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

Dear Sir/Madam:

Subject: Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement
Docket No. 97N-484P

The Orthopedic Surgical Manufacturer's Association (OSMA) welcomes the opportunity to provide comments on FDA's proposed rule to require manufacturers of human cellular and tissue-based products to follow current good tissue practice, which FDA published in the *Federal Register* on January 8, 2001.

I. Background and Introduction

OSMA was formed over 45 years ago and has worked cooperatively with 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, 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 member companies producing over 90 percent of all orthopedic implants intended for clinical use in the United States, and provides significant jobs and income for these U.S.-based companies through their global distribution systems. Furthermore, OSMA's membership includes companies that procure, process and/or distribute donated human bone tissues for transplantation.

OSMA strongly supports the principle of good tissue practice to prevent the transmission of communicable disease from infected donors, and believes that the measures outlined In FDA's proposed good tissue practice rule, for the most part, are basically sound. We have strong reservations, however, about some fundamental/underlying provisions, as well as certain specific aspects of FDA's proposal as these appear to be overly burdensome and/or not supported by risk. OSMA's comments on specific provisions of the proposed rule are provided in the following sections. These comments are provided primarily with respect to the relevance of the proposed GTPs to human bone allografts.

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At the same time, and of equal concern, are FDA's attempts to regulate tissue in a non-transparent manner, for which OSMA has previously submitted comments to the Agency. Thus, OSMA is taking this opportunity to also reiterate in the last section of this letter its previous comments on the lack of procedures and openness by which the agency's Tissue Reference Group is using to make jurisdictional determinations.

II. General Comments on FDA's Risk-Based Regulatory Approach and the Proposed GTPs

In the introduction section of the proposed rule for GTPs, FDA reiterates its risk-based regulatory approach that it had previously espoused in various publications regarding regulation of human tissue products. OSMA strongly supports the Agency's statement that regulations for human tissue should be risk-based such that tissues are subject to a level of regulation commensurate with risk, and that central to the concept of risk for human tissues is the transmission of communicable diseases. With this in mind, OSMA is compelled to comment on the Agency's reliance on the terms "function" and "integrity" in the proposed GTPs.

FDA introduces in Section 1271.150(a), as a general concept underlying the proposed GTPs, the prevention of adverse affects on the function and integrity of tissue products through improper manufacturing. In addition, FDA specifically uses the terms "function" and "integrity" throughout the proposed GTPs as a basis for particular requirements.

OSMA agrees with the concept of ensuring the function and integrity of a tissue-based product in a general sense; i.e., to ensure that the product is fit for use. However, OSMA questions the underlying rationale presented by the Agency for the use of these terms, i.e., that impairment of the function or integrity of a tissue product increases the risk of disease transmission. The rationale presented by the Agency would appear to be largely theoretical, with little or no quantitative evidence of increased risk. As previously stated, we support the idea of risk-based regulations. Moreover, the terms "function" and "integrity" are very broad and open to interpretation such that the use of them in the context of establishing specific requirements or sections of the GTPs, without definition or clarification of these terms, is potentially problematic as explained below. Thus, we oppose the use of "function" and "integrity" as a basis of communicable disease risk in risk-based regulations.

The use of the terms "function" and "integrity" to establish specific GTP requirements implicitly establishes requirements for the manufacturer to be able to specifically assess the function and integrity of their products. In the absence of any definition and/or clarification of these terms by the Agency, these terms are open to subjective and varying interpretation and inconsistent application within the Tissue Industry. Moreover, it is likely that the use of these terms would engender expectations on the part of FDA inspectors that would vary and would lead to inconsistent application and enforcement of the respective sections of the GTPs. Also, the implicit requirements or expectations resulting from the use of the terms "function" and "integrity" pose difficulties in attempting to apply them to such tissues as bone allografts. Some examples of the issues or difficulties presented by the use of these terms are provided in the following sections.

Human bone allografts are processed and made available to surgeons in hundreds of different shapes, sizes and bone types (e.g., cortical, cancellous,

cortical/cancellous). The application, and thus function, of most of these bone allografts is left up to the discretion of the surgeon. Indeed, it is common for a particular size and shape of graft to be used in different applications, with somewhat different functions. Thus, it is not feasible for a manufacturer of bone allografts to define the "function" of all allografts. The term "integrity" also presents potential issues or problems in applying it to the manufacturer of bone allografts. The issue described above for function is also applicable to integrity, such that the breadth of "acceptable" integrity may depend on the particular application of the graft. Furthermore, due to the biological nature or origin of bones, there is inherent variability such that what constitutes integrity may vary widely.

OSMA strongly recommends that the Agency move away from the use of the terms "function" and "integrity" in establishing specific GTP requirements either by deleting these terms from the proposed rule or by replacing them with more concrete, well-defined terms based on a risk-based system. As described below in OSMA's comments on specific parts of the proposed rule, OSMA has attempted to provide alternate, more practical terms where "function" and "integrity" have been used.

If the Agency insists on retaining the terms "function" and "integrity" in the GTPs, then OSMA strongly requests that the Agency provide definitions for these terms that are clear, meaningful and can be implemented and consistently employed. Furthermore, OSMA requests that the Agency provide clarification on how these terms affect a risk-based system and how it intends to interpret and apply these terms as used in the context of specific requirements during the course of inspections.

If the Agency insists on retaining these terms and is unwilling to provide specific definitions for them, at a very minimum the Agency should identify an acceptable means, or otherwise provide guidance to industry as to how these terms can be implemented by industry. OSMA strongly suggests that FDA allow manufacturers to perform a standard risk analysis based on established and recognized standards. This would be consistent with FDA's stated objectives and would provide essentially a safety assessment, based upon which manufacturers would then identify those product characteristics associated with the product's function and integrity that are key to safety. The manufacturer would then use the outcome of this analysis to control for those key characteristics.

III. Comments on Specific Provisions of the Proposed GTPs

1. Definition of "Complaints" (Proposed Section 1271.3(ii)

FDA is proposing that the definition of a complaint include communication that alleges that the function or integrity of a tissue product may have been impaired. For reasons given in Section II of this letter, OSMA believes that the terms "function" and "integrity," without clear definition, are vague, imprecise and impossible to apply and, thus, recommends that they be defined, replaced with alternate wording and criteria (see below), or deleted from the definition of complaints. In addition, OSMA believes that the third part of the complaint definition – "any other problem with a human cellular or tissue based product that could result from the failure to comply with current good tissue practice" - is also overly broad, imprecise and therefore impractical in defining what constitutes a complaint. OSMA also notes that this definition of complaints for tissue products is not limited to a product after it is released for distribution, as is the case with complaints for medical devices.

Therefore, OSMA recommends that subparagraphs (2) and (3) of the complaint definition be replaced by wording analogous to that used to define complaints for medical devices as follows: "deficiencies related to the identity, quality, durability, reliability, safety, or performance of a product after it is released for distribution."

2. Provision for Overall Responsibility to Rest with Establishment That Releases the Tissue (Proposed Section 1271.150(b))

Under this section, the establishment that determines that the tissue meets release criteria and makes the product available for distribution would be responsible for ensuring that the product has been manufactured in compliance with requirements for screening and testing, good tissue practice and any other applicable requirements.

OSMA objects to this provision and finds that the extent to which an establishment could be held accountable for another establishment's actions is undue and unprecedented with respect to FDA regulations. There is no similar provision like this in the Quality System Regulation, for example, whereby the manufacturer has responsibility over all other involved parties for compliance with QSR requirements. Furthermore, this provision is inconsistent with Industry practice and with standards established by the American Association of Tissue Banks (AATB). **OSMA believes that this provision is a misinterpretation by the Agency of AATB standards.**

This section of the GTPs should be deleted. As an alternative, it must be harmonized with current industry operations and AATB standards which basically require that relationships and responsibilities among tissue banks jointly/cooperatively involved in the retrieval, processing or distribution of tissues be documented, and that compliance with the requirements, which is the responsibility of all parties, shall be documented by all parties.

If the Agency insists on retaining this provision that would hold one organization responsible for another organization's compliance to GTPs, then OSMA strongly urges the Agency to include language limiting the penalties that could be imposed on a responsible establishment in situations where the responsible establishment is working in good faith and practicing due diligence to ensure compliance by other parties (e.g. by establishing and following audit procedures), only to have one of the parties found to be non-compliant with GTPs.

3. Requirements Regarding Equipment (Proposed Section 1271.200)

Paragraph (b) of this section would establish requirements for maintaining, cleaning and sanitizing equipment to prevent, in part, "...events that could reasonably be expected to have an adverse effect on product function or integrity."

As explained in Section II of this letter, OSMA is concerned that the terms "function" and "integrity" are open to broad interpretation and could lead to the

evolution of inappropriate expectation/requirements in the course of the Agency's inspection activities. Furthermore, the use of these terms here is not consistent with the language in subparagraphs (a) and (c) of this section. These two subparagraphs present requirements for equipment so as not to have any adverse effect on the product. There is no use of the terms "function" and "integrity" in these subparagraphs. In addition, OSMA believes that the terms "function" and "integrity" are of no use in establishing the requirements of this section within a risk-based approach system centered on communicable disease transmission.

Therefore, OSMA recommends that the phrase in question in subparagraph (b) be revised via the deletion of the terms "function" and "integrity" such that it reads "...events that could reasonably be expected to have an adverse effect on the product."

4. Requirements for Process Controls (Proposed Section 1271.220)

Subparagraph (a) of this section would require that establishments develop, conduct, control and monitor its manufacturing processes to ensure that each tissue-based product conforms to specification is not contaminated, maintains its function and integrity and is manufactured so as to prevent transmission of communicable disease by the product.

OSMA objects, as explained in preceding parts of this letter, to the use of "function" and "integrity" as they are open to varying interpretation and varying application by inspectors. In addition, the use of these terms essentially establishes a requirement that manufacturers of tissue products establish functional characteristics and acceptance criteria for all products. As explained earlier, many bone grafts are simply produced in accordance with approved physical specifications and are left to the discretion of the surgeon as to the particular application and, thus, function to which he/she will employ the graft.

OSMA believes that subparagraph (a) can, and should, be revised such that it provides requirements for process controls that are adequate and yet can be implemented or reduced to practice. OSMA recommends that the terms "function" and "integrity" be deleted from this subparagraph and that the word "established" be inserted before "specifications." This would, in effect, establish a requirement that specifications be established for tissue products. A manufacturer would be required to maintain processes that ensure that the tissue conforms to these specifications, is not contaminated, and does not transmit infectious disease.

Similarly, the use of the terms "function" and "integrity" in subparagraph (b) of this section is not warranted, and these terms should be deleted such that the requirement simply contains language regarding adverse effects on the product as opposed to adverse effects on the product's function and integrity. As noted in OSMA's comments above on proposed Section 1271.200, parts of this section require controls to ensure that there is no adverse effect "on the product"; the terms "function" and "integrity" are not introduced in these parts to raise ambiguous expectations. Similarly, as stated above for Section 1271.200, OSMA believes that the terms "function" and "integrity" are of no use in establishing the

requirements of this section (1271.220) within a risk-based approach system centered on communicable disease transmission.

5. Requirement for Validation of Process-related Claims (Proposed Section 1271.230(b))

This section requires that any process-related claim, e.g., sterility, be based on a validated process. Currently, sterility assurance for human bone allografts is commonly provided by tissue banks via a series of controls that includes bioburden monitoring of incoming tissues, subjecting the tissues to validated/proven decontamination steps, processing under aseptic conditions, and sterility testing of the final product. This approach to sterility assurance is employed by tissue banks and preferred by many surgeons, given that conventional sterilization methods (e.g., steam, irradiation etc.) may adversely affect tissue at sterilizing doses. This approach to sterility assurance has a long history of use, apparently with no significant instances of infection or clinical problems.

Based on the above considerations, OSMA believes that FDA should allow for sterility verification of processed tissue when technology limitations exist and when established manufacturing approaches have not led to clinical problems.

6. Requirements for Control of Storage Areas (Proposed Section 1271.260(a)

This section proposes requirements for the control of storage areas to prevent any condition "...that may adversely affect product function or integrity."

As explained previously, OSMA believes that the terms "function" and "integrity," without definition or clarification, could lead to varying interpretation and application. OSMA believes that these terms should be deleted from this section, and that the phrase in question should be revised to read "...that may result in failure of the product to meet or maintain established specifications." If the Agency is insistent on using the terms "function" and "integrity," then these terms must be defined or otherwise clarified.

7. Requirements for Storage Temperatures (Proposed Section 1271.260(b)).

This section proposes requirements that temperature limits for storage of tissue be established to ensure product function and integrity and prevent product deterioration.

As stated elsewhere in this letter, OSMA is concerned that the use of the terms "function and integrity" here could lead to the imposition by FDA inspectors of unreasonable and inconsistent expectations and requirements upon manufacturers. Also, use of the term "deterioration" in this section is vague and open to interpretation. These terms should be eliminated and the text revised using language similar to that proposed in item 6 above (i.e., express in terms of "...failure to meet or maintain established specifications").

8. Requirements for Making Products Available for Distribution (Proposed 1271.265(c)

This section proposes requirements to prevent the release and distribution of tissue products that, among other things, "...have deteriorated". As stated above in this letter, the term "deterioration" is vague and open to interpretation, and should therefore be deleted. In its place, a revised phrase or requirement based on expiration date or established specifications should be used.

9. Requirements for Tracking (Proposed Section 1271.290)

This section proposes various requirements for the tracking of tissue from donor to recipient and from recipient to donor, in which the manufacturer/distributor of the tissue is essentially responsible for ensuring the cooperation and compliance of the tissue transplant establishments regarding parts of the proposed requirements.

OSMA believes, at least with respect to bone allografts, that such rigorous requirements are unnecessary, that the proposed requirements go well beyond current practice in the tissue banking industry, and that the proposed requirements would be overly burdensome and unfeasible for manufacturers/distributors. Further, OSMA believes that in proposing requirements for tracking, FDA has misinterpreted AATB standards.

Currently in the tissue banking industry, mechanisms are widely employed by which bone allografts tissues can be traced from the donor to the transplant facility and from the transplant facility to the donor. Mechanisms or efforts to allow traceability to the recipient typically exist via the inclusion in the allograft packaging of tissue utilization records to be completed by the transplant facility and returned to the tissue manufacturer/distributor. In addition, the transplant establishments are instructed in the tissue product labeling to return the completed utilization records. However, it is not possible for manufacturers/distributors to force compliance by the user.

Under the proposed regulations, FDA is essentially requiring tissue manufacturers to enforce compliance with tracking provisions by the transplant establishments over which the manufacturers/distributors and FDA have no authority. Among other things, this could impose onerous requirements on tissue manufacturers to audit healthcare facilities. The responsibility to enforce compliance by transplant establishments should rest with the JCAHO, which already requires hospitals to maintain records necessary for traceability.

OSMA also believes that proposed tracking requirements, and the associated burden that would be placed on tissue manufacturers, are unjustified from a risk standpoint. To the best of OSMA's knowledge, there have been no documented cases of disease transmission specific to human bone allografts since 1988, when modern test methods became available.

Furthermore, OSMA wishes to point out that the Agency is proposing requirements for tissues that are seemingly greater than those for devices, where only life-supporting/life-sustaining devices are tracked. Moreover, based on the

history/experience with device tracking, OSMA believes that tracking of tissues would not be feasible.

Finally, tracking of tissue products to the patient level is problematic in light of recent legislation and implementation of regulations regarding confidentiality of health information. The Health Insurance Portability and Accountability Act (HIPAA, Pub.L. 104-191) requires, among other things, consent from individuals for disclosure of their confidential information. This would presumably cover receipt of allograft tissue; patient-identifying information such as name, address, telephone number; etc. There are substantial financial penalties for obtaining this information in violation of the Law. OSMA cannot envision a practical scenario for any entity over which FDA has jurisdiction to obtain the required patient consent. Only treating physicians and hospitals are in such a position. Therefore, OSMA strongly opposes the tracking of human bone allograft tissues as provided for in this section on the basis that: 1) there is no known risk(s) that would justify tracking; 2) the proposed requirements are inconsistent with FDA and industry standards; and 3) the proposed tracking regulation would require collection of confidential patient information in conflict with another Federal Law. OSMA strongly urges the Agency to delete the requirements for tracking tissue products, or exempt human bone allografts from these requirements, or substantially revise the requirements to be consistent with current, accepted practice regarding traceability of allograft tissues.

10. Requirements for Reporting Adverse Reactions (Proposed Section 1271.350(a))

This section presents criteria and timeframes for reporting adverse reactions. OSMA believes that certain aspects of the proposed criteria for which adverse reactions must be reported are broad and need to be further defined, and that the reporting timeframes need to be revised to be consistent with the severity of the reaction.

With regard to reporting criteria, OSMA recommends that subparagraph (iv) ("necessitates medical or surgical intervention") be followed by the qualifying phrase, "to preclude permanent impairment of a body function or permanent damage to a body structure" so that it is consistent with language used in the Medical Device Reporting regulation (21 CFR Part 803). In addition, OSMA notes that the proposed criteria involve consideration of a product's "function" and "integrity." As explained elsewhere in these comments, OSMA believes that these terms are broad and open to interpretation and that they, therefore, need to be defined if they are to be used in the final rule.

With regard to the reporting timeframe, OSMA believes that the proposed 15-day requirement for reporting adverse reactions is unnecessarily short for all adverse reaction reports. OSMA recommends that, for reports not involving death or disease transmission, the reporting timeframe should be 30 days, which is the time afforded for most MDR reports for devices. OSMA believes that shorter reporting times for adverse reaction reports not involving death or disease transmission would result in the filing of reports before adequate information could be obtained by the manufacturer and would not add much value in terms of protecting the public health.

11. Requirements for Reporting Product Deviations (Proposed Section 1271.350(b))

Under this section, a product deviation that could reasonably be expected to lead to a reportable adverse reaction would need to be reported.

OSMA believes that this proposed requirement is burdensome and that the value such reports would provide to the Agency is questionable. It is OSMA's understanding that the Agency lacks the resources to process all the MDR reports that it is currently receiving. In fact, the Agency has in recent years been exploring and pursuing more efficient, more streamlined reporting programs for devices. OSMA believes that the requirement for reporting any product deviation that could result in an event that meets any of the criteria for a reportable adverse reaction would result in the submission of reports that are of little value.

OSMA recommends that this section be revised so that the requirement for reporting product deviations would be limited to instances involving issues of disease transmission. Furthermore, and in concert with the Agency's November 7, 2000 final rule on reporting biological product deviations, deviation reports under GTPs should be required only for those instances where the product involved has left the manufacturer's control; and a maximum reporting period of 45 days should be specified in addition to, or in lieu of, the proposed vague requirement of "...as soon as possible...."

12. Criteria for Claims Considered to be a Use Other than Homologous Use (Proposed Section 1271.370(b)(2).

This section presents proposed criteria by which certain types of claims for a product would be regarded as a claim for a use other than homologous use such that the product would then be subject to regulation under Section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act. OSMA believes that this proposed section is unnecessary and could create confusion regarding the definition of homologous use.

The Agency has established a definition and provided guidance for homologous use in the final rule on tissue bank establishment registration and listing (66 FR 5477, Jan. 19, 2001). The proposed Section 1271.370(b)(2) would essentially establish additional criteria for homologous use that are broad and rather vague. OSMA believes that this attempt to establish criteria beyond the definition for homologous use which is already established would only serve to complicate and confuse the concept of homologous versus non-homologous use that the Agency and Industry have been working hard to clarify.

OSMA requests that the Agency remove this section from the proposed rule and allow the existing definition of homologous use to stand as the sole definition.

13. Provision for Records Review by FDA (Proposed Section 1271.400(d)

Under this section, FDA representatives would be permitted to review any records to be kept under the proposed GTP rule.

OSMA wishes to point out to the Agency that the Quality System Regulation for devices specifically exempts from FDA review certain quality system records, including records of management reviews, internal quality audits, and supplier evaluations. The purpose of this is to encourage/promote the effectiveness of these quality system functions.

OSMA requests that, consistent with the requirements for devices, this section of the proposed rule for GTPs be revised to specifically exempt from FDA review records of management review, quality audits, and supplier evaluations for the same reasons. Also, the revised section should identify other types of information, e.g., financial information, that are exempt from review.

IV. Retrospective Application and Effective Date of GTPs

OSMA is opposed to the retrospective application of any regulation or guidance documents to tissue recovered prior to its issuance. In many cases, conventional tissues, such as frozen or freeze-dried tissues, have a shelf life of up to five years. The retrospective application of the final GTP regulation could potentially cause the needless loss of safe human tissue in order to comply with the new regulation. FDA has already set a precedent by not requiring retrospective application of the current final rule (21 CFR 1270) to tissues recovered prior to its issuance.

OSMA recommends that FDA add to the GTP rule the following wording which is contained in the preamble to current final rule 21 CFR 1270 section III C: "The final rule for Good Tissue Practice (21 CFR 1271) will have an effective date of 180 days after the date of publication and will apply to human tissues and cells recovered after the effective date. For tissues and cells recovered prior to the effective date of the final rule for Good Tissue Practice, the previous rule (21 CFR 1270) applies."

Furthermore, OSMA strongly recommends that the FDA consider specifying in the final rule for GTPs a grace period after the effective date to allow adequate time for all registered tissue facilities to implement quality systems necessary to comply with GTP requirements. It is our understanding that FDA is considering a 1- to 2-year grace period for the final GTP rule. OSMA applauds and supports the Agency's consideration and efforts to provide such a grace period.

V. Comments Concerning Tissue Product Classification Determinations

OSMA would like to take this opportunity to restate its view regarding the Agency's program and practices for determining whether a tissue-based product should be regulated under Part 1270/1271, or whether it should be regulated under Section 351 of the PHS Act and/or the Federal Food, Drug, and Cosmetic Act. OSMA has submitted comments on this topic in its comments on the proposed rule for donor suitability requirements (Docket No. 97N-484S) and in conjunction with the August 2, 2000 public workshop on human bone allografts (Docket No. 00N-1380).

The Agency has established the Tissue Reference Group (TRG) with the authority to make recommendations for a specific product or for a class of products. 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. Thus, OSMA believes that the process, the criteria applied and the decisions made with regard to a product's regulatory status as a tissue, device or combination product should be open and transparent. To this end, OSMA wishes to remind the Agency of the specific recommendations regarding the authority and proceedings of the TRG that it has provided to the Agency via the aforementioned comments.

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.

We thank you for the opportunity to comment.

Sincerely,

Thomas L. Craig
President

Express

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