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

[Docket No. 97N-484P]

To Whom It May Concern:

The Northwest Tissue Center, a division of Puget Sound Blood Center, appreciates the opportunity to comment on FDA's proposed rule, Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement. With certain important exceptions detailed below, in general, we find the proposed new regulations to be helpful and non-controversial. We have the following comments on specific aspects of the rules.

Throughout the rules – references to tissue "function and integrity". Extending authority claimed under PHS act to cover issues of function and integrity of tissue is inappropriate. The rationale presented that a "repeat surgical procedure necessitated by the damaged product would further expose the patient to the additional communicable disease risk..." is a very weak one. FDA has had to seek that specific authority for other products and was not allowed to use the PHS act to rationalize authority.

1271.150(b). Holding the organization that makes the product available for distribution ultimately responsible for regulatory compliance throughout the manufacturing process is reasonable. In reality it is likely to lead to a "cascading" set of responsibilities among the organizations involved. However, it seems more prudent to hold each specifically responsible for the activities that went before. Would FDA not expect that a processing organization would confirm the compliance of the group judging donor suitability before accepting donor tissue for processing, even if only to protect the processing staff from potential exposure and to prevent the inadvertent release of unsuitable tissue?

1271.160. We appreciate the Agency's differentiation between the required Quality Program and the Quality System requirement for devices and blood products. Giving tissue banks flexibility in how those defined functions are accomplished and not requiring that they must be achieved by employing staff with no other responsibilities recognizes the undue burden that would create.

1271.160(b)(7). Since product deviations identified and addressed prior to release of tissue for distribution do not jeopardize public health, we urge the Agency to limit the requirement for reporting them to those identified post-release.

1271.160(d). This indicates that audits may be subject to FDA inspection in order for the FDA to determine compliance. FDA has generally agreed that inspectors do not have access to audit records. This would undermine the audit process by making manufacturers reluctant to document their audit findings. We feel that internal audit findings should not be available to FDA inspectors.

1271.160(e). Requiring that computer systems used in manufacturing and data maintenance be tested to confirm that they perform as intended and that the testing and results be documented is reasonable. Please confirm in the final regulation the comments made in public forums that the Agency is distinguishing between this limited requirement and the term validation as it has been applied to computer systems identified as medical devices.

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A nonprofit community organization established by
- *Puget Sound Blood Center*
- *Northwest Kidney Center*
- *University of Washington Department of Orthopaedics*

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1271.180. What is meant by "relevant" as it is applied to communicable disease agents?

Additionally, changes in processes should be validated and approved before implementation, but deviations from standard processes cannot always be predicted, nor should they necessarily become the standard practice. The statement "any deviation from a procedure shall be authorized in advance by a responsible person, recorded and justified" is unjustified. While we agree that deviations need to be authorized and documented, there are times when staff must accommodate unusual circumstances and they cannot get prior authorization to do so. Deviations would be reviewed and authorized prior to further processing or release of tissue. They should always be documented, investigated, and determined not to have had negative impact on the tissue if it is to be released for transplant. We recommend that the words "in advance" be removed or modified to "in advance of release of tissue".

1271.190. We believe these provisions are too broad and should be limited to requirements for preventing transmission of disease from donor to recipient.

1271.200(a). Again, should this be limited to concerns of transmission of communicable disease?

1271.200(e). This states that equipment maintenance records "shall be available at each piece of equipment". Most tissue banks with modern technology maintain these records electronically or in separate files. It is not functional to keep them "with the equipment" where they are more likely to be lost or damaged. Also, this should be limited to major equipment and not include simple instruments that are regularly washed and disinfected or disposable or to equipment that has a validated procedure for cleaning and disinfecting.

1271.220(a). Although the term "specifications" is used in the regulations and defined in the supplementary information preceding the regulation, it's definition is not included in 1271.3. We suggest adding it.

1271.220(c). We recommend simplifying the definition of "pooling" to read, "tissues from two or more donors shall not be placed in physical contact with one another."

1271.230(b). If verification is performed on each and every finished product, why could that not be "claimed" in the labeling?

1271.230(c). Requiring the reduction in the level of CJD in dura mater is not adequate or responsible for the Agency to propose. There is no acceptable level of contamination.

1271.260(b). Does this mean that tissue establishments must validate storage temperatures and storage periods? Many of these have been established by the tissue industry based on experience.

1271.265(b). Some tissue banks order and receive tissue from other tissue banks that will be distributed to their clients. Often, these come in sealed shippers (CV) ready to send on to the consignee. The receiving tissue bank can inspect the shipper for damage and even the outer packaging in some instances but should not compromise the integrity of the package by opening unnecessarily and cannot be certain of the condition of the contents. In those instances, that can only be ascertained at the time the package is opened at the hospital.

1271.270(b). Please explain what the part of this requirement to maintain records for product types is intended to accomplish. We find the regulation and the commentary explaining how to comply confusing. Specifying what records must be maintained and available for inspection should be sufficient. Detailing how they are to be organized is an unnecessary intrusion. The detailed example is not only unduly complicated, but also may establish an expectation for inspectors that it is the required method.

1271.270(e). We recommend simplifying the requirement to retain records by requiring they be held for ten years after transplantation, or after expiration if transplant date is unknown. A product with a 10-year expiration date might be held in a hospital's inventory for ten years after the tissue bank distributed it and be transplanted just as the records of its manufacture were destroyed, if retention time is linked to distribution.

1271.290. We support the Agency's proposal to require tissue banks to have a system for tracking the tissue or cell product to the patient recipient. Most tissue banks attempt, to varying degrees, to collect transplant data. The reluctance to be held accountable centers on the recognition that a requirement of 100% compliance could be prohibitively expensive to achieve. We recommend that FDA require that tissue banks establish a system that facilitates the return of patient-specific information by the clinician or healthcare provider to enable the tracking from recipient to donor and donor to all recipients. Then, the systems in place in hospitals to track internally could serve as redundant or complementary methods for tracking, if necessary.

In response to the request for comments on the success or failure of tracking methods, we offer the following information. Our tracking system allows the tracking of more than 90% of the tissue we distribute to the patients who received the transplants. We provide a graft-specific transplant record with peel-off labels that identify the unique product and the bank that provided it. The labels can be used by the hospitals both to monitor the receipt of the tissue into their inventory and to record in the patient chart the specific tissue the patient received. We provide tracking logs for their use to control their inventory of transplant tissue. Identifying information about the patient, the procedure in which the tissue was used, the physician, hospital, surgery date, graft rating and comments are completed at time of use and returned to the tissue bank in a self-addressed envelope. Once received, the information is entered into our database and linked by accessing the information about the distribution of the tissue using identifying barcodes on the records. At regular intervals, we generate a report that is sent to each hospital notifying them of tissue for which we have not received transplant records and asking that they return information about its use or its existence in their inventory. Once hospitals recognize their responsibility is much the same as it is for tracking blood products, they willingly participate and appreciate our efforts to support them. The majority of our regional hospitals return 100% of their transplant records. The more than 350 hospitals outside of the region we primarily serve returned 85% of the transplant records on tissue they received from our bank.

Tracking fulfills our ongoing responsibility to the patients who have received our tissue, and it provides a probable database about the clinical uses of tissue, discard rates, and the demographics of recipient populations. It also allows us to provide follow-up information to the families who donate about the many who have benefited from their decisions.

1271.290(e). With regard to the term "prompt," can the Agency confirm that name and hospital or social security # are sufficient information to allow identification?

1271.290(f). Currently, at the time of the first order from a consignee, we speak to them about returning the included transplant record for tracking. In the following week, we send a letter describing tissue center policies and hospital responsibilities and request a signature of acceptance of those terms. Would this regulation require that we receive a signed agreement prior to sending the tissue? This could be very difficult for a new client who has an immediate need for tissue (heart valve, osteoarticular graft, etc). Also, who should be authorized to sign the agreement? Does it have to be the hospital administrator? Is an OR staff member, materials management person or purchasing agent an authority? This is a difficult determination. Whose agreement will best assure that the "tracking" is actually done?

1271.320. We believe that the complaint requirement applies only to tissues that have been released to distribution. We also recommend that the definition of "complaint" in subsection 3 be deleted or clarified to indicate application to tissues released to distribution.

1271.350(a). We believe the Agency's authority to require the report of adverse reactions and of deviations on distributed products that might lead to adverse reactions is limited to those that involve the transmission of communicable disease or product contamination. Because the definition of distribution is somewhat broad, we recommend the phrase be "released for transplant and distributed."

While adverse reaction reporting is very important, the description of reportable events needs clarification. The phrase, "the relationship cannot be ruled out" is particularly concerning. There are patient problems in which a cause cannot be determined because of multiple possibilities/variables. If there is NO evidence that the tissue could have caused the problem but no way of absolutely proving that it was impossible, is that an adverse reaction? Nonunion is common but if a patient had a nonunion after a bone graft and all other recipients of bone from that donor had successful transplants, it is unlikely but within the realm of possibility that the tissue was responsible. If a surgeon reports an infection in a wound of a patient who received a graft but the organism responsible had not been on any donor tissues, it is unlikely the graft caused the infection. Does this "rule out" the relationship? If the surgeon gave the patient "prophylactic antibiotics" because of a false positive gram stain on a tissue in the OR, is that medical intervention and is it due to the tissue?

1271.350(a)(iv). Each report must be submitted "within 15 calendar days of initial receipt of the information". Sometimes, the initial report of information is limited and, if stretched, *might* be a concern, but more information is need to clarify. Getting information from surgeons, OR staff, etc can take some time (more than 15 days) and often, when we reach them, they say, "Oh that wasn't really a problem." But, it was "potentially" a problem without the additional information. We believe the time to report is too limited.

1271.350(b). Reports of product deviations. To clarify.... If a QA review after processing discovers a deviation (mislabel, missed culture, etc) that could have led to an adverse reaction if transplanted, but the tissue is in quarantine and has not been released, is this reportable? The purpose of the reviews is to look for deviations and address/correct them. The introductory section (page 44) seems to indicate that reporting would only be necessary if the product had "been distributed" but this is not clear in the proposed rule itself.

1271.370(a)(3)(ii). It would be helpful to have some guidance re "warnings" for the label or package insert.

1270.400(d). Are photographs and videos common? There must be some parameters for these and some instances where a tissue bank may resist.

1271.440. We take issue with authorities claimed for inspection and enforcement. We recognize the Agency needs to protect public health by preventing non-compliant organizations from distributing tissue that has a likelihood of transmitting infection or disease. We believe that the current proposed rule grants FDA the right to order retention, recall, destruction, and/or cessation of manufacturing for failure to comply with any regulation, regardless of the significance of the infraction. Such orders must be reserved for egregious failures to comply that demonstrate real potential for disease transmission. Furthermore, we believe the regulation should be expanded to define the procedures to be followed to protect the rights of the manufacturer to due process – e.g., opportunities to provide additional documentation to demonstrate compliance, for a court hearing, to appeal, to seek a stay. Currently it provides only for a request to be made within five days for hearing. The only restraint on the FDA is that they may not destroy product until the request for a hearing is resolved.

Thank you for the opportunity to comment on these important proposed regulations.

Sincerely,

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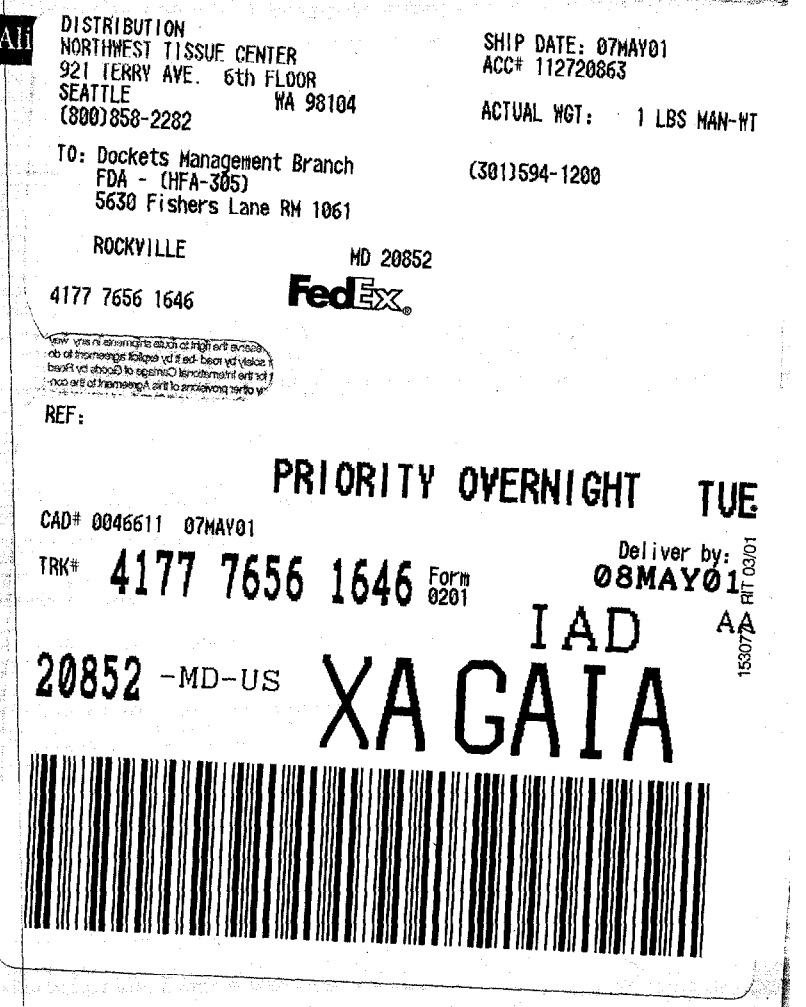
Director



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