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

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

Dear Sir or Madam:

On behalf of the Musculoskeletal Transplant Foundation (MTF), I am responding to the Proposed Approach to Regulation of Cellular and Tissue Based Products. MTF appreciates this opportunity to respond to the Food and Drug Administration (FDA) 21 CFR Part 1271 "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule " published in the Federal Register on January 8, 2001.

Founded in 1987, MTF is the nation's largest non-profit musculoskeletal tissue recovery organization and has recovered more than 22,000 tissue donors to date. The Foundation's membership consists of leading medical/academic/research institutions, as well as 31 tissue/organ recovery organizations throughout the country. The majority of these recovery organizations are OPOs that represent nearly 1/3 of the nation's total. The MTF is also an accredited member of the American Association of Tissue Banks (AATB) and has actively participated with the AATB to develop standards for tissue banking. We have formulated our comments to the discussion document based upon these experiences.

MTF 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. MTF'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.

At the same time, and of equal concern, are FDA's attempts to regulate tissue in a non-transparent manner, for which MTF has previously submitted comments to the Agency. Thus, MTF 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.

We hope that our comments and suggestions will be taken into serious consideration.

Sincerely,

97N-484P C22

Joel C. Osborne, Director of Quality
Assurance and Regulatory Affairs

Musculoskeletal Transplant Foundation
Comments 21 CFR Part 1271 "Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement; Proposed Rule

I. General Comments

1. 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. MTF 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, MTF 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.

MTF 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, MTF 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 poses 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.

Recommendation: MTF 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 MTF's comments on specific parts of the proposed rule, MTF 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 MTF strongly requests that the Agency provide definitions for these terms that are clear, meaningful and can be implemented and consistently employed. Furthermore, MTF 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. MTF 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.

2. Retrospective Application of 21 CFR 1271

MTF is adamantly 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 this regulation could potentially cause the needless loss of safe human tissue in order to comply with the new regulation. FDA has already set a past precedent by not requiring retrospective application of the final rule (21 CFR 1270) to tissues recovered prior to its issuance.

Recommendation: MTF recommends that FDA add the following wording to the proposed rule, which is contained in the preamble to current final rule 21 CFR 1270 section III C.

"The final rule (21 CFR 1271) will have an effective date of 180 days after the date of publication and will apply to human tissues and cells after the effective date. For tissues and cells procured prior to the effective date of the final rule (21 CFR 1271), the previous rule 21 CFR 1270 applies."

Furthermore, MTF recommends that the FDA consider specifying in the Final Rule a grace period of 12 months after the effective date to allow adequate time for all registered HCT/P 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. MTF applauds and supports the Agency's consideration and efforts to provide such a grace period.

3. Preamble

In the preamble, FDA requests *"consultation from the States on any preemption issues raised by the proposed cGTP rule . . .."*

Recommendation: MTF requests that FDA state in the final rule that its provisions preempt state tissue regulations.

II. Comments on Specific Provisions of the Proposed GTPs

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

FDA is proposing that the definition of a complaint includes 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, MTF 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 be deleted from the definition of complaints. In addition, MTF 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. MTF 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.

Recommendation: MTF 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. "

5. Provision for Quality Programs (Proposed Section 1271.160(a))

Subsection (a) of proposed section 1271.160 states (in relevant part):

"An establishment that performs any step in the manufacture of human cellular and tissue-based products shall establish and maintain a quality program that is appropriate for the specific human cellular and tissue-based products manufactured and the manufacturing steps performed and that meets the requirements of this subpart."

Recommendation. MTF agrees that an establishment performing any manufacturing activities for tissue products should have a quality program and that the scope and depth of the quality program should be commensurate with the manufacturing steps performed and the types of tissues involved.

MTF also endorses the statements in the preamble accompanying the proposed rule indicating FDA's intention to permit variations among tissue establishments' quality programs and to impose a lower level of regulatory supervision on tissue products subject to regulation under Section 361 than the agency has established for tissue products that are regulated under the Federal Food, Drug, and Cosmetic Act or under Section 351. This is consistent with FDA's expressed intention to subject conventional tissues to more modest regulation than other tissue-based products, reflecting the relative levels of risk associated with these categories of articles.

Consistent with these statements, MTF requests that FDA include in the final regulations language that distinguishes between "quality programs" as described in the proposed rule and other quality requirements. This will assure that tissue establishments are not held to unsuitable quality requirements.

6. 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.

MTF 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 AATB. MTF believes that this provision is a misinterpretation by the Agency of AATB standards.

Recommendation: 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 MTF 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.

7. Computer Software Validations (Proposed Section 1271.160(e))

Subsection (e) of proposed section 1271.160 states:

"If computers or automated data processing systems are used as part of the quality program, as part of manufacture or tracking, or for maintaining data or records related to the manufacture or tracking of human cellular or tissue-based products, the establishment shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented."

Recommendation: MTF requests that this provision be modified to limit the scope of the requirement for software validation. Regulatory requirements for software validation should be tempered by an analysis of potential impact. Rather than requiring that all software and software changes be validated, FDA should limit validation requirements to the most necessary areas in order to encourage the use of software programs in lieu of manual systems in record keeping. Reliance on manual systems in the quality program of tissue banks could result in a loss of system integrity and an inability to respond quickly in a recall situation.

MTF suggests the following language:

"All software and changes in software that controls tissue tracking information, is the sole source for any information necessary for donor suitability determinations, is the sole source for information used to release products for clinical use, or functions as an expert system in any phase of manufacture shall be validated."

MTF has serious concerns about FDA's use of the term "validation" throughout the proposed rule. The proposed definition of "validation" provides only vague guidance to the tissue community with respect to the nature of the validation requirements in each of the provisions of the proposed rule in which it is used.

It is unclear whether FDA has substituted the concept of "validation" for other words used in analogous provisions of the AATB standards. AATB's standards require a level of review that is tailored to the type of processing used for a particular tissue. Thus, for example, while validation is required for shipping containers intended for use in enclosing tissues that must be maintained at other than ambient temperature, AATB's standards require only verification or confirmation for other aspects of tissue processing.

MTF requests that FDA clarify that tissue establishments that comply with these provisions of AATB's standards will be deemed to comply with the validation requirements of the proposed rule.

8. Deviations (Proposed Section 1271.180)

Proposed section 1271.180 states (in relevant part):

"Any deviation from a procedure shall be authorized in advance by a responsible person, recorded, and justified."

Recommendation: Deviations cannot always be authorized in advance, as they are often the result of unforeseen circumstances. Technical staff in the field at a procurement or even during processing may need to deviate from the specifics of a procedure in unusual circumstances. These personnel are trained to make such decisions and document any deviations thoroughly. Authorization by a "responsible person" prior to the deviation may not be possible, and unyielding application of a prior approval requirement could result in an inability to release a tissue.

MTF requests that the proposed language be modified as follows:

"Any deviation from a procedure, together with the justification for the deviation, shall be recorded at the time of occurrence. The deviation shall be approved by a responsible person prior to release of the tissue or tissues affected by the deviation".

9. Proposed Section 1271.190

Proposed section 1271.190 states (in relevant part):

"Any facility used in the manufacture of human cellular or tissue-based products shall be of suitable size, construction, and location to facilitate cleaning, relevant maintenance, and proper operations. The facility shall be maintained in a good state of repair. Adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities shall be provided. . . .

Any facility used in the manufacture of human cellular and tissue-based products shall be maintained in a clean, sanitary, and orderly manner. . . .

All significant cleaning and sanitation activities shall be documented, and records shall be maintained."

Recommendation: These provisions are too broad and open to inconsistent application. The requirements for facility design and size should be tailored to the processing steps being performed and to the risk of contamination.

MTF requests that this provision be modified to include language that relates the substantive requirements to preventing the transmission of communicable diseases from contaminated tissues to recipients. For example, the provision could state: "Facilities shall be of suitable design and sufficient size to perform necessary operations, prevent contamination with communicable disease agents, and ensure orderly handling without mix-ups."

10. 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, MTF 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, MTF 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.

Recommendation: MTF 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."

11. 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.

MTF 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.

Recommendation: MTF 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. MTF 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 are 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 MTF'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, MTF 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.

12. Process Validation (Proposed Section 1271.230(a))

Proposed section 1271.230(a) states (in relevant part):

"Where the results of a process cannot be fully verified by subsequent inspection and tests, the process shall be validated and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation, shall be documented."

Recommendation: MTF recommends deleting the word "fully" from this provision, as it is too broad and subject to inconsistent application. Once a process has been validated, and changes are required that do not increase the risk of communicable disease transmission to the recipient, a written justification for not revalidating should be sufficient. FDA has previously agreed in similar situations that validation is not always necessary.

13. Requirement for Validation of Process-Related Claims (Proposed Section 1271.230(b))

Proposed section 1271.230(b) states (in relevant part):

"Any process-related claim in labeling or promotional materials for a human cellular or tissue-based product, e.g., a claim for sterility or viral inactivation, shall be based on a validated process."

Recommendation: 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 have been shown to 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, MTF 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.

14. Requirements for Control of Storage Areas (Proposed Section 1271.260(b))

Proposed section 1271.260(b) states:

"(1) Each establishment shall store human cellular and tissue-based products at an appropriate temperature and for no longer than the maximum storage period for the product.

(2) Acceptable temperature limits for storage of human cellular and tissue-based products at each step of the manufacturing process shall be established to ensure product function and integrity, to prevent product deterioration, and to inhibit the growth of infectious agents."

Recommendation: MTF requests that FDA clarify that these provisions do not require tissue establishments to validate storage temperatures or storage periods. The tissue industry has established ranges of storage periods and temperatures for particular products based on experience.

In subsection (b)(2), MTF recommends the following modification of the proposed language: "Acceptable temperature limits for storage of human cellular and tissue-based products at each step of the manufacturing process shall be established to prevent the transmission of communicable disease to prospective recipients of the products." As stated above and discussed further in Part III of these comments, MTF objects to FDA's use of the phrase "product function and integrity" because these concepts are undefined and beyond FDA's legal authority. Also, MTF objects to the introduction of a new and heretofore undefined term, "deterioration," which MTF believes would introduce unnecessary complexity to the regulation of Section 361 products.

15. Requirements for Distribution (Proposed 1271.265(c)

Recommendation: 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.

16. Record Retention (Proposed Section 1271.270(e))

Proposed section 1271.270(e) states:

"All records shall be retained 10 years after their creation. However, records pertaining to a particular human cellular or tissue-based product shall be retained at least 10 years after the date of implantation, transplantation, infusion, or transfer of the product, or if the date of implantation, transplantation, infusion, or transfer is not known, then records shall be retained at least 10 years after the date of the product's distribution, disposition, or expiration, whichever is latest. Records for archived specimens of dura mater shall be retained 10 years after the appropriate disposition of the specimens. The establishment shall make provisions for all records to be maintained for the required period in the event that the establishment ceases operation."

Recommendation: FDA's proposed language is unnecessarily complex and would lead to confusion in the tissue community. Tissue establishments cannot force clinicians to discard expired products or to provide notification with respect to the date of use. Also, it is not practical to try to compel a tissue establishment that has ceased to operate to expend resources on the maintenance of records; in MTF's view, it is adequate to require that they use their best efforts to maintain records.

MTF recommends that proposed subsection (e) be modified as follows:

"All records shall be retained for a minimum of 10 years after their creation. However, records pertaining to a particular cellular or tissue-based product shall be maintained for a minimum of 10 years after the product's expiration date. Records for archived specimens of dura mater shall be retained 10 years after the appropriate disposition of the specimens. The establishment shall use best efforts for all records to be maintained for the required period in the event that the establishment ceases operation."

17. Requirements for Tracking (Proposed Section 1271.290)

Proposed section 1271.290 states (in relevant part):

" (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.

(2) Alternatively, an establishment that performs some but not all of the steps in the manufacture of a human cellular or tissue-based product may participate in a method of product tracking that has been established and is maintained by another establishment responsible for other steps in the manufacture of the same product, provided that the tracking method complies with all the requirements of this section."

(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 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."

Recommendation: 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.

MTF 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, MTF 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.

MTF also believes that proposed tracking requirements, and the associated burden that would be placed on tissue manufacturers, is unjustified from a risk standpoint. To the best of MTF'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, MTF 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, MTF 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 and name, address, telephone number, etc. There are substantial financial penalties for obtaining this information in violation of the Law. MTF 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, MTF 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;, and 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.. MTF 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.

18. Complaint Handling (Proposed Section 1271.320)

Proposed section 1271.320 states:

"Each establishment shall establish and maintain procedures for the prompt review, evaluation, and documentation of all complaints, as defined in § 1271.3(ii), and the investigation of complaints as appropriate."

Recommendation: MTF requests that proposed section 1271.320(a) be modified to include language recognizing that the complaint requirement applies only to tissues that have already been released for distribution. Further, MTF believes that the definition of "complaint" in proposed section 1271.3(ii) should be modified by deleting the reference to tissue function or integrity. As noted elsewhere in these comments, MTF believes that these terms are inappropriate and exceed FDA's statutory authority. Subsection (3) of the proposed definition of "complaint" should also be deleted.

19. Importation Requirements (Proposed Section 1271.420)

Proposed section 1271.420 states:

"(a) When a human cellular or tissue-based product is offered for entry, the importer of record shall notify the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the product is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part.

(b) A human cellular or tissue-based product offered for import shall be held intact, under conditions necessary to maintain product function and integrity and prevent transmission of communicable disease, until it is released by FDA."

Recommendation: MTF requests that proposed subsection (a) be modified to provide:

"When a human cellular or tissue-based product intended for clinical use is offered for entry, the importer of record shall notify the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the product is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part."

MTF believes that the cGTP proposed regulations apply solely to tissues intended for human use, and that tissues and products intended solely for research uses should be exempt from these requirements.

20. Requirements for Reporting Adverse Events (Proposed Section 1271.350(a))

This section presents criteria and timeframes for reporting adverse reactions. MTF 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.

Recommendation: With regard to reporting criteria, MTF 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, MTF notes that the proposed criteria involve consideration of a product's "function and integrity". As explained elsewhere in these comments, MTF believes that these terms are broad and open to interpretation, and that they therefore need to be defined if they are to be used ion the final rule.

With regard to the reporting timeframe, MTF believes that the proposed 15-day requirement for reporting adverse reactions are unnecessarily short for all adverse reaction reports. MTF 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. MTF 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.

21. 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.

MTF believes that this proposed requirement is burdensome and that the value such reports would provide to the Agency is questionable. It is MTF'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. MTF 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.

Recommendation: MTF 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, 1) 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...".

22. Criteria for Claims Considered 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. MTF 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. MTF 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.

Recommendation: MTF 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.

23. 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.

MTF 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.

Recommendation: MTF 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 also identify other types of information, e.g., financial information, that are exempt from review.

III. Comments Concerning Tissue Product Classification Determinations

24. FDA Tissue Reference Group

MTF 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. MTF 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, MTF 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.

MTF agrees in principle with the multi-center approach for regulating products that combine tissue or cellular based products with drugs, devices and biologics. However, even with the full cooperation of all of the branches of the FDA working together through the Tissue Reference Group (TRG), the process of evaluating, classifying and approving these combination tissues appears to be a bit confusing, and could possibly be a potentially time consuming process.

Recommendation: MTF recommends that the regulation stipulate a reasonable time limit for FDA to review and approve combination products. In addition, the proposed regulation should clearly indicate that combination products may indeed follow a process of approval equivalent to a 510K if appropriate.

With respect to the TRG proceedings, FDA should institute the following general procedures for any action taken or proposed which would have broad effects on the industry.

- TRG meetings should be announced by publication in the Federal Register or in some formal fashion, with a general description of the issues to be discussed.
- TRG meetings should be open to the public, except for portions of the meeting involving proprietary information.
- The proceedings of the TRG's including jurisdictional determination should be published.

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