January 24, 2001

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

Ladies & Gentlemen:

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

The Orthopedic Surgical Manufacturers Association (OSMA) welcomes the opportunity to respond to FDA's request for comments by its stakeholders concerning the agency's regulation of human tissue based products. OSMA has carefully reviewed FDA's request for comments, and these comments represent the compilation of the member companies' views.

## I. INTRODUCTION AND BACKGROUND

OSMA was formed over 45 years ago and has worked cooperatively with the FDA, the American Academy of Orthopedic Surgeons (AAOS), the American Society for Testing and Materials (ASTM), and other professional medical societies and standards-development bodies. This collaboration has helped to ensure that orthopedic medical products are safe, of uniform high quality, and supplied in quantities sufficient to meet national needs. Association membership currently includes companies who produce over 85 percent of all orthopedic implants intended for clinical use in the United States. These companies provide for advances in technologies and innovations in products for the surgeons and patients who require them. These activities also provide a significant number of jobs for these U.S.-based companies through their global distribution systems.

OSMA has a strong interest in ensuring the ongoing availability of safe and innovative surgical implants. Historically, OSMA has focused on products composed of metal, ceramic, and other man-made materials. At the same time, OSMA works closely with the surgical community, who have

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long considered human allograft as both the standard of care and, in many cases, the **only** method of care. OSMA members fundamentally believe that the human allograft products currently available to surgeons should **not** be considered a device for regulatory purposes. We believe that the provisions of Section 361 of the Public Health Service Act addresses all relevant concerns. Therefore, Good Tissue Practices standards and the rules associated with 21 CFR 1270 appear to control, and address, all applicable risks. To limit the availability of these clinically necessary materials could adversely affect those very programs which use human allograft in conjunction with OSMA members' surgical implants. These surgical implants are regulated as devices. We shall expand on this point later in these written comments.

OSMA strongly supports FDA's principle of engaging its stakeholders in a dialog specific to these emerging regulations. We also believe that the measures taken to date by the agency regarding the safety of tissue, such as donor suitability rules, are to be applauded. While we have endorsed FDA's actions on donor suitability requirements to ensure a safe supply of tissue, we have strong reservations about certain aspects of FDA's proposed regulatory approach to tissue-based products.

Of greatest concern are, what appear to OSMA as, FDA's apparent attempts to regulate tissue in a burdensome and non-transparent manner. OSMA fears that the potential for these regulatory policies – by either being poorly constructed, unfairly executed, or both – could drive out good science and diminish FDA's very objectives. Poor regulatory policy also poses the prospect of adversely affecting innovation with no clear benefit. We will detail our views on these critical points in greater detail later in these comments.

OSMA continues to have significant questions and reservations about the "minimal manipulation" and "homologous use" criteria FDA is using to determine whether particular tissue-based products will be treated as conventional tissues or as medical devices or biological products.

OSMA also believes that the criteria FDA will use to make jurisdictional determinations cannot be judged separately from the process by which the agency will apply the criteria. Therefore, we have included additional written comments on the lack of procedures and openness by which the agency's Tissue Reference Group (TRG) determines jurisdiction.

## II. FDA'S CRITERIA AND PROCEDURE FOR JURISDICTIONAL DETERMINATIONS

### 1. Jurisdictional Status as Device vs. Biologics

OSMA has previously provided written comments to the agency where we stated that human bone allograft materials, and specifically those human

bone products currently used by surgeons for grafting purposes, should **not** be regulated as devices. They should be treated as tissue under Section 361 of the Public Health Service Act. It may be of value to summarize our perspective on the two laws surrounding tissue regulation and how they relate to the questions posed by the agency per the subject Docket.

Different sections of the Public Health Service Act govern, in the first case, the control of communicable diseases and, in the second, biological products. These are the two key sections which are termed 361 tissue and 351 tissue. The two sections can be easily confused.

For Section 361 tissue, these products are subject to 21 CFR Part 1270 for such critical items as communicable disease risks. They are not subject to premarket clearance. These Section 361 tissues are not like the Section 351 products which are subject to device or biologics regulations. Section 351 tissues require licensure as biologics based on, among other items, their potency.

OSMA supports FDA's effort to distinguish between these two areas of regulation. We believe that the agency is correct in obtaining comment from its stakeholders. We trust that this will be the first of several opportunities at rulemaking in this area. As such, we believe that FDA's regulatory standards for rulemaking procedures, where notice and opportunity for comment will be applied, will be used and are to be encouraged. We urge more requests for comments, as well as public meetings, on these critical matters as the agency clarifies its policies in this emerging area of regulation.

2. *"Minimal Manipulation"* and *"Homologous Use"*

OSMA believes that FDA's definitions of "minimal manipulation" and "homologous use" offer imperfect and uncertain guidance for determining what tissues should be regulated as devices, drugs, biologics, or tissues. As we've described in the distinctions between 351 and 361 tissues, any FDA initiative on the regulation of tissue should address those portions of 361 tissue that are relevant. These include processing controls through Good Tissue Practices. We believe that the development of criteria such as "minimal manipulation" and "homologous use" have no relevance to Good Tissue Practices and are impracticable at best.

OSMA fears that the rigid application of these definitions will lead to the imposition of inappropriate and burdensome requirements for these conventional tissues that are currently used by clinicians. Thus, products currently accepted by the clinical community as the "standard of care" may become unavailable to the surgeons and patients who require them; all because of unneeded and potentially unreasonable regulatory policies.

OSMA has found, therefore, that the current definition for minimal manipulation and homologous use are potentially harmful for the reasons we've stated and will speak to later. As such, OSMA would like to suggest an alternative approach.

OSMA strongly believes that the use of allograft bone in any clinically necessary, orthopedic procedure, as determined by the surgeon, represents homologous use regardless of the amount of manipulation of the product.

In addition, and as previously stated, OSMA encourages an ongoing rulemaking process and suggests that such an approach would present a reasonable alternative to the current impractical definitions. For example, labeling standards as part of a "notice and comment rule making" process would identify permissible claims as part of a class of products. Such a process could also address product composition (such as cortical bone or cancellous bone), physical dimensions, and other product description concerns.

OSMA further believes that current FDA concerns specific to this meeting would likely be addressed by FDA's final Good Tissue Practice (GTP) regulations. Most importantly, OSMA supports a sound and rational approach to tissue processing and welcomes the opportunity to work with the agency in bringing out reasoned and accepted standards such as these GTPs.

It is also important to state that standards currently exist in the form of accreditation requirements from the American Association of Tissue Banks.

Additional national standards are actively being developed by such groups as the ASTM under the Tissue Engineered Medical Products Standards group. Thus, in the absence of GTPs, OSMA believes enacting regulatory policies at this time would be premature. Further, such actions are disproportionate to the degree of risk. The controls that currently exist are capable of addressing all identified risks; and, finally, forcing a regulatory scheme at this time would likely be disruptive to ongoing standard-setting initiatives. We believe such a disruption would be at odds with the agency's own goals to establish standards, either voluntary or under its own GTPs.

As FDA applies its proposed criteria in practice, OSMA expects that there will be occasions when the agency and the medical community disagree over whether a specific product has been only "minimally manipulated" or is being put by physicians to a "homologous use." Also, while there may be cases where there is agreement on the application of the criteria, there will be disagreement about the appropriateness of the regulatory requirements imposed. OSMA believes that such disagreements

should be identified and resolved through transparent, open, and early communication between FDA and the medical community.

To clarify our concerns, vague and imprecise criteria such as "minimal manipulation" and "homologous use" generally lead to a lack of uniformity and transparency in regulatory practice. Thus, even if there may be a consensus on how these terms are interpreted and applied at one point in time, the apparent lack of a clear process to adjudicate these decisions would likely lead in the future to inconsistent, unreliable, and unpredictable regulatory opinions. OSMA is concerned about the prospect of setting a stage for regulatory "creep," where the implementation of regulatory policies will, in the future, be misinterpreted and wrongly applied.

OSMA believes that there are clear public health benefits in maintaining a safe and continued supply of tissue to the medical community and the patients who require them. We have found that the current policies and regulations dealing with donor suitability are sufficient to support the safe and effective use of human allograft tissue.

As previously noted, unnecessary and overly burdensome regulations, in the absence of final Good Tissue Practice (GTP) regulations, are premature and inappropriate to the degree of risk posed by these products. OSMA also finds that such premature regulations are at variance with FDA's stated objectives to streamline government regulations, minimize regulatory burdens, encourage product innovation, and be proportional to the degree of risk the product poses (see *Regulatory Affairs Focus*; Vol 2, No. 9; Sept. 1997, pages 16-19). We cannot emphasize too greatly our agreement with the agency on a proportional degree of regulation and say that, to our knowledge, there have been virtually no reports of infectious disease transmission in the U.S. for processed human bone allografts since 1985, when modern testing methods became available.

As stated, the imposition of these definitions to regulatory practice is considered arbitrary, at best, and would likely disrupt the availability of quality, innovative products. In fact, such action may promote the proliferation of hospital or other intrastate-based suppliers, frustrating the very interests of FDA and OSMA in seeking and maintaining safe and available supplies.

Therefore, a single broad definition, where human bone allograft used for repair, replacement, and restoration of function, embodies what OSMA believes to be the best alternative to the current proposal.

3. The Tissue Reference Group (TRG)

In early June 1999, OSMA received notification from Dr. Celia Witten of CDRH advising that the Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee would be meeting on July 27, 1999, to "focus on the classification of bone dowel devices of human origin". FDA invited OSMA and its members to participate in the panel meeting by presenting testimony and/or submitting written comments. From this language, OSMA concluded that CDRH had already determined that bone dowels should be regulated as medical devices under the FD&C Act. This was later confirmed in direct discussions with CDRH. OSMA presented its position to FDA at that time, where OSMA strongly disagreed with FDA. OSMA continues to object to FDA regulation of bone dowels as medical devices, among other objections.

We now understand that the preliminary determination to treat bone dowels as medical devices was based on a TRG meeting in the fall of 1998. Though FDA subsequently revised the agenda of the classification panel meeting to eliminate consideration of the bone dowel issue, the procedure used by the agency to determine that bone dowels should be treated as medical devices remains of great concern to OSMA and its members.

The TRG apparently holds the view that it has authority to respond to requests for designation from individual product sponsors by issuing either a determination for a particular product or a "recommendation" for an entire class of products. According to the TRG's own Annual Report for fiscal year 1998, the TRG has such authority. Even when the TRG takes action that purports to apply only to a specific manufacturer's product, the action is likely to serve as a precedent for all products in the same class and thus amounts to class-wide regulation. Indeed, there is an argument that failing to apply a product-specific regulation to other similar products would be subject to challenge as arbitrary and capricious. In issuing class-wide recommendations, the TRG purports to "communicate this information through guidance and revisions of regulations where appropriate." Nothing in current FDA regulations or in the TRG's Standard Operating Procedures requires the TRG to allow interested parties the opportunity to participate in their proceedings. This might result in a "recommendation" for regulation affecting an entire class of tissue-based products.

FDA regulations do not permit the Office of the Ombudsman to issue class-wide jurisdictional determinations based on a request for designation from a single manufacturer. Under 21 C.F.R. Part 3, a sponsor of a premarket approval application or investigational filing for a product is permitted to submit a Request For Designation (RFD) to the Office of the Ombudsman. This is where the "agency component with primary jurisdiction [of the product] is unclear or in dispute." Within 60 days of the

filing date, the Ombudsman is required to "issue a letter of designation to the sponsor... specifying the agency component designated to have primary jurisdiction for the premarket review and regulation of the product at issue and any consulting agency components." This regulation does not authorize the Ombudsman to respond to the RFD with a letter of designation covering all products in the class.

FDA should clarify the TRG's authority. At minimum, OSMA believes the agency should amend the Standard Operating Procedures followed by the TRG to preclude the Group from issuing class-wide "recommendations" based on an assessment of a single product. OSMA also urges FDA to: (1) issue a public announcement whenever the TRG determines that a specific tissue-based product is to be regulated under the FD&C Act; and (2) provide general notice whenever the TRG concludes that an RFD might become the basis for treating an entire class of tissue-based products as medical devices or biological drugs under the FD&C Act.

With respect to these TRG proceedings, a number of recommendations were made by stakeholders during the August 2, 2000, public session specific to the TRG. OSMA strongly supports many of these comments and believes that FDA should institute the following general procedures for any action taken by the TRG which were proposed at the August 2nd meeting.

First, TRG meetings should be announced by publication in the *Federal Register* or in some other formal fashion, together with a general description of the issues to be discussed. To OSMA's knowledge, nothing in the TRG's standard operating procedures assures that all interested parties, including companies directly affected by a decision, will be given notice that the TRG intends to consider the jurisdictional status of a particular product.

Second, TRG meetings should be open to the public, subject to the confidentiality requirements in federal law and FDA regulations. The TRG has taken the position that its meetings are not required to be open because proprietary information is submitted by the sponsor requesting the ruling. In fact, FDA routinely holds open meetings on subjects involving proprietary information, closing only those portions of the meeting that require the disclosure of confidential data.

Third, the TRG's standard operating procedures should direct the Executive Secretary of the Group to publicize the group's findings and the basis for its decisions, subject to the confidentiality requirements in federal law and FDA regulations, and that the TRG's standard operating procedures should require the Group to explain jurisdictional determinations of the basis of published criteria.

OSMA acknowledges that the TRG has been operating for more than two years and has made recommendations for more than ten cellular and tissue-based products. OSMA further recognizes that FDA has limitations on its resources to implement the tissue program. In our view, however, the current TRG procedures must be improved to address the legitimate concerns of the medical community to ensure a fair and equitable consideration. FDA must recognize that significant financial investments have been made in these technologies where unnecessary FDA action could put these investments at risk.

We trust you find these comments of value and would request the opportunity to discuss these concerns with the FDA directly should the FDA not agree with our comments.

Again, we thank you for the opportunity to comment.

Sincerely,

Tom Craig, President
Orthopedic Surgical Manufacturers
Association (OSMA)

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