the surgeon in an operating room, or by a manufacturer using more sophisticated machining techniques. So long as the processing does not alter the original relevant characteristics of the tissue as they relate to the tissue's utility for reconstruction, repair, or replacement, the distinction between back room surgical contouring and commercial manufacture of bone dowels is immaterial.

97N-484R

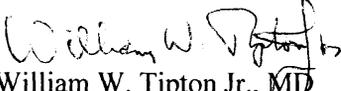
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To simplify the categorization process and to assist in identifying processing methods that do alter the relevant biological characteristics of the tissue, the Academy suggests a format which categorizes tissue based upon the degree of manipulation a product undergoes during its processing (see attachment). As advancements and refinements in tissue processing occur, ongoing research and information obtained may call for adjustments to this scheme. However, it currently offers a straightforward approach with which the FDA's Center for Biologics and Research and Evaluation (CBER) can suitably and efficiently categorize tissue products based upon their degree of manipulation.

The AAOS looks forward to working closely with the FDA on this important subject. We remain committed to ensuring the availability of safe tissues and tissue-based products to enhance the treatment of disease and injury in our patients. Thank you for this opportunity to present our comments.

Respectfully,


William W. Tipton Jr., MD
Executive Vice President



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Categorization of Processed Tissue

Category I: Tissues should demonstrate no change in biologic activity, tissue structure, and material properties.

This would include fresh tissues that have been harvested under sterile conditions within 12 hours of death and utilized within 24 hours. The tissues may be kept in physiologic solutions (without the addition of bioactive factors) and refrigerated at 4°C or incubated at 37°C until use. (Example: fresh meniscal allografts)

Category II: Tissues should demonstrate no change in tissue structure and tissue material properties, and only minimal change in biochemical content and biologic incorporation.

This would include fresh frozen (-80°C) or cryopreserved (-100°C with appropriate cryoprotectorant agents determined for each tissue) tissue that has been harvested and processed under sterile conditions. (Example: deep frozen menisci; cryopreserved menisci; deep frozen patellar tendon grafts/Achilles tendon grafts; cryopreserved ligaments)

Category III: Tissues should demonstrate no change in tissue structure and tissue material properties, and only minimal change in biologic incorporation.

This would include tissues that have been deep frozen and sterilized with gamma irradiation, ethylene oxide, and/or specified virucidal agents. The sterilizing agents and/or their byproducts must remain inert in the tissue matrix or they must be completely removed by a specifically designated protocol. (Example: deep frozen gamma irradiated (<2.5mRad) menisci; deep frozen gamma irradiated (<2.5mRad) patellar tendons)

Category IV: Tissue manipulation results in measurable alterations that do not impact on biological incorporation, tissue structure, or tissue material properties. This would be deemed as minimal impact on the relevant clinical use.

Category V: Tissue manipulation results in measurable alterations that do impact biological incorporation, tissue structure, or tissue material properties. The level of impact continues to allow effective clinical use. (Example: deep frozen gamma irradiated (>2.5mRad) menisci; deep frozen gamma irradiated (>2.5mRad) patellar tendons; lyophilized tissues (menisci/tendons +/- ETO sterilization)

Category VI: More than minimally manipulated.

The above classification is predicated on specific guidelines being developed and validated for the various preservation and secondary sterilization procedures.

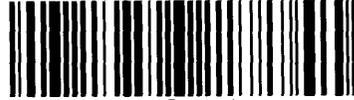
Harvesting of cells from ligament, tendon, and meniscus constitute more than minimal manipulation. Specific procurement and processing techniques must be evaluated on a case to case basis. The effects of the chosen harvesting procedures on the biologic activity and biological incorporation of these cells or cell-based constructs should be demonstrated to be in accordance with the above categorization system in order to receive proper tissue/cell manipulation designation.



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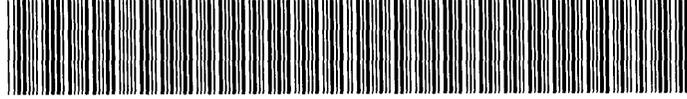


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