Guidance Document

Current Good Tissue Practice

[No. 3, June 27, 2006]

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AATB GUIDANCE DOCUMENT
Current Good Tissue Practice

I. INTRODUCTION

A. History and Purpose

In August of 2003, the Current Good Tissue Practice (CGTP) Guidance Document Task Force was formed by the AATB. The goal of the Task Force was to collect information regarding industry operational practices and to address specifics of tissue banking operations and how the CGTPs should be applied to these operations from the perspective of our tissue banks. The Food and Drug Administration (FDA) has indicated that there is a need for guidance to accompany subpart D of 21 CFR Part 1271, the Current Good Tissue Practices (CGTP) Rule. Under Good Guidance Practices (21 CFR 10.115), an individual or association can submit drafts of proposed guidance documents to FDA for consideration. This was a unique opportunity for our membership to assist FDA in developing its recommendations (refer to the federal leveraging initiative accessed at http://www.fda.gov/cber/gdlns/leverhnbk.pdf). This document is constructed using plain language, in a question and answer format, so it is easy to read and understand. This collection of questions and answers was approved by the AATB Board of Governors in November of 2005 and sent to the FDA on December 2, 2005. FDA is reviewing the questions and answers for possible incorporation into FDA draft guidance. Some revisions have been made in recent months and now this AATB guidance is published. FDA has not concurred with the answers to these questions, and the answers are subject to change in any FDA draft guidance on CGTP. Therefore, this AATB Guidance Document should be considered a work in progress, providing interim recommendations to assist you with complying with the requirements in 21 CFR Part 1271, subpart D.

FDA defines "manufacture" to include **recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution**. In 2003 when this Task Force was formed, it was decided that these eight operational areas should be individually addressed by work groups within the Task Force. Approximately one hundred volunteers from the AATB membership were organized into eight groups to address each of these specific operations. The questions and answers constructed were directed at suggesting how daily tissue banking operations should be performed or controlled, to meet the intent suggested by the proposed CGTP Rule. This document is formatted into sections following the original division of specific operational areas of the tissue manufacturing process as described by FDA.

The FDA's CGTP Final Rule was published on November 24, 2004 and became effective on May 25, 2005. Questions remain regarding acceptable interpretations of how to adequately meet the intent of the Rule. The purpose of the initial version of this Guidance is to communicate AATB's current interpretations of the Rule for those working in a conventional tissue bank. There are no references in this version to operations specific to reproductive tissue banking since that specialty is currently exempt from this Rule.

B. Abbreviations

AAMI: Association for the Advancement of Medical Instrumentation

AATB: American Association of Tissue Banks

ANSI: American National Standards Institute

AOPO: Association of Organ Procurement Organizations

CBER: Centers for Biological Evaluation and Research

CFR: Code of Federal Regulations

CGTP: Current Good Tissue Practice

CLIA: Clinical Laboratory Improvement Amendments

CMS: Centers for Medicare and Medicaid Services

CMV: Cytomegalovirus

EBAA: Eye Bank Association of America

FDA: Food and Drug Administration

HCT/P: This FDA acronym means "human cells, tissues, and cellular and tissue-based products." This is used in this document only when quoting parts from the FDA Rule. The term "tissue" can be used interchangeably and is the preferred term used throughout this Guidance Document. Any reference to tissues as products has been consciously avoided.

HBV: Hepatitis B Virus

HCV: Hepatitis C Virus

HIV: Human Immunodeficiency Virus

HTLV: Human T-cell Lymphotropic Virus

ISO: International Organization for Standardization

SOPs: Standard Operating Procedures

TSE: Transmissible Spongiform Encephalopathy

Section II.

Recovery

II. RECOVERY

Q1. What is the responsibility of the tissue recovery agency upon receipt of additional donor information (i.e, relevant medical/behavioral risk history, additional serological testing, autopsy reports, pre-processing/ recovery-related microbiological culture results) when it is received/obtained after recovery (meaning: days, perhaps weeks or months later)?

A1. The recovery agency must have a quality program in place that contains written procedures (§1271.180) describing how they will ensure that a system exists for receiving, investigating, evaluating, and documenting donor information (§1271.160(2)), as well as how they will share records with all establishments who are known to have recovered or received tissues from the same donor (§1271.160(2)(b)). This notification should be made without delay and be documented and remain as part of the records (§1271.270). Any entity that will determine donor eligibility must receive all relevant medical records (§1271.3(s)) that could affect their donor eligibility determinations. The purpose of this requirement (§1271.160(b)(2)) is to ensure that procedures are in place to efficiently communicate any information pertaining to the possible contamination of the tissue or the potential transmission of communicable disease by the tissue. Communicable diseases attributable to manufacturing controls include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents (§1271.150). Establishments who determine donor eligibility should develop and maintain policies and procedures that clearly describe donor records that they deem relevant to their manufacturing operations. These decisions could be communicated as part of the expectations described in the arrangements between establishments (§1271.150(b)(c)(ii)). Also, under a records management system (§1271.270(b)), records pertaining to a particular tissue must be maintained in such a way as to facilitate review of the tissue's history before making it available for distribution and, if necessary, subsequent to the tissue's release as part of a follow-up evaluation or investigation. Any tissue testing performed after it has been decontaminated/disinfected or subjected to processing (e.g., in-process testing, post-processing microbiological testing, final cultures/tests) are not considered relevant records for the recovery agency and, if such results are reported, would not be expected to be shared with all consignees of the recovered tissues from a donor.

Q2. How does a recovery agency establish that their recovery technicians are competent to perform their assigned duties?

A2. This would involve staff training (education), re-training when necessary, and methods to evaluate competency (§1271.170(b)) related to activities they perform which should be described in their job/position description. The recovery agency must develop and maintain a training program (§1271.160(b)(4)) for new staff and periodic reviews of the performance of trained staff (§1271.170(c)). New training would be expected when additional tissue types are incorporated into the recovery procedures, and when current recovery procedures are revised. Personnel must perform only those activities for which they are qualified and authorized (§1271.170). Staff training and performance reviews (or some form of competency testing) must be documented and should be reviewed periodically by management (§1271.160). Performance reviews, however conducted, may reveal that re-

training is necessary. Recovery operations should be conducted in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the tissue (§1271.145, §1271.215). Examples of methods to evaluate competency could be by establishing a program using scheduled or unscheduled: written tests; web-based learning/evaluations; on-site observations (audits); and, by establishing, tracking, and trending performance indicators (e.g., technical recovery errors, pre-processing microbiological culture results, occurrence/severity of documented or discovered departures from procedures, proficiency testing of the cell/tissue type, such as testing for analytes). Evaluation of performance indicators can lead to developing benchmarks and attainable goals. This could be considered a quality program approach to functions (§1271.160(b)) that ensure that recovery activities are being monitored and adjusted as needed, and staff training/competency is being evaluated and staff are re-trained as necessary to ensure that there are controls in place to reduce the risk of contamination and cross-contamination at recovery (§1271.145, §1271.215).

Q3. How does a recovery agency ensure procedures are readily available to recovery personnel during recovery and ensure that procedures being referenced are current?

A3. Standard operating procedures specific to recovery should be readily available to recovery staff at retrieval (§1271.47(c)) in case there are questions or uncertainty regarding correct procedures. For example, copies (e.g., on paper, CD, diskette) of recovery SOPs may travel to recoveries with personnel, they could be accessed electronically from the place of recovery, or obtained verbally (via telephone) from a location manned at all times by personnel who can reference applicable current manuals/files and communicate this to personnel at recovery. Recovery personnel must be trained and be able to demonstrate competency regarding knowledge of available methods to them from which they can access procedures they perform. A document control system should be in place to ensure that procedures and forms being referenced anywhere, in any format, are current, not out of date (§1271.270), and ensure that revised forms and procedures are archived so past recovery operations can be referenced if necessary (§§1271.270(d), 1271.290(a)).

Q4. Is it necessary for recovery agencies to validate recovery procedures?

A4. No, recovery is not considered to be processing. According to 1271.3 (ff) "Processing means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage." Recovery procedures need not be validated, but they must be approved by a responsible person (§1271.180(b)) and reviewed periodically (§1271.160(c)). Recovery procedures must be designed/written in ways that do not introduce or cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the tissue (§1271.215). Also, process control requirements as described in §1271.220 do not apply to recovery procedures.

Q5. When does tissue "recovery" end and "processing" begin?

A5. This delineation can be determined by procedures (§1271.47(e)) provided by the specific tissue processor determining tissue release (§1271.265(c)(d)(e)) and communicated to the recovery establishment. Such determinations could be communicated as part of the expectations described in the arrangements between establishments (§§1271.150(b)(c)(ii), 1271.270(e)). Rinsing of recovered tissues with isotonic, sterile solutions to remove blood or other undesirable matter is not considered a processing step. However, processing usually begins when recovered tissues are placed into, or subjected to, solutions containing reagents such as antibiotics, decontaminants or detergents, or other agents designed to inactivate or remove microorganisms (§1271.3(ff)). Both the processor and the recovery establishment should verify that these reagents meet established specifications (§1271.210(a)). Processors would be expected to provide evidence that they have verified that proper steps are being performed by recovery personnel and that the reagents, supplies, and procedures used during recovery, packaging, and subsequent transport to them are acceptable to their manufacturing processes (§1271.150(b)(c)(ii)). Some aspects of this information should be determined to be acceptable upon tissue receipt (§1271.265(a)) and all records would be required to be reviewed prior to determination for release (§1271.265(c)). Documentation of all supplies and reagents that were used at recovery, as well as the relevant procedural steps that were performed and when (§1271.270(a)(b)), would be an acceptable method of verification. Tissue processing establishments have the flexibility to determine whether verification or validation is appropriate (§§1271.210(c), 1271.225) for their procedures. The processing establishment should have the requisite knowledge of the processes and operations conducted on their behalf to determine which actions are needed.

Q6. How can a recovery agency ensure that they retrieve cells/tissues in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the tissue?

A6. All recovery-related operations should be evaluated, as part of an establishment's quality program, to determine how these activities can be performed to control contamination and cross-contamination. These operations could include: agreements or arrangements that are in place, technical procedures used, personnel involved, equipment and supplies that are used to recover tissues, and evaluation of facilities where recoveries take place and where supplies/reagents are stored. For instance: adherence to appropriate donor eligibility guidelines should be followed (e.g., specify body cooling parameters and time limits for retrieval, documentation of observations that could identify physical assessment findings related to sepsis or infection); technical recovery methods should be performed using aseptic or clean techniques appropriate to the specific cells/tissues being recovered; utilization of recognized, published industry practices to control contamination would be appropriate (e.g., zone recovery, isolation draping, and sequencing as described in AATB's Guidance Document No. 2 Prevention of Contamination and Cross-Contamination at Recovery: Practices and Culture Results); equipment and supplies should be appropriate for the intended use and instruments verified to be cleaned, disinfected, and sterilized

according to established procedures; recovery site suitability parameters can be established and documented; staff training and education must be provided and competency evaluated by predetermined methods; recovery activities that are monitored and related to microorganism contamination (e.g. technical errors, pre-processing culture results) can be tracked and trended since this information is collected and available and corrective actions can be taken by the recovery agency to offer control (CAPA system); and, procedures should be developed and maintained for sharing of all records related to possible donor eligibility determinations.

Q7. How should a recovery agency identify the donor prior to tissue and/or cell recovery?

A7. Verifying the donor identity and documenting it appropriately establishes the beginning of tissue tracking. Prior to the beginning of actual recovery of the tissues, the potential donor's identification shall be compared with the donor's name as stated on the consent/authorization document. The method of donor identity verification must be documented and will include the source of the verification information (e.g., photo ID such as a driver's license, ID tag or band attached to the body, identification by appropriate recovery site personnel) as well as indicate the recovery staff member(s) who made the identification and when. The donor's identification tag or band can be reproduced by documenting its content, or alternatively, a photograph of the identification tag/band can be taken. Records shall indicate all steps in the manufacturing process (§1271.270(a)). Industry best practice recommendations and standards can be used (e.g. AATB Guidance Document No.1: Tissue Donor Physical Assessment Form).

Q8. How does a recovery agency ensure that adequate measures are taken to control contamination and cross-contamination during tissue recovery when it occurs in an environment other than a hospital operating room?

A8. Controls to prevent contamination and cross-contamination during tissue recovery should be described in standard operating procedures. This could define the following elements:

- the facility offers a suitable location, contains adequate equipment or furniture, and is constructed so that an aseptic recovery can be successfully performed;
- there is limited access to the recovery site during recovery;
- the site is in a good state of repair;
- there is adequate lighting and space for recovery operations;
- ventilation and airflow that are present are not suspect as sources of contamination;
- there can be proper removal of potential biohazardous materials produced by recovery operations;
- all working surfaces used for recovery operations can be cleaned with antiseptic solutions before recovery or collection; and,
- that the procedures that have been developed for performing aseptic technique can be followed at this location.

Documentation that was made that the site where the recovery took place met established, desired parameters would be used later to verify that specifications were met.

Q9. What is expected regarding any environmental control and monitoring procedures or policies for tissue recovery sites?

A9. For tissue recovery sites, the goal is to set specific guidelines/suitability parameters that define how you will provide proper conditions for operations (much like any step in manufacturing). There is not an expectation of actual monitoring to be performed at each recovery site, however, controls need to be in place to provide assurance that the site of recovery is not adversely affecting the potential for contamination and cross-contamination of tissues. If a tissue establishment sets specific parameters for recovery site suitability and verifies (and documents) for each recovery that these parameters have been met, this would be an acceptable approach. A controlled environment, such as an operating room setting, is preferred (refer to Class II Special Controls for Industry and FDA Staff: Guidance Document, Human Dura Mater, published 12/19/03, in 10. Manufacturing Controls, part B. Excision Facilities).

Q10. Does the sterilizer that is used to perform final sterilization of tissue recovery instruments need to be "validated"? Are manufacturer recommendations for preventive maintenance/servicing/calibration 'enough'?

A10. No, validation of the sterilization process would not be required under the regulations as "Process Validation" applies to processing, not recovery operations. As the sterilizer is used specifically for preventing contamination and cross contamination during recovery of tissue by rendering the recovery instruments sterile, you would have to ensure that the sterilizer is performing its intended function. A common practice that offers a level of assurance and verification that a set of instruments has been adequately sterilized during a cycle is the use of chemical indicator strips. These can be strategically placed in a challenged area of penetration of the set as well as superficially as an external indicator (sterility indicator tape). Upon opening the sterilized set of instruments at recovery, the change to the indicator tape and/or strip are observed and documented to verify that the set met expectations for sterilization. Another method to verify sterilization cycle operations is the use of biological indicators that are used in each sterilization load or other acceptable schedule (e.g. schedules which may be used by a hospital sterile processing department suggested by standards-setting organizations or other accrediting entities with oversight of such sterilization operations).

Q11. If a tissue recovery agency cleans and disinfects their tissue recovery instruments, there are published, established standards that can be followed. Is it acceptable to clean and disinfect tissue recovery instrument sets together that were used for recovery of tissues from different donors? Examples are eye recovery instruments (which are small) or just two sets of heart or bone recovery instruments.

A11. No, it is not a requirement, however, it may be prudent to separately clean and disinfect instruments used for different tissue types (e.g., segregate those used for tissues considered a prion risk). Cleaning and disinfection (sanitizing) steps would not require validation if not part of processing.

Q12. If the recovery instruments are (ideally) cleaned and disinfected as separate sets, does that also mean that the there can be no re-use of the cleaning/detergent baths and soaking solutions that are used to clean and disinfect instruments? By manufacturers' instructions for product use of such solutions, re-use is acceptable and change of solutions varies by once a day to once a week or until visually unsuitable.

A12. No, following the manufacturer's instructions for solution re-use/changing is acceptable.

Q13. Can 'containers' or basins used for instrument soaks/washes/rinses be re-used? Some of these are actually bath units (ultrasonic cleaners) that are used to dislodge debris from the instruments.

A13. Yes, as long as the containers used for the instrument cleaning are also cleaned and sanitized after each use, it is acceptable to re-use these containers. Cleaning procedures should exist and cleaning operations should be documented.

Q14. If 'prions' are an issue regarding equipment cleaning/disinfecting/ sterilization, how can these processes be adequately controlled to meet expectations?

A14. While prion contamination is a significant concern, existing technology and current scientific limitations offer neither a definitive recommendation, a procedure for rapidly identifying the presence of prions, or methods for removing them. However, heightened screening and more stringent recovery procedures be employed. So, for example, consideration should be given to use of disposable instruments for recovery of high-risk tissues (for prions), where possible. Thought should be given to the ability to track instruments that were used on particular donors as well as instruments that are washed together. The Transmissible Spongiform Encephalopathy Advisory Committee (TSEAC) voted that instruments are not required to undergo special cleaning procedures prior to sterilization, even for high-risk tissues. There was plenty of discussion, however, that if a particular donor was found after recovery to have or be suspected of having a TSE, then the instruments (used for recovery) should be destroyed. If proper tracking is not done of the instruments, it may result in destruction of more equipment (and donor tissues and/or tissue types) than would otherwise be necessary. At a minimum, tracking of the recovery instrumentation (each set) that is used for each donor recovery is expected as well as documentation verifying that the procedures used to sterilize the recovery instruments were successful.

Q15. Are automated washers used for disinfecting instrumentation that can 'process' four trays at once an acceptable method for washing tissue recovery instrumentation?

A15. Yes, placing multiple instrument trays in the automated washers, and if possible, disinfecting the same type of instruments together in these loads (such as those used for musculoskeletal tissue recovery) is acceptable. Ensuring that the automated washer is properly cleaned after each use is recommended.

Q16. How can a recovery agency verify that supplies and reagents meet specifications?

A16. If the recovery agency receives supplies and/or reagents from a vendor or a processing establishment, the recovery agency should verify that the vendor or processing establishment has a system in place to certify that the supplies and/or reagents meet established specifications. Additionally, the recovery agency must store, maintain, and utilize these supplies and/or reagents in accordance with the vendor, manufacturer, or processor requirements. In the case of supplies and/or reagents assembled or produced by the recovery agency, it is the responsibility of the recovery agency to verify that these supplies have been selected because they lend to preventing the introduction, transmission or spread of relevant communicable disease agents or diseases (e.g., instruments, wraps, containers and/or reagents (e.g., solutions,) meet specifications you determine such as: instruments are surgical grade; solutions are sterile, or fall within a specific pH range/contain pH change indicators; etc.). Specification sheets, certificates of analysis, and manufacturer's package inserts describing the reagent or supply can be referenced to verify suitability. The processor may require that specific supplies and reagents must be used by the recovery agency so the processor bears the burden of reagent/supply verification but communicates this information to establishments with whom they hold recovery agreements. For example, supplies used to wrap/package the individual tissues at recovery should be designed to prevent leakage that can cause contamination, cross-contamination, or mix-ups, and should be able to perform in this capacity when subjected to expected storage temperatures for that tissue type. Shipping containers used to transport tissues from the recovery site to storage or to the processor, and/or from storage to the processor, should be qualified/verified to maintain the expected storage environment relative to controlling contamination. The storage and/or shipping process (utilizing the procedure and supplies together) would require validation of the processes and/or documented verification of expectations each time these processes are performed (fully verifiable).

Q17. What should a recovery agency do to ensure that the recovered tissues and related donor specimens are properly identified to avoid mix-ups?

A17. Tissues must be traceable by using a distinct identifier code and must indicate that tissues are quarantined during storage or shipment that occurs prior to the determination of donor eligibility. A distinct identification code assigned by another establishment engaged in the manufacturing process can be used, or a new code can be assigned. If a new code is assigned, there must be procedures established and maintained for relating the new code to the old code. To prevent mix-ups, identification methods should be used and recorded which verify that distinct identifier codes and dates are properly documented and indicated on recovered tissues and related donor specimens and on all forms that will be used as manufacturing records. This can be accomplished by verification methods (double-checks) involving more than one person or, if not possible, accuracy and content can be verified by one person using a procedure that reduces the chance for identification errors (e.g., clerical errors). Copies of relevant medical records sent with the recovered tissue, or on a subsequent date, shall contain either the donor name or an assigned distinct identifier code.

Q18. In recovery operations, pre-printed labels are usually not generated, but rather, information can be handwritten directly on the wrap/packaging or container, as needed. Is it appropriate or adequate to have another employee verify that the information is correct or are other controls required?

A18. Proper identification of tissues to include accurate, legible, and indelible documentation is expected at any step of manufacturing. Specific prescriptions for meeting the new rule are not published. It's up to the establishment to define the methods of controls for complying with the regulation. Procedures used that verify identification and documentation accuracy of tissues at recovery are required. One acceptable method would be to follow SOPs that suggest using multiple personnel for verifying labeling, if more than one person is present, like the example used in this question. Other verification methods may also be acceptable.

Q19. Is a consent/authorization document considered to be part of "donor identification documents" or "relevant medical records" that would need to be records that must be in English, if the consent/authorization document was in a non-English language?

A19. No. There are no federal regulations regarding informed consent for tissues regulated as "361 products". If an inspector from FDA should ask to specifically review a consent document or listen to a tape of the consent process (if it is done by telephone), the firm could question this (and have the investigator contact CBER for clarification), because there is no federal authority in the area of consent regarding 361 tissues.

Section III.

Donor Screening and Donor Testing

III. DONOR SCREENING & DONOR TESTING

Q1. What expectations are there for ensuring that the collection of donor eligibility information by a recovery agency meets the processors' expectations (since they are performing a function on behalf of a tissue processor or the entity determining suitability)?

A1. Expectations would include the information that is assigned or implied (usually listed as "responsibilities" of each party) via a contractual agreement between the two entities. Compliance, however, would also include establishment and maintenance of a quality program by both entities, which includes, but is not limited to, periodic internal/external auditing, procedures describing proper information sharing, evidence of training/educational programs, and assurance of competency of personnel who collect information that will be used by others to determine donor eligibility.

Q2. How would the contracting establishment provide proof that work being done on their behalf is performed in compliance with CGTPs?

A2. The contracting bank should verify the work performed on their behalf using a number of quality program operations. Documented review of each donor record shall be performed as well as documentation of significant errors found which should be tracked and trended according to written SOPs. Performance indicators are established by the tissue bank and maintained as part of the quality program. Scheduled, routine, and unscheduled (when indicated) quality audits should be performed by the contracting bank. Each organization should possess current registrations, certifications, and accreditations held by those with whom they contract (e.g. FDA, ISO, CLIA, CMS, AATB, EBAA, AABB, AOPO, etc.)

Q3. How does the tissue bank that contracts with another establishment to perform another step in the manufacture of tissues ensure the contracted bank's compliance with CGTPs?

A3. This could be achieved through periodic auditing in conjunction with recognition of accreditations held (e.g. CLIA, CMS, AATB, EBAA, etc.) from the contracted establishment. Audit/inspection content should, at a minimum, contain a review for compliance to all requirements of 21 CFR 1271 applicable to the operations that the establishment performs.

Q4. Are testing laboratories included in the list of "manufacturers" of tissues and how would a tissue bank ensure compliance of such establishments?

A4. Yes, laboratories that perform tissue donor testing that includes required infectious disease screening tests (i.e., HIV, HBV, HCV, syphilis, HTLV, CMV) that are used to determine tissue donor eligibility would need to comply with applicable CGTPs. Testing labs that do not register and list as required will be subject to FDA enforcement. If a tissue establishment has an agreement with a testing entity, verification of compliance to requirements should be periodically reviewed by acquiring up-to-date certifications (i.e.

CLIA, CMS) and registration (i.e. FDA). Since an agreement of some magnitude exists between the two programs, responsibilities and expectations should be clearly defined and understood, such as requiring the use of FDA-licensed, cleared, or approved donor screening tests, where applicable, including those approved for cadaveric specimens when that specimen type is used. Testing labs should be encouraged to follow test kit manufacturers' instructions when performing these tests (e.g., acceptance of proper sample types; individual donor testing, when indicated). If triplicate testing of initial runs is being performed, as may be applied to organ donor testing (see MMWR Vol. 43, No. RR-8, May 20, 1994, Guidelines for Preventing Transmission of HIV Through Transplantation of Human Tissue & Organs, on page 11 in Recommendations, Donor Testing, listing 4), this knowledge must be communicated to tissue establishments who might use these infectious disease test results for tissue donor eligibility determinations. Tissue donor eligibility determination must include a review of all individual tests results when triplicate testing is performed. Tissue donor eligibility should be based upon the results of tests labeled as donor screening tests, not those labeled as diagnostic tests, however, the results from a diagnostic test, if performed, cannot be ignored if it is positive for a required screening test.

Q5. Must testing laboratories that perform microbiological testing related to any step of tissue manufacturing also be required to register with FDA?

A5. Yes, if a lab performing microbiological testing is doing so for activities related to in-process testing that will be used for final release determinations for tissues, then the testing lab must register and list with FDA. A testing lab that performs microbiological testing that is not related to tissue processing or donor eligibility screening is not required to register and list that activity with FDA.

Q6: Must a tissue/eye bank (or any other tissue "establishment") terminate its affiliation with a testing laboratory if the laboratory has not registered with the FDA as required under §1271.10?

A6: Yes. A tissue/eye bank is required to terminate its affiliation with a testing laboratory if the laboratory refuses to register as a tissue establishment with FDA. Tissue donor infectious disease test results cannot be used for donor suitability determinations if they are generated by a laboratory that is not registered with the FDA as a tissue establishment.

Q7. If compliance of donor testing laboratories is assured by periodic auditing/inspection as well as possession of documents demonstrating certification from agencies such as CLIA and CMS, what would be the frequency required for auditing and could certification alone be accepted once auditing has established a level of comfort with the contracted establishment? Would the bank be able to establish its own criteria, and as long as procedures were followed, would this be acceptable?

A7. Since auditing is a function within a quality program, periodic auditing of the operations of those who perform core CGTP functions on your behalf is expected and periodic reporting to management is usually performed. The establishment should define 'periodic'. On-site audits are not necessarily expected since a 'paper' audit that verifies procedures and test

kits being used and communicates responsibilities and expectations may also accomplish auditing goals. Certifications held by testing laboratories offer a level of comfort but periodic communication to review expectations and check operational compliance is essential to proper administration of a quality program.

Q8. If a tissue processor (or the entity who determines donor eligibility) applies for and is granted an exemption or alternative from any section of 21 CFR 1271, what would the expectations be for a contracted recovery agency regarding this exemption since they may participate in the use of the exemption/alternative (as directed by the tissue processing establishment or entity determining eligibility)?

A8. Granted exemptions or alternatives that shall be maintained by the establishment applying for them should also be shared with, or immediately available to, a contracted agency performing work that may be affected by the exemption/alternative. The exemption/alternative may not apply to other establishments who recover tissue from the same donor. Approval start dates, all documentation, and renewal of expiration dates (and/or extensions) should be readily available for inspection and/or training and re-training.

Q9. What type of donor screening operations would fit into a quality system review that's designed to control errors, deviations, and complaints, and/or utilize corrective/preventative action reporting?

A9. There are aspects of the donor screening process that can be tracked and trended to show where weaknesses or system breakdowns occur. Examples can be when tissue donor recoveries occur but the donor is later determined to be ineligible due to controllable reasons such as tissues recovered outside of published donor criteria that result in tissue destruction; and, potential tissue donor cases that are ruled-out then not recovered but, upon later review of the information, are found to have been suitable. Proper documentation of root cause analysis, corrective action taken to prevent recurrence, tracking and trending, and benchmarking should be instituted to control such incidents while screening potential tissue donors. This should be reviewed periodically and would be applicable to all agencies involved in the screening of a donor.

Q10. If a tissue bank contracts with another establishment to perform the donor screening function, how would the contracting bank ensure that the contractor has necessary elements of a quality program in place, and how can this be reported to management?

A10. Verification of contractor functions can be performed and the results reported to management. There must be procedures established, maintained and followed for qualification and monitoring of establishments with whom an agreement exists. Expectations of both parties to the agreement should be clearly defined and listed. Verification by both establishments that each entity is following prescribed federal regulations (core CGTPs) should ideally be performed initially and periodically.

Q11. Some recovery agencies contract with multiple processors; how would one ensure that all known donor screening and test result information is made available, and that the processors are notified of relevant complaints, adverse events, positive microbiological cultures and/or positive infectious disease test results, etc., in a timely manner? Who should coordinate this?

A11. Each tissue establishment involved in the manufacturing of tissue should have responsibilities defined in agreements with other establishments. Tissue recovery agencies must have procedures in place and employ an adequate number of personnel to establish and maintain a quality program that includes the sharing of relevant records with all agencies with whom they hold a contractual arrangement. This is explained in 1271.160 (b)(2) within "Establishment and maintenance of a quality program." The tissue establishment who arranges for recovery of all tissues and/or those who will receive pertinent information that could affect eligibility, including those which can cause contamination or cross-contamination by communicable diseases agents and diseases, should be responsible for coordinating dissemination of applicable information. Any tissue testing performed **after** tissue is decontaminated/subjected to processing (e.g., in-process testing, post-processing microbiological testing, final cultures/tests) are not considered relevant records for the recovery agency and, if such results are reported, would not be expected to be shared with all consignees of the recovered tissues from a donor.

Q12. What are the minimum, expected elements of a document control system so that tissue establishments may use this as a guide?

A12. A document control program assures that there is a review and approval process in place for all forms as well as a method to historically track changes made and ensures that there is a controlled implementation system. This process should be defined in written SOPs. The revision tracking system that is used and described in policy could be included on all document pages to provide a reference and all pages shall be numbered and contain revision dates. There must be procedures in place to assure that proper communication has been made to all entities involved who use or review the forms so that only the current form versions are being used, preventing the use of obsolete forms. Donor information forms that are formatted by tissue recovery and/or tissue processing establishments are considered "relevant medical records" and should be controlled by use of a document control system/management. It's realized that the tissue establishment will not have control of, or be responsible for, the various forms (formats) used by healthcare providers (hospitals, medical examiners) and cannot control form control/revision methods that these other entities may use.

Q13. How should obsolete documents be handled?

A13. In accordance with individual agency policies that assure the outdated documents are removed and archived to provide a timeline of all revisions (i.e. a document control management system).

Q14. What documentation requirements and release options should be followed if some relevant medical information is "not available" when initially reported or if unknown at time of review?

A14. The tissue bank should document if relevant medical records are not available, and this information be made available to the Medical Director or responsible party for their discretion at the time of donor eligibility determination. Documentation that describes that attempts were made to obtain information, but failed, should be made available for eligibility review. Justification for suitability determinations shall be documented.

Q15. Qualifications for those who perform donor screening can vary quite a bit from one organization to another. What are the expectations for those who perform this function?

A15. The qualification for the performance of any position should be established by the tissue establishment and reflected in the job/position description. If one entity contracts with another to perform donor screening, or donor information collection that's used for donor screening and suitability determination, then the contracting agency shall review the qualifications that have been established for the position (e.g. via periodic audits) and approve of them (or otherwise rectify differences). Contractual agreements should list and define expectations and responsibilities of both parties (1271.170(b)).

Q16. Are there minimum training requirements for personnel directly involved in donor screening? Are competency assessments suggested?

A16. These requirements are developed by the establishment that will determine donor eligibility. Appropriate training should be provided to or by the contracted recovery agency. Competency evaluation systems may be part of each entity's quality program.

Q17. Must recovery establishment records mirror those of processing establishments?

A17. No. Tissue processing-related records and distribution records are not expected to be found in donor records kept by the recovery agency. Each entity must establish what is necessary or expected, but at a minimum, the information should reflect the operations that were performed for another entity as well as tissue tracing responsibilities for each establishment's operations.

Section IV.

Packaging

IV. PACKAGING

Q1. Does the immediate package of, or the packaging system for, a tissue need to be verified or validated?

A1. No. Process validation or verification only applies to processing. Packaging and shipping are not part of processing [see 1271.3(ff)]. Therefore, packaging and shipping containers are not required to be validated or verified. At a minimum, the requirement for packaging is that the containers be designed and constructed to protect the tissue from contamination and cross-contamination. Also, you must establish appropriate storage parameters and shipping conditions to be maintained during transit. So, for example, a shipping container would have manufacturer's specifications when packed with gel packs or wet ice, and the tissue establishment could ensure that those specifications were followed and resulted in the desired temperature range during shipping. Another example would be to have an indicator device placed in shipments that registers what the highest and lowest temperatures were during shipment, but it would not be required to use such an indicator.

Section V.

Labeling

V. LABELING

Q1. Given that new infectious diseases are emerging, SARS and WNV for example, should the label make any claims about the safety of the tissue?

A1. Any tissue safety claims should be supported by appropriate verification or validation data so they are true and accurate. For example this could include suitable inactivation and/or sterility studies data (i.e., terminal sterilization, viral inactivation, specific data regarding level of log reduction), wherein the organization has determined the starting bioburden and applied appropriate processes to demonstrate the level of assurance being claimed.

Q2. Does tissue labeling have to take place in an area that has controlled access?

A2. Labeling operations are required to be controlled in a manner that prevents labeling errors/mix-ups.

Q3. What types of control systems are required to prevent improper labeling? Is a completely separate and dedicated area required for this function?

A3. The establishment must demonstrate that adequate controls are in place. Typically this is accomplished through a specific labeling procedure, dedicated work area, and controlled separation of activities to assure there will be no mix-ups.

Q4. Should a claim that is made on the label of a tissue be accompanied by supporting evidence listed in the package insert?

A4. It would be overly burdensome to expect detailed supporting evidence to accompany each tissue graft. Rather, verification/validation data should be retained by the tissue establishment and a review of labeling claims may be included as part of routine inspection activities.

Q5. If a process-related claim is made on the label, package insert or other promotional materials, is it acceptable to use the data/information from the manufacturer (i.e.; manufacturer's claim to the sterility of a chemical used in processing) or must the tissue establishment perform their own validation in order to make "claims"?

A5. The establishment whose name appears on the label and releases the tissue for distribution is ultimately responsible for ensuring that process validations are acceptable and completed to support labeling claims. Information from the manufacturer should be verified by the labeling establishment and it should meet the validation requirements of the tissue establishment.

Q6. What sterility standards are recommended for labeling human tissue as "sterile"? If no current applicable standards exist, what is expected in order for a sterilization claim to be substantiated?

A6. There are industry guidelines and standards available that should be used to guide sterilization validation activities. These include: "Guidance for Industry and FDA Staff: Class II Special Controls Guidance Document: Human Dura Mater" (12/18/2003) for human tissue based products labeled as sterile; ANSI/AAMI/ISO 11134 [Industrial moist heat sterilization]; ANSI/AAMI ST67-2003 [Sterilization of medical devices – Requirements for products labeled "sterile"]; and, ANSI/AAMI/ISO 11137 [Radiation sterilization]. Other standards are available such as estimating bioburden by ISO 11737-1, performing sterility tests in accordance with AAMI/ISO 11737-2, sterilization dose validation in accordance with ANSI/AAMI/ISO 11137, Annex B, AAMI/ISO 13409, AAMI/ISO 15844, or AAMI TIR27; family grouping and reducing frequency of dose audits per accordance with AAMI/ISO 15843, and the International Atomic Energy Agency's Code of Practice for the Radiation Sterilization of Tissue Allografts: Requirements for Validation and Routine Control (IAEA INT/6/052).

Q7. If the term "aseptic" ("aseptically processed," processing performed using aseptic methods," and the like) is used as a process-related claim, what standards or guidance is recommended for substantiating that claim?

A7. The tissue bank must demonstrate that adequate aseptic processes are established for their particular operations. Although not directly applicable to a tissue establishment, useful guidance has been published: one is titled, "Guidance for Industry - Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice" published in September 2004; and another is titled, "Aseptic Processing of Health Care Products" from ISO 13408-1.

Q8. Are you required to make tissue claims?

A8. No

Q9. What if the tissue graft's label is too small to list "claims" and/or the summary of records? Can they be included on the package insert?

A9. Yes, the package insert is an acceptable location to list claims and information related to the summary of records.

Q10. Are new shipments of labels required to be qualified before being released into inventory?

A10. Yes, label accuracy, legibility and integrity must be verified for incoming (pre-printed) or produced labels. Procedures should be written that ensure this activity is completed in a controlled manner and documented.

Q11. Must labeling operations, such as label verification, be completed as a function by two people?

A11. No, there is no specific requirement for the number of people to control labeling operations or verification. The establishment must have in place adequate procedures and controls based on their size, scope and complexity of operation.

Q12. Can you suggest how the summary of records should be "attached" since the summary of records must accompany the tissue ((§1271.55(b))?

A12. The summary of records requirements can be met in a variety of ways including use of a separate insert that accompanies each tissue or by adding the required information to an existing package insert, or it can be attached by a tag.

Q13. What control practices are expected to meet the requirements for acceptable verification of label accuracy, legibility and integrity?

A13. The control practices required are based on the establishment's scope and complexity of operation. Typically a designated function such as a quality assurance check verifies label acceptability to a written procedure. Also, non-conforming labels should be quarantined and their disposition designated per a written procedure.

Q14. What level of label accountability needs to be included in processing records?

A14. A sample label can be provided in the processing record in addition to a labeling accountability record.

Q15. If a computer generated labeling system, such as bar coding is used, what validation standards or guidance can be offered regarding software validation for these systems?

A15. Refer to "General Principles of Software Validation; Final Guidance for Industry and FDA Staff" issued on January 11, 2002.

Q16. Given that labeling systems for allografts have been in use for many years at most organizations, how much consideration will be given to historical label stock performance with respect to legibility and integrity, as opposed to full scale validation of these systems/materials (i.e. will there be 'grandfathering' provisions for proven legacy systems)? In making such an argument, what quantities and types of historical data are expected to substantiate legibility and integrity?

A16. Labeling systems are expected to meet the requirements of the new regulation. There will be no 'grandfathering' of these systems. In §1271.250 it is stated that the label stock performance must be compatible with legibility and integrity requirements and need only be verified (not validated).

Q17. Are copies of completed labels required to be maintained, or is it acceptable to be able to re-create a label from your computer system, if requested?

A17. The establishment must demonstrate that labeling is completed per the labeling procedure. Typically this includes enclosing an extra label in the processing record as evidence of the actual label used. For electronic systems retaining an electronic copy is acceptable, otherwise, it is advisable to create an extra label copy for inclusion in the processing record.

Q18. If the tissue establishment maintains records in more than one location, are faxed or e-mailed records considered adequate for review prior to release for distribution?

A18. This method is acceptable provided the records can be adequately evaluated (they are legible and accurate) and there is a controlled approval process.

Q19. If labels are hand-generated on a daily basis, is documentation of the labeling system adequate, or does each label have to be logged?

A19. The labeling process must be adequately defined to ensure the required level of control is achieved. Typically hand-generated label processes cannot be validated and must be 100% verified.

Q20. If tissue is processed by an initial processor then is further processed at another facility, are all processing facilities' names required to appear on the allograft labeling?

A20. AATB *Standards* require that this information appear on labeling or package inserts, however, these federal regulations only require that procedures are in place to facilitate the tracking from establishment to establishment (consignee to consignee) and/or to final disposition, and accurate tracking of the tissue throughout all manufacturing steps must be accomplished and be readily available.

Q21. Must the name and address of the processing facility, if different from the establishment that determines release and the establishment that distributes the tissue, be made available on the labeling or to the final end user?

A21. Yes. It has been clarified that tracking requirements apply to those facilities that handle the tissue and that the purpose of a tracking system is to facilitate the investigation of actual or suspected transmission of communicable disease and any appropriate and timely corrective action. The CGTP rule requires that tissues be labeled clearly and accurately, with information including a description of the tissue along with its distinct identification code, the name and address of the manufacturer, a description of the tissue and the graft expiration date. The storage temperature, appropriate warnings, and adequate instructions for use when related to the prevention of the introduction, transmission, or spread of communicable disease must also be provided on the label or on a package insert.

Q22. Is a tissue establishment required to "validate/verify" the tracking method process when adopting a distinct identification code assigned by another establishment engaged in manufacturing, to insure distinct identification codes are used by the second tissue establishment?

A22. The establishment must ensure the tracking method is effective both forward and backward. It is advisable to utilize validation and/or verification techniques to demonstrate that the tracking system is effective.

Q23. Is the term "medical record number" analogous to the donor number (distinct identifier) assigned at the tissue bank, or is it a reference to the patient's medical record number that may be obtained prior to donation? Accession/donor numbers assigned at the time of receipt at the tissue bank may be used to track the donor records internally, and may be used throughout the processing and distribution of tissues.

A23. Except in the case of autologous or directed donations, the donor's hospital medical record number is never the tissue distinct identification assigned by the tissue bank. Regulations provide flexibility regarding how an establishment assigns a distinct identifier. It is up to the establishment to define the system and ensure it meets the requirements for tracking and traceability.

Q24. To what extent are tissue banks responsible for tracking of the released allograft for transplant?

A24. The tissue establishment needs to assure that tissue tracking can be made to the facility or person (consignee) to which it distributed tissue. This is typically accomplished through maintaining accurate distribution records. Further tracking methods are provided by way of written notification from the distributing establishment to the consignee that describes that the consignee must maintain the required records traceable to the recipient. In this case, the traceability process should be verified by the establishment as being effective. If the end user is a hospital, JCAHO Standards apply and tracing to the recipient is required by them and return of graft implant cards is supported by their Tissue Storage and Issuance Standards that became effective on July 1, 2005 in updates to five manuals: Laboratories, Hospitals, Critical Access Hospitals, Ambulatory Care, and Office Based Surgery Practices. At or before the time of distribution of a tissue to a consignee, you must inform the consignee in writing of the requirements of the tracking system that you have established and are maintaining to comply with these requirements. An example of a labeling statement that would comply with this requirement is: ''IMPORTANT NOTICE TO END-USER: Please record this distinct identification code in your records and in the patient's file.'' Expectations to complete and return graft disposition information can also be included in these instructions.

Q25. Since tissue grafts are not medical devices, the instructions for use of the graft may be followed by the surgeon or could be used in an alternative fashion. How does a tissue bank satisfy the CGTPs in this case regarding "instructions for use"?

A25. There is a distinction between "instructions" and "indications" for use. "Instructions for use" means the graft handling requirements to be used during the surgical procedure. Examples of this would be: thawing the allograft or re-hydration of it prior to use; removing the outer layer of packaging prior to introduction to the sterile field, etc.

Instructions for use should be followed. "Indications for use" dictate the surgical procedures or clinical use the graft shall be limited to for the repair, replacement, reconstruction or supplementation of the patient. The actual use or application is up to the discretion of the licensed physician.

Q26. To what degree are symbols allowed on tissue labels such as those used for medical devices?

A26. Standardized symbols such as those used to depict sterilization methods, expiration dates, etc., are acceptable provided they are defined within the instructions for use.

Q27. How do the "instructions for use" relate to allograft claims? Will the use of terms such as "in order to achieve optimal result" be restricted?

A27. Any claim is required to be fully verified or validated. It is up to the establishment to determine their claims and degree of verification/validation required to demonstrate that the claim is true and accurate.

Q28. What is considered "misleading" with respect to label claims? For example, if the phrase "graft sterilized" is used without documented validation of a terminal sterilization process, could this be considered misleading to the end user regarding the sterility of the final graft?

A28. Labeling statements must be truthful, accurate and not misleading. It's advisable to consult FDA guidance documents for labeling, use industry standards, and use standardized symbols.

Q29. Will negative claims be held to the same scrutiny? For example, if promotional materials contain the statement that implies that an alternative processing method may be detrimental, will there be requirements to substantiate such a claim?

A29. Any claim is required to be fully verified or validated and justified with data.

Q30. How will labeling claims be distinguished between for reconstruction, repair, replacement or supplementation, and therapeutic or clinical outcome? The term "repair" implies an outcome or result of clinical use. In this context, it is difficult to conceive of a therapeutic or outcome-based claim that is not directly related to repair. As an example, if a graft is labeled as being "non-immunogenic", the implication is that the repair process will be less hindered by immune response in the patient.

A30. Any claim is required to be fully verified or validated and justified with data. The establishment must decide how to best demonstrate through fully verifiable testing.

Q31. It's understood that the distinct identifier code must appear on an individual allograft's immediate label of the package it is packaged within, but is it also expected that the distinct identifier code appear on the generic package insert information that

accompanies the distributed allograft ? This package insert may also include information that serves as the "summary of records."

A31. No, there is not an expectation that the distinct identifier code appear on all package inserts or specifically, on the summary of records. It's understood that the requirements of the summary of records content can be fulfilled by using a well-crafted description used in a generic fashion for that tissue type. The ability to successfully perform tracking of tissues (the intent of 1271.290) is not compromised if the distinct identifier does not also appear on the allograft package insert. The package insert information is distributed with the allograft but when received by the consignee, what they do with this type of information is at their discretion and not within the scope of federal regulations. The ability of the bank to provide successful tracking to the consignee is not compromised by not including the distinct identifier on the package inserts sent with distributed allografts. Also, the components of the summary of records as described in 1271.55(b) do not include the distinct identification code and the intent of 1271.55(a) is met with the distinct identification code clearly indicated on the allograft's immediate label.

Section VI.

Distribution

VI. DISTRIBUTION

Q1. Why is a tissue expiration date important?

A1. The expiration date is the maximum allowable storage period. Expiration dates are assigned by the tissue processor and should appear on labeling. Expired tissue should not be transplanted. If possible, storage methods should be applied so that tissue that will outdate first is arranged so it will be selected for distribution first.

Q2. In general, how should a consignee store tissue?

A2. Tissue must be stored in a secure area and in accordance with processor's (manufacturer's or "source facility's") instructions. Continuous monitoring would be expected for tissues that require specific environments (i.e. refrigerated, frozen).

Q3. What comprises a documented receipt and inspection of tissue?

A3. Receipt and inspection is a visual check of incoming tissue. The inspection may include visual inspection of the shipping carton as well as the tissue packaging. Criteria for acceptance or rejection of a tissue shipment must be defined in procedures. If there are indications that contamination or cross-contamination of the tissue has occurred, the shipment should be rejected.

Documentation may be performed by using a packing list, a checklist, or similar document which identifies the sender, donor/tissue identification number(s) of tissues in the shipment, identity and quantity of tissues included in the shipment (e.g. femur, fascia lata, dowel, wedge, etc.), date/time of receipt, and acceptance or rejection of the incoming tissue based on set specifications defined in procedures.

Tissue processors/manufacturers may require consignees to return rejected tissue for final disposition. Final disposition of the rejected tissues must be documented.

Q4. Who must document receipt and inspection of tissues?

A4. Processors, Distribution Intermediaries and Consignees should document receipt and inspection of tissue and note acceptance or rejection of tissue using established parameters. Refer to § 1271.265. You must evaluate each incoming tissue for the presence and significance of microorganisms and inspect for damage and contamination. You must determine whether to accept, reject, or place in quarantine each incoming tissue, based upon pre-established criteria designed to prevent communicable disease transmission. Tissue Consignees should refer to JCAHO standards section QC.5.300 and PC.17.10 pertaining to requirements for written procedures for documentation of receipt and storage conditions. Other recognized industry standards can also be used.

Q5. Is shipping container qualification/verification or shipping method validation required?

A5. Different tissue types may require different shipping containers depending on established storage requirements. Verification that the shipping container will maintain the required environment (i.e. frozen, cryopreserved, refrigerated) for a specified time period ensures that the storage (temperature) requirements are maintained for the tissue being transported. The procedure is validated to ensure that when the container is used with addition of specific amounts and types of refrigerant, this ensures that the required tissue storage environment is maintained when these instructions (procedures) are followed.

Q6. How do I determine appropriate shipping conditions?

A6. Shipping conditions should be based on acceptable temperature limits for storage of the specific tissue type. Shipping conditions should be supportive of any claims that are made. Recognized industry standards can be used.

Q7. What do you do if damaged tissue is discovered when preparing for distribution?

A7. Each tissue bank should establish a procedure to define the handling of damaged tissue. The procedure should describe whether the tissue should be returned to the manufacturer or appropriately destroyed.

Q8. Explain traceability pathway related to distribution and responsibilities of each member in the pathway.

A8. Potential segments of pathway are described here:

a) Retrieval agency to intermediary or processor:

The retrieval agency is responsible for tissue retrieval, assignment of a unique donor identifier, appropriate tissue packaging, and shipping. It is also responsible for tracing the donor cells/tissues from date/time of retrieval to date/time of cell/tissue shipment to the processing facility (ies).

Distribution records – donor identification number, tissue identity, date/time retrieval, relevant and complete retrieval information, date/time of shipment and receiving facility identity (ies). All personnel involved with these significant steps shall be identified and all steps properly documented when they occurred.

b) Intermediary or Processor to (another) tissue manufacturer:

The processor is responsible for the implementation and maintenance of records that provide for tissue traceability back to the original donor information and includes the date/time of tissue receipt from the retrieval agency. If further or adjunct manufacturing will occur, the date/time and the method of shipment that is used to send the tissue to another tissue processor would be required documentation.

Receipt Records – The processing tissue bank should perform a documented receipt & inspection of all incoming donor cells/tissues and document acceptance or rejection, date/time received, and personnel performing these significant steps.

Distribution Records include but are not limited to: tissue ID number, expiration date, type, quantity, date/time of shipment to manufacturer as well as the identity of the receiving facility.

c) Tissue manufacturer to Distribution Intermediaries:

Tissue manufacturer is responsible for the implementation and maintenance of records that provide for tissue traceability back to the original donor ID number from the date/time of tissue receipt from tissue bank sender (e.g. processing tissue bank) to date/time of shipment to Distribution Intermediary. This includes, but is not limited to, receipt and distribution records.

Receipt Records should contain evidence of documented receipt & inspection performed at the time of receipt of tissue by Distribution Intermediaries for storage and/or further transport & delivery to end-user. Inspection should note if shipment and/or tissues were accepted or rejected. Documentation of all personnel involved with each step is advised.

Distribution Records include but are not limited to: tissue ID number, expiration date, type, quantity, date/time of shipment to and/or from Distribution Intermediary and/or end-user locations as well as the identity of the receiving facility. Documentation of all personnel involved with each step is advised.

d) Distribution Intermediary to End-user (consignee) location:

A Distribution Intermediary is responsible for the implementation and maintenance of records that provide for tissue traceability from the date/time of tissue and/or tissue device receipt to date/time of transport & delivery to end-user.This includes receipt, storage and/or transport and delivery to end-user. This is accomplished by:

Receipt Records should contain evidence of documented receipt & inspection performed at time of receipt by agent for transport and delivery or receipt by agent facility for storage and further transport & delivery. Inspection should note if shipment and/or tissues were accepted or rejected. Distribution Intermediary is responsible for notifying the tissue bank and/or tissue manufacturer if shipment and/or tissues are damaged.

Inventory-in-storage records include but are not limited to: tissue ID numbers, expiration date, date/time of receipt into inventory and by whom as well as date/time removed from inventory and by whom.

Distribution Records include but are not limited to: tissue ID numbers, identity of tissue type, quantity, date/time of transport & delivery, end-user facility to which tissues or tissue devices were delivered, identity of person transporting tissues and identity of person at end-

user facility accepting tissue. Distribution Intermediaries should also provide documentation for ALL final dispositions (i.e. not implanted due to expiration or contamination, etc.).

If tissue is returned to the manufacturer for any reason, distribution records should document that tissue was returned to the manufacturer per manufacturer's instruction, date/time of return, and the reason for return.

Q9. What records must Distribution Intermediaries (such as independent sales agencies or representatives) maintain?

A9. Applicable records include:

a) Receipt, inspection and acceptance or rejection of tissue,
b) Storage temperature records, if applicable, and
c) Disposition records documenting the identification number, tissue type and quantity, date of shipment and identity of consignee (if shipped) or date of destruction (if applicable).

Q10. How should a consignee participate in tissue tracking?

A10. At or before the time of distribution of tissues, the tissue establishment distributing the tissue must inform the consignee in writing describing expectations and requirements for tissue tracking. The consignee is responsible for documenting disposition of the tissue while it is in their possession and providing tracking to the next destination or final disposition.

Q11. Are tissue returns permitted?

A11. Each tissue facility should establish a procedure regarding return of tissue. If returns are not permitted a simple policy stating that the facility does not accept tissue returns is all that is required.

If returns are permitted, the facility must have a policy that states that tissue returns are permitted and identify the conditions under which the return may be accepted. Returning establishment should follow the instructions from the tissue bank from which the allograft was received.

Q12. Tissue manufacturers often request that a Distribution Intermediary return damaged tissue (allografts) to them for destruction. This allows the manufacturer to inspect the tissue and determine final disposition. What type of record, if any, is a Distribution Intermediary required to maintain for this type of transfer?

A12. The Distribution Intermediary should maintain a distribution record, which demonstrates when tissue was returned to the manufacturer per manufacturer's instruction and the reason for the return.

Q13. What are the requirements for tissue transport by a Distribution Intermediary, such as an independent sales representative?

A13. Distribution Intermediaries must store tissues at the storage temperatures (or other parameters) established by the tissue manufacturer. Storage outside the established storage requirements may adversely affect contamination control. Tissues must be shipped or transported at the shipping conditions defined by the processor.

Q14. What type of package inserts should be shipped with tissue?

A14. Package inserts may vary with each tissue type. Package inserts may include a return policy (if one exists), tissue transplant record/implant card (to track tissue disposition), instructions for use and storage, indications for use, any claims made, instructions for adverse event reporting, tissue description, an expiration date (if applicable), and any warnings or warranties, if applicable.

Q15. What should I do if I discover that a tissue graft is mislabeled?

A15. Each establishment should develop a written procedure for handling mislabeled tissues. The procedure should include evaluation of the mislabeling severity, assessment of risk to patients, and disposition of the mislabeled tissue.

Q16. Who is responsible for the handling of tissues during shipment?

A16. The carrier designated for the shipment of the allograft assumes the responsibility of the package during shipment. Shipping containers selected should be of proper construction and design for the purpose for which they are used. If tissues are transported by a Distribution Intermediary, such as an independent sales representative, the Distribution Intermediary assumes responsibility for tissue during transport and delivery and must follow instructions provided.

Section VII.

Processing

VII. PROCESSING

Q1. In §1271.190 Facilities (a) General, it requires that a facility used in the manufacture of tissue shall be of "suitable" size, construction, and location to facilitate cleaning, "relevant" maintenance, and "proper" operations. How is an organization to determine if their facility is of suitable size, construction and location to facilitate cleaning, relevant maintenance and proper operations?

A1. It's up to each establishment to determine and establish the qualification of their facility related to facility cleaning and sanitation. If a facility, for whatever reason, cannot be adequately cleaned so as to minimize the risk of tissue contamination or cross-contamination between donors and consistently operate within established control limits, it is not appropriate for the manufacture of tissues. For processing operations, this should be determined by a verifiable cleaning program supported by environmental monitoring activities, as specified in 1271.160 (b) Functions (5), and 1271.195 Environmental control and monitoring.

Q2. What temperature and humidity controls should be in place?

A2. If processing steps in the manufacture of tissue have identifiable parameters for maintaining a certain temperature and/or humidity, or the potency and efficacy of the reagents used in the manufacturing of tissue may be affected adversely by temperature and/or humidity, methods to monitor and document these conditions must be established. Each establishment would have the responsibility of developing an appropriate stability protocol to determine if temperature and humidity could reasonably be expected to have an adverse effect on the tissue. In these situations, an establishment would be required to establish and maintain procedures to adequately control and monitor environmental conditions and to provide proper conditions for operations.

Q3. How often should I perform environmental monitoring?

A3. Depending on the particular environmental factors at a processing facility, and the type of operations performed there, environmental controls, along with the type and frequency of monitoring should be defined in procedures. Regular monitoring should be performed to show cleaning procedures are adequate, and that the environmental control systems are capable of maintaining the degree of control specified. Establishing pass/fail criteria, along with alert and action limits, for test results should be defined in procedures along with corrective action measures for out-of-spec (OOS) conditions identified. The following is a list of areas that might be considered as candidates for environmental monitoring:

- Non-viable particulate air monitoring;
- Viable particulate air monitoring;
- Surface Monitoring – taking into account all different surfaces in the processing environment; and,
- Clean area, positive pressure levels.

Q4. What types of equipment must be identified in records as being used in the manufacture of tissue?

A4. Any equipment that can affect the contamination status of tissues must be recorded, such as freeze-drying equipment.

Q5. How would an organization determine that its equipment utilized in manufacture of tissues is of appropriate design for its use, and is suitably located and installed to facilitate operations including cleaning & maintenance?

A5. Determination that equipment is appropriate for use is based upon its design, location, installation and operation in regard to the potential to control contamination and cross-contamination of tissues during use. This should be accomplished through the development of a Design Qualification (DQ) protocol developed and executed prior to the routine use of the equipment to ensure that the equipment would not adversely affect/contaminate the tissue. The development and execution of an Installation Qualification (IQ) of the equipment, if applicable, would then ensure that the equipment is suitably located and installed (in accordance with the equipment manufacturer's specified requirements) to facilitate operations as expected.

Q6. In §1271.200(c) Calibration of equipment, it states that equipment requiring calibration be routinely calibrated according to established procedures and schedules. How should an organization determine the frequency of calibration of its equipment?

A6. An organization may consult the Operations Manual or contact the manufacturer of the equipment to determine and establish appropriate intervals for which equipment should be calibrated. The organization should also take into consideration the specific use of this equipment within the manufacturing facility to determine if special conditions may warrant more frequent calibration (or less) than is recommended by the equipment manufacturer. Calibration accuracy should be traceable to accepted standards (National Institute of Standards and Technology).

Q7. This section requires that calibration procedures shall include specific directions, and where applicable, shall include limits for accuracy and precision. What is the difference between "accuracy" requirements and "precision" requirements?

A7. Accuracy should never be confused with precision. Accuracy measures how close to a true or accepted value a measurement lies (in calibration of tolerances, it is the upper and lower limit capabilities of a specific instrument relative to a referenced standard), and would specify the tolerances within which a specific piece of equipment could be expected to hold, as measured against a referenced known standard. "Precision" is the ability of an instrument to consistently reproduce those accuracy requirements; or the number of significant digits to which a value has been reliably measured.

Q8. In section (e) Records, it's required that records of recent maintenance, cleaning, sanitizing, calibration, and other activities shall be available "at each piece of

equipment"… Is this to be interpreted that all documentation of preventive maintenance and calibration must be physically kept at each piece of equipment?

A8. No. This does not necessarily mean that all preventative maintenance and calibration records must be physically kept directly with each piece of equipment. It may be appropriate for an establishment to implement a method of identifying the current preventative maintenance and/or calibration status of each piece of equipment. It should be clear and obvious to the operator, prior to each use of the equipment that the equipment is in a state of preventative maintenance and/or calibration and may be confidently and safely used.

Section VIII.

Storage

VIII. STORAGE

Q1. What are expectations regarding documentation of storage temperatures?

A1. Procedures shall be established and maintained describing scheduled review of storage temperatures of tissues that require specific storage environments (tolerance limits) and documentation of such reviews should be performed. A temperature monitoring system for specific storage environments (refrigerated, frozen, cryopreserved) would be necessary to document (verify) storage temperatures and it should be capable of alerting staff before temperatures have ultimately strayed outside acceptable limits. Appropriate documentation regarding tissue disposition or transfer to alternative storage would be expected if storage temperature limits were exceeded or were recognized to be in danger of being exceeded. Corrective actions shall appropriately be taken and documented. Continuous monitoring of tissues maintained at ambient room temperature is not indicated. Whoever has possession of the tissues during each step of manufacturing must maintain records that indicate that specified environmental temperatures were maintained during manufacturing steps (i.e. at point of origin and upon receipt). Records shall be retained for at least 10 years beyond the date of distribution, date of transplantation (if known), date of disposition, or date of expiration of the tissue (whichever is the latest).

Q2. In §1271.260(a) Control of storage areas, what are expectations for identifying a storage unit?

A2. Each unit used for storage of tissues should be identified to facilitate monitoring of temperature and location of in-process, quarantined, and tissues designated for distribution inventory. Each storage unit shall be labeled with the general nature of the contents and with a biohazard symbol, if indicated. Areas containing storage units shall be organized to prevent mix-ups, commingling and/or improper cell/tissue release.

Q3. What constitutes a reportable deviation?

A3. You are required to report those tissue deviations that could reasonably be expected to lead to a reportable adverse reaction for a tissue recipient, such as one that: is fatal; is life-threatening; results in permanent impairment of a body function or permanent damage to body structure; or, necessitates medical or surgical intervention, including hospitalization. Problems that occur in areas of manufacture other than processing, such as at recovery and during storage, would be included as possible areas from which the deviation originated, but the deviation would only qualify if it had an affect on an tissue that was distributed.