



Current Good Tissue Practices

The Core Requirements when Donating Human Tissue

by Randy Prebula

The decision to donate a loved one's organs and tissues often is a complex balancing of the past wishes of the deceased, the survivor's grief over their loss, and the desire to provide an anatomical gift for the benefit of others. Once the survivors make a decision to donate tissues, processors, distributors and doctors wishing to transplant the gift face an equally complex balancing between ensuring the tissues do not transmit disease or are not contaminated during processing, shipment, storage and distribution, on one hand, and the need to ensure that the donated tissues are available when and where needed by patients.

Reports of contaminated tissues and recipient injury or death, or of improper harvesting of tissues from donors without consent, make both balancing acts more difficult. For example, in September 2005, tissue processing companies receiving donated tissues from Biomedical Tissue Services (BTS), of Fort Lee, New Jersey, learned that the medical and social history records collected as part of donor screening process and accompanying at least some BTS tissue were, in all likelihood, fraudulent. The tissue processors notified FDA of their findings and voluntarily recalled tissues obtained from BTS. In February 2006, after an extensive FDA investigation, the agency ordered BTS to cease operations and issued a public news release stating:

FDA's inspection of BTS uncovered serious violations of the regulations governing donor screening and record keeping practices, as well as failures to follow their own standard operating procedures (SOPs), failure to recover [human tissues] in a manner that does not cause contamination or cross-contamination during recovery, and failure to adequately control environmental conditions. Despite records maintaining otherwise, the firm had inadequately screened donors for risk factors for, or clinical evidence of, relevant communicable disease agents and diseases. In addition, FDA found numerous instances where death certificates maintained in BTS' files were at variance with the death certificates FDA obtained from the state where the death occurred, on important information such as cause, place, and time of death, and the identity of the next of kin.¹



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Family members considering tissue donation are likely to hesitate to agree to a donation if they believe the industry disrespects the donor, or that tissues might be misused. Similarly, tissue processors are likely to weigh carefully the risks associated with accepting human tissues for processing if the processor is unable to assess the tissue's origin and purity.

Fortunately, the BTS example highlighted above was detected by the tissue processors and brought to FDA's attention. The processors' adherence to FDA's regulatory framework for human tissue processing, known generally as the current Good Tissue Practices (cGTPs), provided the companies with the necessary tools to identify, control, document and track the tissues from the donor to the recipient, and to recognize areas where the purity of the tissue and the potential for disease transmission might have been suspect. In the same light, the cGTPs (and additional state and/or voluntary standards) provide a mechanism to reduce the potential for future occurrences of undocumented (or poorly documented) donations, increase processor assurance that tissue are not likely to transmit disease or become contaminated, and alleviate donor family concerns that the donated tissues might be lost, discarded or misused.

What Are Core cGTPs?

The cGTP provisions in 21 CFR Part 1271, Subpart D require firms to recover, process, store, label, package and distribute human cells or tissue products (HCT/Ps), and screen and test donors, so as to prevent the introduction, transmission or spread of communicable disease. Like the counterpart FDA Good Manufacturing Practice regulations (21 CFR Part 820 for medical devices and

21 CFR Parts 210 and 211 for pharmaceutical products), the cGTP requirements provide a framework. Within this framework, each firm or entity that has responsibility for a human tissue at any point between donor and recipient must establish a Quality Program that encompasses personnel, procedures, facilities, environmental control and monitoring, equipment, supplies and reagents, recovery, processing and process controls, process changes, process validation, labeling, storage, receipt, predistribution shipment, and distribution, records, tracking and complaints.

The Quality Program must address all core cGTP requirements for the activities conducted by and on the authority of the facility, and requires the facility to create and maintain procedures appropriate to meet core cGTP requirements for all steps performed in the manufacture of HCT/Ps. FDA broadly defines "manufacture" to include storage and distribution, although FDA excludes transportation from the definition of manufacture (such as by postal carriers or third-party shipping companies). FDA further requires that these procedures be designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases. Specific examples of these core areas and FDA requirements (as described in 21 CFR Part 1271, SubPart D) are outlined below:

- **Facilities:** Any facility used in the manufacture of HCT/Ps must be of suitable size, construction, and location to prevent the introduction, transmission, or spread of communicable disease in the produced HCT/Ps, and to ensure orderly handling of HCT/Ps without mixups.

- **Environmental Control and Monitoring:** The establishment must adequately control environmental conditions, but this requirement is built around a flexible approach that allows each establishment to assess its particular needs, appropriate to the activities of that business. The facility should control and monitor environmental conditions that could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents.
- **Equipment:** Equipment used in manufacture of HCT/Ps should be of an appropriate design and suitably located, with records of the maintenance, cleaning and calibration on or near each piece of equipment, or readily available to those who maintain or inspect the equipment.
- **Supplies and Reagents:** The establishment must enact a system under which particular lots of supplies and reagents can be linked to individual HCT/Ps.
- **Recovery:** If the establishment recovers HCT/Ps from the donor, the establishment must recover each HCT/P in a way to not cause contamination or cross-contamination of the HCTP/s, or increase the risk of introduction, transmission, or spread of communicable diseases.
- **Processing and Processing Controls:** The establishment should have appropriate and objective mechanisms to control and monitor each validated process used to prepare HCT/Ps from the donated tissue, such as statistical process-control methods, periodic review of product acceptance criteria and

meaningful quality audits. FDA does not expect the processed tissues to be sterile, but aseptic techniques should be used in processing. Because FDA believes the risks of pooling HCT/Ps outweigh the benefits, tissues may not be pooled from more than 1 donor, unless a request for exemption under 21 C.F.R. § 1271.155 is received and granted by FDA, showing data that the processing method adequately addresses risks associated with pooling.

- **Labeling Controls:** The facility should have in place procedures to control labeling of HCT/Ps, designed to ensure proper product identification and prevent mixups. Those procedures should include verification of label accuracy, legibility and integrity, and help ensure that each HCT/P is labeled in accordance with all of the applicable requirements.
- **Storage:** Each establishment must control its storage areas and stock rooms to prevent the contamination, cross-contamination, commingling and mix-ups. Establishments may follow voluntary industry standards, when appropriate to the tissue type (such as JC or AATB standards), or the facility may establish and validate their own criteria for storage temperature and period. Currently, tissue processors, including distributors and individuals storing HCT/Ps during the distribution chain, are required to establish acceptable temperature limits to inhibit the growth of infectious agents and/or protect the HCT/Ps from exposure to disease agents.
- **Receipt, Predistribution Shipment, and Distribution:** The establishment must create, maintain, and document procedures for receipt, predistribution, packaging

and shipping. Prior to making an HCT/P available for distribution, the establishment must review the manufacturing and tracking records pertaining to that HCT/P, and verify and document that the release criteria are met. Procedures should include tests and spell out criteria for rejecting incoming HCT/Ps. Packaging and shipping containers must be designed to prevent contamination of the HCT/Ps, but the establishment is allowed to determine the shipping conditions for each type of graft or tissue.

Labeling Requirements

In addition to the core GTP requirements in SubPart D, FDA has established both labeling requirements and adverse event reporting requirements for HCT/Ps, as follows:

- Each HCT/P must be labeled clearly and accurately, with an identification code, description of type of HCT/P, the expiration date (if any), and with any applicable warning, such as if the HCT/P is from an unapproved donor to use only under urgent medical need.
- The labeling additionally must include: the name and address of the establishment that determined the HCT/P met release criteria and made it available for distribution; storage temperature; and any instructions for use that are related to the prevention of the introduction, transmission or spread of communicable disease.
- Any establishment processing or distributing an HCT/P that receives information from any source that the distributed HCT/P has been associated with an adverse reaction involving a communicable disease or any noxious or unintended response to any HCT/P

for which a reasonable possibility that the HCT/P caused the response must investigate the adverse reaction.

- The adverse event must be reported if the reaction was fatal, life-threatening, resulted in permanent impairment of body function or structure; or necessitated medical or surgical intervention, including hospitalization. The event must be submitted to FDA on FDA form 3500A within 15 days of receipt of information.
- Manufacturers must also report any HCT/P deviations relating to the core cGTP requirements. Deviation is defined as either: the departure from the applicable standards or specifications that relate to the prevention of the introduction, transmission, or spread of communicable disease or HCT/P contamination; or an unexpected or unforeseeable event that may relate to the spread of disease or HCT/P contamination. Each deviation must be investigated and those related to core cGTP requirements must be reported on Form FDA-3486 within 45 days of discovery.

Applicable State Laws

Aside from Federal regulations governing organ and tissue donations, such as the National Organ Transplant Act of 1984 (NOTA) and the Uniform Anatomical Gift Act (UAGA), discussed elsewhere in this edition of *Update*, the processing and distribution of human tissues are subject to a number of state regulations. As of September 2007, at least nine states have some form of tissue banking regulations, with California, the District of Columbia, Georgia, Florida, Maryland, New York and Oklahoma having the most stringent regulations, while Delaware and Illinois require only establishment registration.

Any business that processes tissues, or ships tissues into a state should consider the state's tissue banking regulatory scheme. Even firms engaged in storage, distribution or direct delivery to in-state clients can be subject to state regulatory requirements. In some states, these regulatory requirements extend to entities with a minimal role in tissue manufacturing and distribution. For example, in Maryland, the state tissue banking requirements extend to facilities whose sole role is taking orders for tissues from tissue banks out of state.²

If a facility falls under the state regulatory scheme, it must register with the state, seek a license, and contract with the necessary staff to carry out the functions they perform, e.g. hiring medical directors. Companies with central headquarters must determine if their distribution centers require individual licenses, or may be brought under the overall umbrella of a corporate license. Companies also should be aware that the state regulations may incorporate by reference voluntary standards, such as the American Association of Tissue Banks (AATB) standards, at least as needed for the entity to perform the functions it is contracted to perform in the human tissue supply chain.³

Voluntary Industry Standards

Human tissue processors also can choose to rely on voluntary standards, such as the AATB Standards and Joint Commission (JC) requirements,⁴ to ensure that the tissue they process and distribute are available for patient use. Companies involved with human tissue processing also may refer to these standards to help potential donors and family members understand that donated tissues will be received, pro-

cessed, distributed, and used as the gifts they are intended to be. For example, companies may voluntarily seek accreditation by AATB for the activities they perform in relation to human tissues. Accreditation involves the on-site visit of an AATB trained inspector, who will review the site and evaluate: the premises; operations occurring during the inspection; statements of operations and procedures; case histories; donor reports; processing records and data; labeling procedures; storage and distribution records; equipment preventative maintenance, calibration activities and documentation; accident, error and complaint documentation; quality assurance program; personnel records; and document archiving.⁵

AATB accreditation also is very helpful because several states, such as Maryland, that require tissue bank or tissue processor licensing also incorporate by reference the AATB standards into the state regulations as a condition for licensure. Thus, although AATB accreditation is voluntary, adherence to AATB standards in procedural operations is required for tissue banks licensed in Maryland.

Tissue processing companies, especially tissue distributors, also may be asked by hospitals and medical providers to demonstrate conformance with JC requirements. JC has issued standards of accreditation for hospital facilities, including clinics and tissue banks associated with hospitals. Since the JC standards are written with an express concern towards patient safety, they tend to be more stringent than either AATB or FDA standards. JC standards generally apply to the patient oriented facilities, such as hospitals and point of care laboratories. The Centers for Medicare and Medicaid Services (CMS) requires

outside accreditation as a condition for reimbursement, and, for over forty years, has specifically accepted JC accreditation. This is important to note since there is the distinct possibility that a JC accredited hospital, to avoid potential reimbursement issues, may require that any distributor who delivers tissues to the hospital be accredited by JC as well.

JC has written fifteen standards specifically for "organizations that store or issue tissue, which may include areas outside of the clinical laboratory, for example surgery and outpatient centers and tissue banks." These standards include specific temperature ranges for blood products and blood derivatives, procedures for tissue storage, record keeping, and adverse event reporting. For example, JC has enacted strict temperature monitoring standards:

- For tissues stored in refrigerators, freezers and nitrogen tanks, organizations should have the following: temperature recording at least once daily, documented manually, mechanically, or electronically; continuous temperature monitoring with an alarm system responded to 24 hours a day, 7 days a week; and a back-up storage plan implemented if the primary storage equipment fails.
- For tissues stored at room temperature, the temperature must simply be recorded at least once daily, as continuous temperature monitoring and alarm systems are not required.⁷

Thus, while JC standards are often more rigorous than FDA or AATB standards, it is likely that a JC accredited hospital may require tissue distributors to comply with those stricter JC standards, such as the temperature monitoring standard, to avoid potential Medicare reimbursement issues.

Conclusion

In conclusion, FDA tissue regulations primarily focus on ensuring that products are not contaminated or capable of transmitting disease, whether the source of disease comes from the donor or is introduced during tissue processing, storage, or distribution. The cGTP regulations provide FDA authority to ensure that HCT/Ps prevent the introduction, transmission, or spread of communicable disease. Although the cGTP regulations do not address HCT/P safety or efficacy otherwise, they do provide an effective framework by which processors can ensure that donated tissues are recovered safely, identified appropriately, screened, tested, and processed effectively, and delivered for timely use.

Apart from FDA regulations, tissue banks should consider that federal and

state regulations apply to tissues and facilities engaged in the human tissue industry. There are also voluntary accreditation standards, such as the AATB and JC standards, that apply to these activities. These other standards and regulations can often prove more stringent than FDA regulations with respect to specific aspects of tissue processing, storage, and distribution activities, such as storage temperature monitoring. Companies and facilities involved in any step of the tissue distribution chain, from recovery to transplantation, must assess whether their actions fall within the scope of any or all of these standards and regulations, and follow these regulations to encourage potential donors, to protect the tissue being donated from contamination, and to ensure that the gift of donated tissue safely reaches patients. Δ

- 1 FDA News P06-17, February 3, 2006 - <http://www.fda.gov/bbs/topics/news/2006/NEW01309.htm>
- 2 Md. Regs. Code tit. 10 § 50.01.03(20), (28).
- 3 For example, Maryland has adopted AATB standards. See Md. Regs. Code tit. 10.50.01.04.
- 4 JC was formerly known as the Joint Commission on Accreditation of Healthcare Organizations ("JCAHO").
- 5 American Association of Tissue Banks, *AATB Accreditation Process*. Available at <http://aatb.timberlakepublishing.com/files/aatbaccrreditation-process.pdf>.
- 6 Emphasis added. *2007 Laboratory Accreditation Standards*, Joint Commission on Accreditation of Healthcare Organizations, 261-269. Available at <http://store.trihost.com/jcr/product.asp?dept%5Fid=26&catalog%5Fitem=777>
- 7 *Id.* at 267, and JC FAQ on Temperature Recording, Monitoring, Alarms, and Back-Up Storage. Available at http://www.jointcommission.org/AccreditationPrograms/LaboratoryServices/Standards/FAQs/Quality+Control/Tissue+Storage+and+Issuance/temp_rec.htm

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