

14th Edition

Standards for TISSUE BANKING

AATB

American Association of Tissue Banks
STANDARDS FOR TISSUE BANKING

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by American Association of Tissue Banks

14th Edition

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About the cover: Scanning electron micrograph of freeze-dried, decellularized cancellous bone, taken with a Carl Zeiss Sigma FESEM, magnification 99x. Colorization has been used to accentuate the porous structure of the bone. Used with permission from the owner, Scott Bible, at Wright Medical, Memphis, Tennessee.

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Co-Editors

Joel C. Osborne, CTBS (Chair, Standards Committee, 2012-2013)
Karen G. Norman, CTBS (Chair, Standards Committee, 2014-2015)
Timothy Maye, CTBS (Chair, Standards Committee, 2016-2017)
Patty Malone, MT (ASCP), CQA (Vice Chair, Standards Committee, 2016-2017)
Scott A. Brubaker, CTBS (AATB, Senior Vice President of Policy)

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Jenny Chatman, CTBS (Coordinator)
Michelle Lewis, ASQ CBA, RAC, CTBS (CAPA Analyst)
Jason LoVerdi, MHA, CTBS (Manager)

2015 Work Group Volunteers

The following volunteers worked during 2015 to review sections and parts of the 13th edition of *Standards* to provide recommendations for updates to the Standards Committee:

Introduction - Karen Norman and Timothy Maye

Section A - **Jason LoVerdi** (leader) and Scott Brubaker

Section B - **Jonna Turner** (leader), Debbie Sage, Michelle Bute and Phil Mellinger

Section C - **Joel Osborne** (leader), Jessica Donovan, Patty Malone and Diane Wilson

Section D - **Glenn Greenleaf** (leader), Jeff Cox and Greg Ray MD

Section E - **Tracy Ross** (leader), Sheldon Dean, Glenn Greenleaf, Rebecca Hurst, Phil Mellinger, Josh Murphy, Jonna Turner and Diane Wilson

Section F - **Jonna Turner** (leader), Casey Ming, Marc Germain MD, Alan Tillis MD, Diane Wilson, and Jennifer Wright

Section G - **Bridget Reardon** (leader), Sharon Berardi, Michelle Bute, Miriam Estrano, Debbie Sage and Guobao Wei

Section H - **Bridget Reardon** (leader), Sharon Berardi, Michelle Bute, Miriam Estrano, Debbie Sage and Guobao Wei

Section J - **Patty Malone** (leader), Stephanie Cozby, Christine Crone, Carla Johnson, Rochelle Maney, Peter Mecnas, Darilyn Million and Diane Wilson

Section K - **Patty Malone** (leader), Stephanie Cozby, Christine Crone, Carla Johnson, Rochelle Maney, Peter Mecnas, Darilyn Million and Diane Wilson

Section L - (update planned later)

Section M - **Sarah Lopez** (leader), Rusty Adams, Tonya Carraway, Lisa Cranford, Chuck Hall and Lindsay Kiolbassa

Appendix I - Karen Norman

Appendix II - Marc Germain, MD and Greg Ray, MD

Reproductive tissue (R) - Donna Ridder and Martha Wells

2014 -2015 Voting Members

Michael A. Bergevin, MD, CTBS
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Marc Germain, MD, FRCP
Glenn Greenleaf, CTBS
Peter Jenkins, CTBS
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James Rogers
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Chris Talbot, MS
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Martha Wells, MPH, RAC

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Patrick Ooley (AABB)
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Sharon A. Van Wicklin, MSN, RN, CNOR, CRNFA, CPSN-R, PLNC (AORN)
Martell Winters (AAMI)

AATB Inspectors

Murray L. Anderson, CTBS
Karen Baier, MT (ASCP)
Sue Brewster, RN, CQA (ASQ), CTBS
Connie Jones
Sam Jones
Sabrina Qualley BA, MLT (ASCP), CQA (ASQ), CTBS

AATB Accreditation Program Staff

Scott A. Brubaker, CTBS (Senior Vice President, Policy)
Jenny Chatman, CTBS (Coordinator)
Jason LoVerdi, MHA, CTBS (Manager)
Debbie Newman (Manager)

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2012-2013 Non-voting Members

David Campagnari (ASTM)
Karoll Cortez, MD, MHS (FDA/CBER)
Jennifer DeMatteo, MCM, CIC (EBAA)
Liz Anne Gillham-Eisen (Health Canada)
Melissa A. Greenwald, MD (FDA/CBER)
Matthew Kuehnert, MD, CAPT, USPHS (CDC)
LCDR Elizabeth Lybarger, USPHS (FDA/CBER)
Stephen Patten, MSN, RN, CNS, CNOR (AORN)
Debbie Seem, RN, MPH (CDC)
Martell Winters (AAMI)

AATB Inspectors

Murray L. Anderson, CTBS
Sam Jones
Sabrina Qualley, BA, MLT (ASCP), CQA (ASQ), CTBS

AATB Accreditation Program Staff

Scott A. Brubaker, CTBS (Chief Policy Officer)
Debbie Newman (Manager)

AMERICAN ASSOCIATION OF TISSUE BANKS

STANDARDS FOR TISSUE BANKING

PREFACE

The American Association of Tissue Banks (AATB) was founded in 1976 as a voluntary, scientific, and educational not-for-profit organization to promote the exchange of information, methods, and procedures that would increase donation and provide safe, transplantable tissues of uniform high quality in quantities sufficient to meet national needs. A year later, a book of *Proceedings* [1] from the first annual meeting was published that offered a detailed overview of current tissue banking practices and described the ethics of donation and transplantation.

Between 1978 and 1981, provisional ‘*Guidelines*’ for proposed standards were drafted, discussed, adopted and published. They encompassed specific cells, tissues, and organs divided into the following categories: renal, ocular, cell and tumor tissues, bone marrow, musculoskeletal, semen and skin.

The first edition of AATB’s *Standards for Tissue Banking* was published in 1984, combining similar, general operational standards from all of these categories. This collection marked the first professional standards ever developed in the field of banking transplantable human tissues, other than ocular. An excerpt from the Scope and Purpose of this inaugural edition reads:

“These general Standards are intended to be applicable to any and all forms of tissue banking: retrieval, storage, and distribution of human tissues for medical use. They represent the current thinking of a diversified group of experienced practitioners of tissue banking who have pooled their efforts to extract general principles and philosophies of banking operations common to all and to highlight specific considerations which pertain to certain categories of tissues.”[2]

A voluntary accreditation program for tissue banks was launched in 1986 with inspection and accreditation based upon adherence to these *Standards*. This first publication of *Standards* was followed by the publication of a *Procedures Manual* (1986) aimed at assisting musculoskeletal, skin, and ocular tissue banks to standardize methods being used.

The following year was notable for another AATB publication titled, *Technical Manual for Tissue Banking*. It contained individual tissue-specific manuals for the banking of musculoskeletal, skin, reproductive, and (living donor) surgical bone. These manuals described step-by-step procedures to facilitate successful tissue banking operations for each tissue type. They were created by their respective councils, which had been formed within the Association.

The Technical Manual was updated with a final publication in 1992. It contained a new section for cardiovascular tissues as well as introducing the “*Protocol for Reporting an Event with the Potential for Disease Transmission.*” In time, much of the contents of these manuals were incorporated into a subsequent edition of the *Standards*, since tissue bank accreditation inspections included assessment of compliance with these technical manuals as well as *Standards*.

In the 1993 sixth edition, a section first appeared in *Standards* titled, “*Medical Facility Tissue Storage and Issuance.*” This section was directed at medical facilities to offer structural and functional guidelines for the handling of human tissue allografts and autografts. It required the establishment of

procedures and maintenance of records for tissue storage and disposition to ensure safety and traceability of tissue from receipt through clinical transfer or destruction. Other requirements included: supervision by a licensed physician (or dentist for a dental facility); monitoring of freezers and refrigerators used to store tissue; maintenance of records that included documentation of condition of tissue upon receipt; and steps involved with storage, issuance, return, disposal, recall and handling of adverse outcome reports. These standards were sent to the College of American Pathologists (CAP) as well as The Joint Commission on Accreditation of Hospitals resulting in inclusion of similar tissue handling requirements in their standards and checklists in 1993 and 1996 respectively.

By the seventh edition (1996), the AATB *Standards* had grown from 21 pages to a book of 108 pages. It included new sections, such as: Records Management; Release and Transfer of Tissues; General Operations (i.e., procedure manual, staff training/competency, safety practices, and facilities/equipment requirements); and, Quality Assurance and Quality Control. The application of a quality systems approach to all tissue banking operations, and the establishment and maintenance of a quality program became required in *Standards*. Additions to the *Standards* resembled concepts related to good manufacturing practices (GMPs), which had been adopted by a handful of AATB-accredited tissue banks that were processors of cryopreserved allograft heart valves. At that time, this group of cardiovascular tissue processors was mired in an investigational device exemption (IDE) application with the Food & Drug Administration (FDA). This resulted from FDA's unforeseen and surprising designation of these tissue banks as a "manufacturer of a replacement heart valve" [3], or better known as a Class III medical device manufacturer, the strictest device classification.

The 10th edition was published in 2002 and was the first edition to be numbered. The 11th edition in 2006 was the first to provide the *Standards* on a CD-ROM and the style of the publication changed dramatically. The cover was modernized and the publication size expanded from a 6" x 9" booklet to an 8.5" x 11" notebook with a durable, coiled spine, which allowed the book to lie flat when opened. Three-hole punches along the spine provided an option to maintain the book in a binder and the capability to insert printable updates when issued to the *Standards*. Frequent revisions became commonplace during modern times and the format changes increased user satisfaction so this publication style remains.

Similar to the 12th edition (2008), the 13th edition of *Standards* included a number of guidance documents developed by the Association's constituency to fill gaps and complement specific standards. For ease of reference regarding expected compliance, the current version of the AATB's Accreditation Policies for Transplant Tissue Banks was also included.

The 14th edition (2016) of *Standards* includes three new appendices. To clarify expectations for compliance, three documents previously referred to as "AATB Guidance Documents" each became incorporated as a separate appendix to the *Standards*. Where their title previously included reference as a "Guidance Document," the title was changed to reflect they are "Requirements". Therefore, the following appendices are unambiguous and compliance is mandatory:

- Appendix III Tissue Donor Physical Assessment Form Requirements (formerly AATB Guidance Document No. 1, v2 Tissue Donor Physical Assessment Form, 6-27-05)
- Appendix IV Prevention of Contamination and Cross-contamination at Recovery: Practices & Culture Results Requirements (formerly AATB Guidance Document No. 2, v2 Prevention of Contamination and Cross-contamination at Recovery: Practices & Culture Results, 6-29-07)
- Appendix V Recovery Partner Audit Tool Requirements (formerly AATB

Guidance Document No. 6, Recovery Partner Audit Tool, 9-1-11)

The 14th edition is the first to be published online but the printed book continues to also be available for purchase. Notice of updates to the 14th edition was provided via publication of two documents; one shows additions and deletions made throughout [4], and another provides a descriptive overview [5].

From the inception of the AATB in 1976 to the present, the passionate dedication of numerous, knowledgeable tissue banking professionals has led to improvements to a variety of published guidelines, manuals, and standards. Their willingness to share experiences and best practices, to educate each other, and their ability to be forward-thinking regarding application of a quality culture to tissue banking operations, has led the way to maintaining a template (the *Standards*) that continues to be referenced not only by tissue banks, but also by end-user healthcare facilities, other standards- setting associations, and regulators worldwide. Global cooperation and the sharing of information among tissue banking professionals continues today, the same spirit that led to the formation of the AATB and the development of these *Standards*.

Scott A. Brubaker, CTBS
Senior Vice President of Policy

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- [2] *Standards for Tissue Banking*, American Association of Tissue Banks (AATB), 1984, Arlington, Virginia
- [3] U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, “Requirement for Pre-market Approval; Replacement Heart Valve Allograft,” 6/26/91
- [4] 14th Edition of AATB’s *Standards for Tissue Banking with Amendments.pdf*
- [5] Overview and Updates – 14th Edition of AATB’s *Standards for Tissue Banking.pdf*

AMERICAN ASSOCIATION OF TISSUE BANKS

STANDARDS FOR TISSUE BANKING

INTRODUCTION

Progress in medical science and cell biology has resulted in the *transplantation* of human cells and *tissue* from one human into another, enhancing the quality of life by restoring form and function and facilitating reproduction. For more than 60 years, society has recognized the medical and humanitarian value of donating and *transplanting* organs and *tissues*. The universal significance of this is made apparent by the enactment of legislation based on the Uniform Anatomical Gift Act. The American Association of Tissue Banks (AATB), through its constituency, is committed to providing stewardship for gifts of donated human *tissue* and promoting the public trust in donation and *transplantation*.

A mission of the AATB is to establish and promulgate standards to provide *tissue banks* with performance requirements intended to prevent disease transmission and support *quality* measures that assist clinical performance of *transplanted tissue*. Furthermore, the AATB fosters education and research, and promotes *quality* and *safety* in cell and *tissue banking* and *transplantation*.

The AATB's "*Standards for Tissue Banking*" (*Standards*) reflect the collective expertise and conscientious efforts of tissue bank professionals to provide a comprehensive foundation for the guidance of *tissue banking* activities. The *Standards* are reviewed periodically and revised by the AATB Standards Committee to incorporate scientific and technological advancements. The Standards Committee receives input from the Association's Councils (Accredited Tissue Bank, Physicians', Processing and Distribution, Quality, Recovery and Donor Suitability, and Reproductive) and appropriate standing committees and/or ad hoc task forces, as needed. All revisions are subject to approval by the AATB Board of Governors.

In the *Standards*, terms and related words with a similar meaning that are defined in A2.000 Definitions of Terms appear in italics [e.g., *verification* (*verify*, *verified*)]. Additionally, the *Standards* contain appendices that *must* be followed.

These *Standards* establish performance requirements for *informed consent* or *authorization*, *donor eligibility assessment* through *donor* screening and testing, as well as for the *recovery*, *processing*, *storage*, *packaging*, *labeling*, and *distribution* of *transplantable human tissue*. The *Standards* are intended to be applied to *tissue bank* functions that relate to *quality*, staff, *donors*, and *tissue*, but do not encompass the clinical use of *tissue*. In addition, unless otherwise stated, these *Standards* apply only to *tissue* intended for clinical use or *transplantation* to *recipients* (including use in *assisted reproductive technology* procedures).

Accreditation by the AATB is based on *verified* compliance with these *Standards* and the Accreditation Policies for Transplant Tissue Banks and is strongly encouraged. Use of the words "*shall*" or "*must*" in *Standards* indicate mandatory compliance, whereas use of the words "*should*" and "*may*" indicate recommended compliance. If an accredited *tissue bank*, or one seeking accreditation, does not comply with any mandatory standard, a written rationale that sufficiently demonstrates equivalency is required. Details regarding the process to request a variance from *Standards* are specified in Appendix I.

The format of this edition of *Standards* is that of general requirements applicable to all *tissue* with subsections delineating *donor* and *tissue* standards for:

(A) *autologous tissue*,

(BT) *birth tissue*,

- (C) *cardiac tissue*,
- (CT) *cellular tissue*,
- (DM) *dura mater*,
- (LD) *living donors*,
- (MS) *musculoskeletal tissue*,
- (OA) *osteoarticular graft*,
- (R) *reproductive tissue*,
- (S) *skin*,
- (SB) *living donor surgical bone for allogeneic use*, and
- (V) *vascular tissue*.

- For all *living donors*, (LD) standards apply, then tissue-specific standards apply.
- For *tissue* that falls into one or more of these categories, both the general and *tissue-specific* standards apply.
- When a particular numbered item appears in both the general section and *tissue-specific* subsection, both requirements shall apply unless noted otherwise.
- The *tissue-specific* standard is not a replacement for the general standard for that item, except as noted.
- For *tissue* not included in these categories (e.g., parathyroid *tissue*), the general standards shall apply.

AMERICAN ASSOCIATION OF TISSUE BANKS

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Guidance Document No. 4, v2 Providing Service to Tissue Donor Families (March 9, 2015)

Guidance Document No. 5, v2 Microbiological Process Validation & Surveillance Program (July 18, 2016)

Guidance Document No. 7, v2 Evaluation of Body Cooling at Standard D5.400 (December 9, 2013)

Guidance Document No. 8, Environmental Controls & Monitoring of a Dedicated Tissue Recovery Site, (date forthcoming)

AATB-AOPO-EBAA Guidance Document, Effective Quality Assurance of the DRAI, v2 (September 16, 2013)

AATB-AOPO-EBAA Implementation Guidance Document, UDRAI Forms, v2 (May 20, 2015)

SECTION A GENERAL INFORMATION

A1.000 ACCREDITATION

AATB accredited *tissue banks* must comply with these *Standards*, the Accreditation Policies for Transplant Tissue Banks, as well as all applicable laws and regulations.

A1.100 Failure to Comply with Standards

Failure of an accredited *tissue bank* to comply with *Standards* and/or the Accreditation Policies for Transplant Tissue Banks shall be reviewed in accordance with the Accreditation Policies for Transplant Tissue Banks. Accreditation may be denied, suspended, or withdrawn upon a determination that significant *noncompliance*, such as repeated violations, one or more egregious violations, uncorrected violations, or deliberate falsehoods, have occurred.

A1.200 Requesting a Variance to Standards

Tissue banks wishing to implement a *variance* from current *Standards* must provide the following information to the AATB Senior Vice President of Policy by using the Request for Variance to AATB *Standards* Submission Format. The format must be completed in entirety and include:

- 1) A request for *variance* or modification including the particular standard number(s) that applies to the request;
- 2) Justification of the alternative *procedure(s)*, policy or process that assure(s) equivalency to the intent of *Standards*; and
- 3) Supporting information such as worksheets, *records*, data, or other information (e.g., *validation* of the protocol to be used in the proposed *variance*, including the scientific data and *quality assurance* steps).

Until the Board of Governors approves the *Variance* request, the *tissue bank* must comply with existing *Standards*. See Appendix I. A *record* of the approved *variance* must be maintained at the requesting *tissue bank* as well as at any other accredited *tissue bank* directly affected by the approval. Evidence of approval of the request for *variance* must be available during an accreditation inspection.

A2.000 DEFINITIONS OF TERMS

Words that are defined here also appear in italics throughout the *Standards*. Related words with a similar meaning in the form of a noun, verb, or adjective, or in the plural form or as past tense, as applicable, may also be italicized, but are not defined separately. Examples include “*recovery/recover/recovered*,” “*establish/established/establishment (of)*,” “*verification/verify/verified*,” “*validation/validate/validated*” and “*distribution/distribute/distributed*.”

Unless otherwise defined in the *tissue*-specific standards or otherwise used in another context in these *Standards*, the following terms shall be defined as follows:

ACCIDENT – Any occurrence, not associated with a *deviation* from standard operating *procedures* (SOPs), standards, or applicable laws and regulations, during *donor* screening or testing, or *tissue* *recovery*, *collection* or *acquisition*, *processing*, *quarantining*, *labeling*, *storage*, *distribution*, or

dispensing that *may* affect the performance, biocompatibility, or freedom from transmissible pathogens of the *tissue* or the ability to *trace tissue* to the *donor*.

ACQUISITION (BT) – The point after delivery at which *tissue* is under the control of the *tissue bank*.

ADEQUATE INFORMATION – Information sufficient for the *donor*, the *authorizing person* or the *living donor* to make a voluntary decision regarding the gift of *tissues* for *transplantation*, therapy, research and/or education. The parameters of what constitutes *adequate information* must include “*Core Elements*” contained in D2.400 or D3.400, and such additional information as the *donor*, *authorizing person*, or *living donor* requests or which the *donation coordinator* reasonably believes the *donor*, *authorizing person* or *living donor* should know. When the *donor* is *authorizing* the gift of *tissue*, publicly available information concerning the scope and use of the gift *shall* be deemed *adequate information*.

ADVERSE OUTCOME – An undesirable effect or untoward complication in a *recipient* consequent to or reasonably related to *tissue transplantation*.

ALLOGENEIC – Used as an adjective to modify donation, *tissue*, *donor* or *recipient* when *transplantation* is intended for a genetically different person.

ALLOGRAFT – *Tissue* intended for *transplantation* into a genetically different person.

ANONYMOUS DONOR (R) – A *reproductive donor* of *tissue* whose identity is unknown to the *recipient* (R).

AORTOILIAC GRAFT (C) - The distal segment of the abdominal aorta including the bifurcation and proximal segments of both the left and right common iliac arteries.

ARTERIAL GRAFT (V) – A segment of peripheral artery that is recovered, processed and *preserved*.

ARTIFICIAL INSEMINATION (R) – The placement of *semen* within the reproductive tract of a *recipient* (R).

ASEPTIC PROCESSING – The *processing* of *tissue* using aseptic techniques where *tissue*, *containers* and/or devices are handled in a controlled environment in which the air supply, materials, equipment and personnel are regulated to prevent microbial contamination of *tissue*.

ASEPTIC RECOVERY – The *recovery* of *tissue* using methods that restrict or minimize contamination with *microorganisms* from the *donor*, environment, *recovery* personnel, and/or equipment.

ASSISTED REPRODUCTIVE TECHNOLOGY PROCEDURE (R) – A medical *procedure* intended to result in conception, including, but not limited to, therapeutic insemination, in-vitro fertilization (including intracytoplasmic sperm injection), and *gamete* intrafallopian *transfer*.

ASYSTOLE – The reference time for cardiac death. A documented pronounced time of death is used as *asystole* when life-saving *procedures* have been attempted and there were signs of, or documentation of, recent life (e.g., witnessed event, agonal respirations, pulseless electrical activity). If a death was not witnessed, *asystole* *must* be determined by the last time known alive. *Asystole* will be ‘cross clamp time’ if the *tissue donor* was also a solid organ *donor*.

AUDIT – A documented review of *procedures, records*, personnel functions, equipment, materials, facilities, and/or suppliers to evaluate adherence to the written *SOPM*, standards, applicable laws and regulations.

AUDIT TRAIL - A process that captures details such as additions, deletions, or alterations of information in an electronic *record* without obliterating the original *record*. An *audit trail* facilitates the reconstruction of the course of such details relating to the electronic *record*. (FDA Guidance for Industry, Computerized Systems Used in Clinical Investigations, May 2007)

AUTHORIZATION – Permission given after *adequate information* concerning the donation, *recovery* and use of *tissues* is conveyed.

AUTHORIZING PERSON – Upon the death of the *donor*, the person, other than the *donor*, authorized by law to make an anatomical gift.

AUTOGRAFT (A) – *Tissue* intended for implantation, *transplantation* or infusion into the *living donor* from whom it was *recovered*.

AUTOLOGOUS – Used as an adjective to modify donation, *tissue, donor* or *recipient* when donation is intended only from him/herself and *transplantation* is intended only to him/herself.

BATCH – A specific quantity of *tissue* produced according to a single *processing* protocol during the same *processing* cycle.

BIOBURDEN – The number of contaminating organisms found on a given amount of material.

BIRTH TISSUE (BT) – gestational *tissue* donated at the time of delivery of a living newborn. This includes placenta, Wharton’s jelly, amniotic fluid, chorionic membrane, amniotic membrane, placental/chorionic disc, umbilical veins, and umbilical cord tissue.

BLOOD COMPONENT – Any part of a single-donor unit of blood separated by physical or mechanical means.

CARDIAC TISSUE (C) – *Tissue* type that includes, but is not limited to, *valved conduits, non-valved conduits, aortoiliac grafts*, and *patch grafts*.

CELLULAR TISSUE (CT) – viable cells that are *autologous* or *allogeneic*, committed or uncommitted, and non-expanded.

CERTIFIED COPY – Relating to a death certificate, an original, authenticated form produced by a governing authority.

CLAIM – Any written or oral communication alleging the *quality, durability, reliability, infectious disease risk, or performance of tissue*.

CLIENT DEPOSITOR (R) – A person who consents to *collection* and/or *storage* of *reproductive tissues* for *artificial insemination* or *assisted reproductive technology procedures* for themself(ves) or a sexually intimate partner; not considered a *reproductive tissue donor*.

COLD ISCHEMIC TIME (C) – The time interval from subjecting cardiac *tissue* to cold rinse (or transport) solution at *recovery* to the beginning of *disinfection*.

COLD ISCHEMIC TIME (V) – The time interval from subjecting *vascular tissue* to transport solution and wet ice temperatures at *recovery* to the beginning of *disinfection*.

COLLECTION (R) – The acquisition of *reproductive tissue* from a *donor* or *client depositor* by surgical or non-surgical *procedures*.

COLLOID – A protein or polysaccharide solution that can be used to increase or maintain osmotic (oncotic) pressure in the intravascular compartment such as albumin, dextran, hetastarch, or certain blood components, such as plasma and platelets.

COMPLAINT – Any written or oral communication concerning dissatisfaction with the identity, *quality, packaging, durability, reliability, safety, effectiveness, or performance of tissue*.

COMPETENCY – The ability of an employee to acceptably perform tasks for which he/she has been trained.

COMPETENCY ASSESSMENT – The evaluation of the ability of an employee to acceptably perform tasks for which he/she has been trained.

CONSIGNEE – Any *tissue bank, tissue distribution intermediary, tissue dispensing service, or end-user* (whether individual, agency, institution, or organization) that receives *finished tissue*.

CONTAINER – An enclosure for one finished unit of *transplantable tissue*.

CONTRACT SERVICES – Those functions pertaining to the *recovery, screening, testing, processing, storage, and/or distribution* of human *tissue* that another establishment agrees to perform.

CONTROLLED AREAS – Restricted work areas of low microbial and particulate content in which non-sterile materials are prepared.

CORRECTION – Related to conformity, remedial action to eliminate a detected *nonconformity*.

CORRECTIVE ACTION – Action to eliminate the cause and prevent recurrence of a *nonconformity* or other undesirable situation; *may* be performed in conjunction with *preventive action(s)*.

CRITICAL – Classification of a supply, reagent, material, instrument or equipment that can affect the *quality and/or safety of tissue*.

CRITICAL AREAS – Restricted work areas where cells, tissue, containers and/or closures are exposed to the environment.

CROSS-CONTAMINATION – The transfer of infectious agents from one *tissue* to another from either the same *donor* or a different *donor*.

CRYOPRESERVED – Frozen with the addition of, or in a solution containing, a *cryoprotectant* agent such as glycerol or dimethylsulfoxide.

CRYOPROTECTANT – An additive that serves to minimize osmotic imbalances that occur with the progression of freezing fronts through a substance, and is intended to limit the amount of cell damage caused by cell shrinkage and intracellular ice formation.

CRYSTALLOID – A balanced salt and/or glucose solution used for electrolyte replacement or to increase intravascular volume, such as saline solution, Ringer’s lactate solution, or 5 percent dextrose in water, or total parenteral nutrition (TPN).

DECONTAMINATION - Cleaning the environment, facilities, and/or surfaces (sanitation), or instruments, supplies, and equipment (sanitization), with intent to remove or reduce pathogenic microbes.

DEHYDRATION – The removal of water from *tissue*. For example, dehydration methods *may* include chemical (alcohol), critical/supercritical drying, simple air drying, or drying in a dehydrator.

DESICCATION – The removal of water from *tissue*. For example, desiccation methods *may* include chemical (alcohol), critical/supercritical drying, simple air drying, or drying in a desiccator.

DEVIATION – An event that is a departure from a *procedure* or normal practice.

DIRECTED DONOR (R) – A *reproductive tissue donor* who is known to the *recipient* (R) but is not the *recipient’s* (R) sexually intimate partner.

DISINFECTANT – An agent (e.g., heat or a chemical) capable of reducing the number of viable *microorganisms*. A disinfectant might not kill spores. Use of antimicrobials in *tissue processing* is included here.

DISINFECTION – A process that reduces the number of viable *microorganisms* on *tissue*, but *may* not destroy all microbial forms, such as spores and viruses. Use of antimicrobials in tissue processing is included here.

DISINFECTION TIME (C, V) – The time interval between subjecting *tissue* to *disinfection* solution and transferring *tissue* to rinsing solutions in preparation for *preservation*.

DISPENSING SERVICE – A facility responsible for the receipt, maintenance and delivery to the ultimate user (e.g., *transplanting* surgeon, surgical center or research facility) of *tissue* for *transplantation* or research.

DISPOSITION – The final destination of *tissue*, e.g., use for *transplantation*, therapy research, education, or discard; also, the final destination of *critical* supplies, reagents, materials or equipment that can affect the *quality* and/or *safety* of *tissue*, e.g., release for use or discard.

DISTRIBUTION – A process that includes receipt of a request for *tissue*, selection of appropriate *finished tissue*, preparation for transport, any required inspections, and subsequent shipment and delivery of *tissue* to another *tissue bank*, *tissue distribution intermediary*, *tissue dispensing service*, or *end-user*.

DOCUMENT OF AUTHORIZATION – Legal *record* of the gift of *tissue*, permitting and defining the scope of the postmortem *recovery* and use of *tissues* for *transplantation*, therapy, research and/or education *signed* or otherwise *recorded* by the *authorizing person*, pursuant to law.

DOCUMENT OF GIFT – The *donor’s* legal *record* of the gift of *tissue* permitting and defining the scope of the postmortem *recovery* and use of *tissues* for *transplantation*, therapy, research and/or education. It *must* be *signed* or otherwise *recorded* by the *donor* or person authorized under law to make a gift during the *donor’s* lifetime.

DOCUMENT OF GIFT/AUTHORIZATION – Term used when the standard refers to both a *document of gift* and a *document of authorization* as defined above.

DONATED HUMAN TISSUE – For the purposes of *labeling*, this is *tissue* provided for *storage* or *transplantation*, either *allogeneic* or *autologous*.

DONATION COORDINATOR – A *responsible person* who seeks *authorization* from an *authorizing person*, or who makes *notification* concerning donation, *recovery*, and use of the gift, or in the case of a *living donor* a *responsible person* who seeks *informed consent* from a *living donor*, a birth mother, or a *client depositor*. For *authorization* purposes, this person *may* also be referred to as a “designated requestor.”

DONOR – A living or deceased individual whose body is the source of the *tissue*.

DONOR ELIGIBILITY ASSESSMENT – The evaluation of all available information about a potential *donor* to determine whether the *donor* meets qualifications specified in the *SOPM* and *Standards*. See *relevant medical records*.

DONOR REFERRAL SOURCES – Entities such as hospitals, medical examiners, coroners and individual allied health care professionals who identify potential *tissue donors* and refer them, or their next of kin, to *tissue banks*.

DONOR REGISTRY – A database established in accordance with law, consisting of legally valid *documents of gift*.

DONOR RISK ASSESSMENT INTERVIEW (DRAI) – A documented dialogue in person or by telephone with an individual or individuals who would be knowledgeable of the *donor’s* relevant medical history and social behavior. For example this *may* be: the *donor*, if living; the next of kin; the nearest available relative; a member of the donor’s household; other individual with an affinity relationship (e.g., caretaker, friend, significant life partner); and/or the primary treating physician. Alternatively, a *living donor may* complete a written questionnaire. The relevant social history is elicited by questions regarding certain activities or behaviors that are considered to place such an individual at increased risk for a relevant communicable disease agent or disease (RCDAD).

DOSIMETRIC RELEASE – *Tissue* release based on dosimetry instead of sterility testing.

DURA MATER (DM) – A type of soft *tissue* that includes the pachymeninx (thick, membranous) tissue covering the brain.

DYNAMIC – Operational condition during *aseptic processing* where the controlled environment is functioning in the specified manner, with the specified number of personnel present and working in the manner agreed upon [ISO 14644-1].

ELECTRONIC SYSTEMS – Computerized systems that create source documents (electronic *records*).

EMBRYO (R) – Pre-implantation, *reproductive tissue* resulting from the combination of oocyte and sperm.

EMBRYO BANK – A facility that performs cryopreservation or *storage* of embryos intended for use in creating pregnancy.

EMBRYO CLIENT DEPOSITOR (R) – A woman and/or man who provides *gametes* or contracts with a *gamete donor(s)* responsible for creation of an *embryo(s)* intended for *transfer* (R).

EMBRYO DONOR (R) – *Embryo client depositor(s)* who choose(s) to donate his/her (their) *embryos*. Ownership of the *embryos* is transferred to a new *client depositor(s)* who was (were) not *gamete* providers.

END-USER – A health care practitioner who performs *transplantation procedures*.

ENVIRONMENTAL CONTROL – Activities performed to control the environment for the purpose of minimizing the potential for contamination or *cross-contamination of tissue*.

ENVIRONMENTAL MONITORING – Activities performed to systematically observe and *record* data to characterize the environment to identify conditions under which the potential *may* exist for contamination or *cross-contamination of tissue*.

EQUIPMENT QUALIFICATION STUDIES – Protocols designed to adequately evaluate, prior to use, whether pieces of equipment will perform to expectations, and normally function within the required *tolerance limits*.

ERROR – A *deviation* from the *SOPM, Standards*, or applicable laws or regulations.

ESTABLISH – Define, document and implement.

FIELD CORRECTION – For *distributed tissue*, the repair, modification, adjustment, *relabeling*, destruction, or inspection (including patient monitoring) without its physical removal to some other location. Reference 21 CFR Part 7, 7.3(h).

FIELD NOTIFICATION – The provision of additional information pertaining to the *safety, quality, identification, function and/or use of distributed tissue*.

FINISHED TISSUE – *Tissue* that has been fully *processed*, enclosed in its final *container, labeled*, and released to *distribution* inventory.

GAMETE (R) – Mature human germ cell, whether an oocyte or sperm.

INFORMED CONSENT – Permission given by a *living donor (LD)* or *client depositor* who is presented with a description of the scope, use and any risks or benefits to her or him of the proposed donation, and who has been given the opportunity to ask questions and receive accurate answers. An LD who gives her or his *informed consent* to donation *shall sign* a record of the *informed consent*.

IN-PROCESS CONTROLS – Any tests, samples, evaluations, monitoring, or measurements performed during *processing* or *preservation* that are designed to ensure conformance to specifications in the *SOPM*.

IN-PROCESS MATERIAL – Any material that is used in the *processing* of *tissue*, including, but not limited to, incoming *tissue*, water, alcohol, acid, *containers*, and closures.

LABEL – Any written, printed, or graphic material used to identify *tissue*, cultures, blood specimens or other *donor* specimens.

LABELING MATERIAL – Any printed or written material, including *labels*, advertising, and/or accompanying information (e.g., *package insert*, brochures, and pamphlets), related to the *tissue*.

LIVING DONOR (LD) – A person who consents to the *recovery* or *collection* of his or her *tissue*, where *recovery* or *collection* is to take place while she or he is alive. For all *living donors*, (LD) standards apply, then *tissue*-specific standards apply. A *living donor* is a type of *donor* and, unless otherwise specified, standards that apply to *donors* in general apply to *living donors*.

LOT – *Tissue* produced from one *donor* at one time using one set of instruments and supplies. Also refers to a quantity of reagents, supplies, or *containers* that is *processed* or manufactured at one time and identified by a unique identification number.

LYOPHILIZED – *Tissue* dehydrated for *storage* by conversion of the water content of frozen *tissue* to a gaseous state under vacuum that extracts moisture.

MANAGEMENT WITH EXECUTIVE RESPONSIBILITY – Those senior employees of a *tissue bank* who have the authority to establish or make changes to the *tissue bank's quality policy* and *quality system*.

MARKET WITHDRAWAL – A *field correction* or *removal* of distributed *tissue* that involves a minor violation that would not be subject to legal action by the FDA or that involves no violation (e.g., normal stock rotation practices). Reference 21 CFR Part 7, 7.3(j).

MAY – Used to indicate an acceptable method that is recognized but not essential.

MICROORGANISM – A microscopic organism including bacteria and fungi; viruses, while sometimes included in this classification, are not included here.

MUSCULOSKELETAL TISSUE (MS) – *Tissue* type that includes, but is not limited to, bone and cartilage, and soft *tissue* such as tendon, ligament, nerve, fascia, pericardium, peritoneal membrane, adipose, and *dura mater*.

MUST – Used to indicate a mandatory requirement. The same as *SHALL*.

NONCONFORMITY - A finding that identifies non-fulfillment of an accreditation requirement, a standard, policy, process, *procedure*, or specification.

NON-TERMINAL IRRADIATION – Ionizing radiation used to reduce microbes prior to *processing*.

NON-VALVED CONDUIT (C) – A length of cardiac outflow tract (aortic or pulmonic) from which the valve structure has been removed or intentionally rendered completely non-functional.

NOTIFICATION (OF GIFT) – Provision and documentation of notice concerning an anatomical gift that was made by the *donor* during the *donor's* lifetime.

OOCYTE DONOR (R) – A person who donates oocytes for use in *assisted reproductive technology procedures*. An *oocyte donor* can be further categorized as a *directed donor* or an *anonymous donor* but is not a *client depositor*.

OSTEOARTICULAR GRAFT – A weight bearing *allograft* with intact articular surfaces, consisting of a joint with associated soft *tissue* and bone.

PACKAGE – A *labeled* box, carton, receptacle, or wrapper containing *tissue* and may contain one or more *containers* and accompanying *labeling materials*.

PACKAGE INSERT – The written material accompanying an *allograft* or *autograft* bearing further information about the *tissue*, directions for use, and any applicable warnings.

PATCH GRAFT (C) – A segment of cardiac *allograft* conduit to be used in cardiovascular repair, replacement, construction, or reconstruction.

PERFUSION SOLUTION (V) – A room temperature, sterile isotonic solution such as tissue culture media or PlasmaLyte® utilized to gently perfuse veins at *recovery*. This solution *may* also contain an antithrombotic agent (i.e., sodium heparin).

PERFUSION TIME (V) – The time interval from *asystole* to subjecting the *vascular tissue* to *perfusion solution*.

PHYSICAL ASSESSMENT – A recent ante-mortem or postmortem documented evaluation of a deceased *donor's* body that can identify evidence of: high-risk behavior and signs of HIV infection or hepatitis infection; other viral or bacterial infections; or, trauma to the potential *recovery* sites.

PHYSICAL EXAMINATION – A recent documented evaluation of a *living donor's* body to determine whether there is evidence of high risk behavior and that determines overall general health of the *donor*. After a *donor risk assessment interview* is completed and if any history is suspect, the physical examination *should* also encompass a directed examination (of a body part or region).

PLASMA DILUTION – A decrease in the concentration of the *donor's* plasma proteins and circulating antigens or antibodies resulting from the transfusion of blood or blood components and/or infusion of fluids, e.g., *colloid(s)* and/or *crystalloid(s)*.

POOLING – The physical contact or mixing of *tissue* from two or more *donors* in a single receptacle.

PRE-STERILIZATION/PRE-DISINFECTION CULTURE - A culture of *tissue* obtained prior to exposure to antibiotics, *disinfecting* chemicals, or *sterilizing* agents.

PRESERVATION – The use of chemical agents, alterations in environmental conditions or other means during *processing* to prevent or retard biological or physical deterioration of *tissue*.

PREVENTIVE ACTION – Action to eliminate the cause of a potential *nonconformity* or other undesirable situation; *may* be performed in conjunction with *corrective action(s)*.

PROCEDURE – A series of steps, which when followed, is designed to result in a specific outcome.

PROCESS CONTROLS – A system of checks and balances incorporated into *standard operating procedures* involving critical operations to prevent errors.

PROCESS VALIDATION – Establishing by objective evidence that a process consistently produces *a* results meeting predetermined specifications.

PROCESSING – Any activity performed on *tissue* other than *donor* screening, *donor* testing, *tissue recovery*, *collection*, or *acquisition* functions, *storage*, *distribution* or dispensing. It includes but is not limited to *disinfecting*, *sterilizing*, *packaging*, *labeling*, and testing *tissue*.

PROFICIENCY TESTING – The evaluation of an individual laboratory’s performance against pre-established criteria by means of inter-laboratory comparisons. (Adapted from ISO/IEC 17043:2010 Conformity assessment – General requirements for proficiency testing)

QUALIFICATION – The process of establishing confidence that equipment, materials, reagents, and ancillary systems are capable of consistently performing within established limits and tolerances. Process performance qualification is intended to establish confidence that the process is effective and reproducible.

QUALITY – The conformance of *tissue* or a process to pre-established specifications or standards.

QUALITY AGREEMENT – an agreement that establishes the *quality* specifications or standards that *must* be met for defined activities and delineates responsibilities of each entity involved. It *may* be a separate document or included as part of a written agreement/contract.

QUALITY ASSURANCE (QA) PROGRAM – The policies and environment required to meet standards of *quality* and safety, and to provide confidence that the processes and *tissue* consistently conform to *quality* requirements.

QUALITY CONTROL (QC) – Specific tests defined by the *QA program* to be performed to monitor *recovery, processing, preservation and storage, tissue quality*, and test accuracy. These *may* include but are not limited to, performance evaluations, inspection, testing, and controls used to determine the accuracy and reliability of the *tissue bank’s* equipment and operational *procedures*, as well as the monitoring of supplies, reagents, equipment, and facilities.

QUALITY POLICY – The overall intentions and direction of an organization with respect to *quality*, as established by *management with executive responsibility*.

QUALITY SYSTEM – The organizational structure, responsibilities, *procedures*, processes, and resources for implementing quality management.

QUARANTINE – The identification of *tissue* as not suitable for *transplantation*, including *tissue* that has not yet been characterized as being suitable for *transplantation*. Quarantine includes the *storage* of such *tissue* in an area clearly identified for such use, or other *procedures*, such as automated designation, to prevent the release of this *tissue* for *transplantation*. This also applies to reagents, supplies, materials and equipment pending approval for use or that has been determined to be nonconforming.

RECALL – A *field correction* or *removal* of *distributed tissue* initiated to reduce a risk to health posed by the *tissue* or to remedy a violation of regulatory requirements that *may* present a risk to health.

RECIPIENT – A person into whom *tissue* is *transplanted*.

RECIPIENT (R) – A woman undergoing an *assisted reproductive technology procedure*. A *recipient* (R) can be an intended parent, a gestational carrier, or a gestational surrogate.

RECORD - Information that is inscribed on a tangible medium or that is stored in an electronic or other medium and is retrievable in perceivable form.

RECOVERY – Obtaining *tissue* other than *reproductive tissue* from a *donor* that is intended for use in human *transplantation*, therapy, research or education.

RECOVERY SITE – The immediate area or room where a *tissue recovery* takes place (e.g., dedicated *tissue recovery site*, healthcare facility operating room, autopsy suite).

RELEVANT MEDICAL RECORDS – A collection of documents including a current *donor risk assessment interview*, a *physical assessment/physical examination*, laboratory test results (in addition to results of testing for required relevant communicable disease agents), relevant *donor records*, existing coroner and autopsy reports, a *certified copy* or *verified copy* of the death certificate (when applicable), as well as information obtained from any source or *records* which *may* pertain to *donor* eligibility regarding high risk behaviors, and clinical signs and symptoms for any relevant communicable disease agent or disease (RCDAD), and/or treatments related to medical conditions suggestive of such risk.

REMOVAL – The physical removal of *distributed tissue* from its point of use to some other location for repair, modification, adjustment, *relabeling*, destruction, or inspection. Reference 21 CFR Part 806, 806.2(i).

REPRODUCTIVE TISSUE (R) – Any *tissue* from the reproductive tract intended for use in *assisted reproductive technology procedures*. This includes, but is not limited to: oocytes, ovarian *tissue*, *embryos*, *semen*, spermatozoa, spermatids, testicular *tissue*, and epididymal *tissue*.

REPRODUCTIVE TISSUE BANK (R) – A *tissue bank* that *collects, processes, stores, and/or distributes* human *reproductive tissue* for use in *assisted reproductive technology procedures*.

RESOLUTION – Adjustment, clarification, and/or correction of practices and/or *procedures* that results in compliance with the *SOPM* and/or standards.

RESPONSIBLE PERSON – A person who is authorized to perform designated functions for which he or she is trained and qualified.

SAFETY – A *quality of tissue* indicating handling according to standards and substantial freedom from the potential for harmful effects to *recipients*.

SATELLITE FACILITY – A facility operated or owned by the *tissue bank* and located in a physically separate location from its primary address, and where any tissue banking activities occur or where any tissue banking services are provided.

SEMEN (R) – The fluid of man’s reproductive system consisting of spermatozoa and secretions of accessory glands.

SEMEN DONOR (R) – A man who donates *semen* for use in artificial insemination or *assisted reproductive technology procedures* where the *recipient* is not a sexually intimate partner. A *semen donor* can be further categorized as a *directed donor* or an *anonymous donor* but is not a *client depositor*.

SERIES OF STANDARDS – A group of standards related to a particular topic presented as a capitalized heading (e.g., B2.000) followed by indented subsections (e.g., B2.100, B2.120, B2.121). The heading and everything indented under it are considered part of the series.

SERVICES TO DONOR FAMILIES – A defined policy or support program describing *tissue* donation follow-up offered to the *authorizing person* (or party). This *may* include written communications regarding: potential uses of *tissue*; *recovery* outcome information; bereavement information and support; provision of a copy of the *document of gift/authorization*: and/or guidance

describing how to contact the *tissue bank* if any questions arise regarding the donation. Frequency of follow-up and program maintenance is at the discretion of the *tissue bank*, however, periodic evaluation of services is required.

SHALL – Used to indicate a mandatory standard, same as *MUST*.

SHOULD – Used to indicate a recommendation; advisory, indicating a commonly accepted activity for which there *may* be effective alternatives.

SIGNATURE – A *record* is signed when it has been authenticated or adopted by the signer by means in writing, or an electronic signature, symbol, sound, process or *recording* pursuant to applicable law.

SKIN (S) - A membranous soft *tissue* type that includes, but is not limited to epidermis and dermis.

SKIN PREP - The application of antiseptic solution to decontaminate the *skin*. This is a continuous process that is performed without delay between steps; it does not include shaving hair, although this can be done if preferred. The manufacturer’s written recommendations *must* be followed, including that the antiseptic solution *should* remain in place for the recommended contact time and be allowed to air dry completely before the surgical drapes are placed.

STANDARD OPERATING PROCEDURES MANUAL (SOPM) – A group of standard operating *procedures* (SOPs) detailing the specific policies of a *tissue bank* and the *procedures* used by the staff/personnel to carry out the functions of the *tissue bank*.

STANDARDS – AATB *Standards for Tissue Banking*

STATIC - At-rest condition during *aseptic processing* where the controlled environment is complete with equipment installed and operating in a manner agreed upon, but with no personnel present [ISO 14644-1].

STERILE – For *tissue*, the absence of detectable, viable, *microorganisms* (refer to ANSI/AAMI ST67:2011). For reagents, supplies, materials and equipment, free from viable *microorganisms*.

STERILITY ASSURANCE LEVEL (SAL) – The probability of a single viable *microorganism* occurring on a product after *sterilization* (refer to ANSI/AAMI ST67:2003).

STERILIZATION – A validated process used to render *tissue* free from viable *microorganisms* (refer to ANSI/AAMI ST67:2003) including spores.

STOCK RECOVERY – Retrieval of *tissue* that has not left the direct control of the *tissue bank* (manufacturer), i.e., the *tissue* is located on the premises owned, or under the control of, the *tissue bank* (manufacturer), and no portion of the affected *tissue* has been released for use. Reference 21 CFR Part 7, 7.3(k).

STORAGE – The maintenance of *tissue* for future use.

STRUCTURAL SUPPORT – Those *tissue* grafts that contribute biomechanical strength to a surgical construct.

SUMMARY OF RECORDS – A condensed version of the *donor* testing and eligibility determination *records*. This can be combined with the *package insert*.

SURGICAL BONE (SB) – Any bone from a *living donor* for *allogeneic* use such as a femoral head removed during surgery.

TERMINAL STERILIZATION – A validated process whereby *tissue* within its final *sterile* barrier system (e.g., *package, container*) is *sterilized* (refer to ANSI/AAMI ST67:2011).

THIRD PARTY RECORDS – *Records* produced by an entity not involved in *tissue recovery, acquisition, or donor screening*. Examples of third party *records* include: hospital medical *records*; emergency medical services *records*; coroner/medical examiner *records*; prenatal *records*, and police reports.

TISSUE – A functional group of cells. The term is used collectively in *Standards* to indicate both cells and *tissue*.

TISSUE BANK – An entity that provides or engages in one or more services involving *tissue* from living or deceased persons for *transplantation* purposes. These services include obtaining *authorization* and/or *informed consent*, assessing *donor* eligibility, *recovery, collection, acquisition, processing, storage, labeling, distribution* and dispensing of *tissue*.

TISSUE DISPENSING SERVICE – Any entity that receives, *stores*, and provides *tissue* directly to an *end-user* for *transplantation*. *Tissue dispensing services* may or may not be *tissue banks*, depending on what other functions they perform.

TISSUE DISTRIBUTION INTERMEDIARY – An intermediary agent who acquires and *stores tissue* for further *distribution* and performs no other *tissue banking* functions.

TISSUE IDENTIFICATION NUMBER – Any unique combination of letters, numbers, and/or symbols assigned to *tissue* and linked to a *donor*, from which the complete history of the *recovery, collection or acquisition, processing, packaging, quarantine, labeling, storage, distribution* and dispensing of *tissue* can be traced. Identical *tissue processed* under the criteria defined in “*lot*” may be assigned the same *tissue identification number*.

TOLERANCE LIMITS – The limits that define a range of acceptable values that are established for each testing *procedure* which, when exceeded, require the implementation of *corrective actions* designed to produce results within the acceptable range in future tests.

TOTAL ISCHEMIC TIME (C, V) – The time interval from *asystole* to subjecting *tissue* to *disinfection* solution. This is the sum of *warm ischemic time* and *cold ischemic time*.

TRACEABILITY – The ability to locate *tissue* during any step of its donation, *recovery, collection, or acquisition, processing, testing, storage, distribution or disposition*. It implies the capacity to identify the medical facility receiving the *tissue* and, at the medical facility, the ability to identify the *recipient*.

TRANSFER (R) – The placement of human *reproductive tissue* into a human *recipient* (R).

TRANSPLANTATION – The transfer of an *allograft* or *autograft* to a *recipient*.

TRANSPORT MEDIUM – Any microbiological medium capable of maintaining cellular viability during the transport of a culture from field to laboratory.

VALIDATION – Confirmation through the provision of documented objective evidence that predefined specifications have been fulfilled and can be consistently reproduced.

VALVED CONDUIT (C) – An *allograft* heart valve with an attached length of cardiac outflow tract (aortic or pulmonic).

VARIANCE – A departure from *Standards* that is pre-approved by the AATB Board of Governors prior to implementation.

VASCULAR TISSUE (V) – *Tissue* type that includes, but is not limited to *arterial grafts* and *vein grafts*.

VEIN GRAFT (V) – A segment of vein that is *recovered*, *processed* and *preserved*.

VERIFICATION – The confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

VERIFIED COPY - A copy of a death certificate without the raised seal but issued by an authorizing agency.

VETERINARY USE – Treatment of a condition or disease in a non-human animal.

WARM ISCHEMIC TIME (C) – The time interval from *asystole* to subjecting cardiac *tissue* to cold rinse (or transport) solution at *recovery*.

WARM ISCHEMIC TIME (V) – The time interval from *asystole* to subjecting *vascular tissue* to transport solution and *wet ice temperatures* at *recovery*.

WET ICE TEMPERATURES – Temperatures ranging from above freezing (0°C) to 10°C.

WITNESS – An individual who signifies in writing, or in electronically *recorded* format, that he or she has observed the execution or verbal authorization of the *document of gift/authorization* or *informed consent*. The *witness*' signification *must* be contemporaneous with execution and the *witness must* be identified by name, address and/or such other contact information as is relevant and feasible. A *witness should* not be an employee or agent of the *tissue bank* or requesting entity.

A3.000 ACRONYMS AND ABBREVIATIONS

The following acronyms and abbreviations are used in *Standards*:

AAMI – Association for the Advancement of Medical Instrumentation

AATB – American Association of Tissue Banks

ANSI – American National Standards Institute

AORN – Association of periOperative Registered Nurses

ASQ – American Society for Quality

ASTM – ASTM International

CAP – College of American Pathologists

CBER – Center for Biologics Evaluation and Research

CDC – Centers for Disease Control and Prevention

CFR – Code of Federal Regulations. Published by the Office of the Federal Register, National Archives and Records Administration, Washington, DC

e.g. – *exempli gratia*; for example, such as; the list is not finite

FDA – The United States Food and Drug Administration

i.e. – *id est*; that is; indicates a finite list

ISO – International Organization for Standardization

USP – United States Pharmacopeia

SECTION B
GENERAL ORGANIZATIONAL REQUIREMENTS OF A TISSUE BANK

B1.000 GENERAL INSTITUTIONAL REQUIREMENTS

B1.100 Purpose, Institutional Identity, and Affiliations

The purpose of the *tissue bank shall* be clearly formulated and documented. The *tissue bank shall* state whether it is a freestanding entity or part of an institution.

B1.200 Governing Body

The *tissue bank shall* have a Governing Body that *may* consist of a Board of Trustees, Board of Governors, Board of Directors or a designated responsible individual in whom policy- making authority resides, unless otherwise provided by the institution of which it is a part. A Board *shall* consist of individuals from various professions. This Board or designated individual *shall* determine the scope of activities to be pursued by the *tissue bank*.

The Governing Body *shall* designate one or more senior employees as *management with executive responsibility*. Issues of liability, ethical considerations, fiduciary responsibility, and compliance with applicable laws and regulations, these *Standards*, and the *tissue bank's SOPM shall* be the responsibility of the Governing Body and *management with executive responsibility*.

B1.300 Medical/Scientific Support

A *tissue bank should* establish and maintain a mechanism to access medical, technical, and scientific advice as needed. Decisions *shall* be documented.

B1.400 Satellite Facilities

Satellite facilities shall be operated in accordance with the *tissue bank's SOPM*.

B1.500 Written Agreements/Contracts

Each *tissue bank shall* have written agreements or contracts with all other individuals or organizations that perform or for whom they perform tissue banking activities or services such as, but not limited to:

- 1) *donor referral*;
- 2) *authorization*;
- 3) *informed consent*;
- 4) *donor eligibility assessment*;
- 5) *recovery, collection, and/or acquisition*;
- 6) *post-delivery functions*;

- 7) laboratory services (see exception at B1.600);
- 8) testing services;
- 9) *processing*;
- 10) *storage*;
- 11) *tissue* release;
- 12) *distribution*; and/or
- 13) *consignment*.

For additional controls regarding testing services and other services performed by others, see the *series of standards* at K1.300.

Written agreements or contracts *shall* indicate the nature of the relationships, division of tasks performed, division of issues of liability, specific responsibilities of each party and a summary of the protocols and procedures relating to the services provided. The *tissue bank shall* maintain a copy of each such agreement, which *shall* be made available for review if requested by AATB inspectors. Compliance with *Standards* by all parties *shall* be required and documented in a *quality agreement*. The following examples provide a few of these expectations:

- 1) A *tissue bank* that *recovers* tissue that is *processed* and/or *distributed* by another *tissue bank* *shall* be responsible for being in compliance with these *Standards* for all operations it performs. This includes, but is not limited to, the requirement to have a Medical Director (see B2.220), to follow applicable standards in Section D and Appendix II, and to share records (see D4.300). A *tissue bank* that *recovers tissue* is not required to *audit* its contracted *tissue bank* processor(s).
 - (BT) There *shall* be a written agreement/contract with the entity that performs post-delivery functions and/or *acquisition* on behalf of the *tissue bank*; or, if there is no written agreement or contract, there *must* be an attestation *record* from a *responsible person* that post-delivery protocols and *procedures* are followed.
- 2) A *tissue bank* that *processes tissue recovered* and/or *distributed* by another *tissue bank* *shall* be responsible for being in compliance with these *Standards* for all operations it performs. The *tissue processing* organization *must* bear the burden of proof, and document in writing, that operations performed by other organizations prior to the receipt of *tissue* for *processing* were performed in a manner consistent with these *Standards* as well as the *processing tissue bank's* requirements.
- 3) A *tissue bank* that *distributes tissue recovered* and/or *processed* by other *tissue banks* *shall* be responsible for being in compliance with AATB *Standards* for all operations it performs. The distributor *must* also bear the burden of proof, and document in writing, that operations performed by other organizations prior to its receipt of *tissue* for *distribution* were performed in a manner consistent with AATB *Standards*. Any *records* necessary to demonstrate compliance *shall* be readily accessible to the *distributing tissue bank*.
- 4) A *tissue bank* that determines *donor* eligibility *shall* develop and maintain policies and *procedures* that clearly describe *donor records* they deem relevant to their operations. Agreements *must* address how this information is to be communicated in a timely fashion

and clearly define expectations and responsibilities of the appropriate entities.

- 5) A *tissue bank* that provides another *tissue bank* with *critical* supplies, reagents, materials, and/or equipment *shall* develop and maintain policies and *procedures* that clearly describe responsibilities for notification of changes and recalls, and both entities *should* report problems (e.g., defects). The *tissue bank* providing supplies containing *labels* is responsible for archiving and notification responsibilities described at G2.330.
- 6) A *tissue bank* that *distributes tissue* for transplantation *shall* restrict *distribution* to entities described in *Standards* (see H1.100). If *tissue* is provided to a *tissue distribution intermediary*, the *tissue distribution intermediary shall* meet the requirements of Section M of these *Standards*.

If an AATB-accredited *tissue bank* obtains from and *processes tissue* for a *tissue bank* not accredited by the AATB that is located outside of the United States (U.S.), the requirement for compliance with *Standards* does not apply to the foreign *tissue bank* if the *processed tissues* will not be *distributed* within, or to, the U.S. All *tissues* imported from entities that do not follow AATB *Standards shall* be appropriately *quarantined* throughout import, *storage*, *processing*, and export. The AATB-accredited *tissue bank must verify* that the foreign *tissue bank* not accredited by the AATB complies with regulations of the governmental authority having jurisdiction in their country for the functions they perform (e.g., *informed consent/authorization, donor eligibility assessment, recovery, acquisition, donor testing*). Additionally the *tissue bank* not accredited by the AATB *should be verified* to be in compliance with existing standards or guidelines, as appropriate. Examples of established standards include the current editions of: Health Canada’s “Safety of Human Cells, Tissues and Organs for Transplantation Regulations;” the Directive (and Commission Directives) 2004/23/EC of the European Parliament and the Council; or, expectations as described in the World Health Organization’s “Aide Mémoires for Human Cells and Tissues for Transplantation.”

B1.510 On-Site Inspections

(Refers to any AATB accreditation inspection.)

A *tissue bank* will be inspected and accredited for the specific activity(ies) or service(s) that it performs. However, if the *tissue bank* participates jointly with other entities that provide *tissue banking* activities or services on their behalf, the accredited *tissue bank* is responsible for providing evidence of compliance to these *Standards* for all *tissue banking* activities or services performed by other entities on its behalf.

B1.520 Inspections/Audits of Other Facilities

(Refers to inspections/*audits* that an accredited *tissue bank must* perform for activities/services rendered by another entity.)

Before an entity performs any activity/service under contract, agreement or other arrangement, the accredited *tissue bank must* ensure that the entity will comply with applicable *Standards*, laws and regulations. Thereafter, the accredited *tissue bank* is responsible for *verifying*, at least biennially, that the activity(ies) or service(s) has/have been performed in conformance with applicable *Standards*, laws and regulations. This requirement does not apply to any other AATB-accredited entity. The *verification* of activities or services performed by others *shall* be documented (e.g., a paper *audit*, on-site *audit*, on-site inspections, etc.).

Regardless of whether the facility performing activities or services for others is accredited, it is the responsibility of the *tissue bank* receiving those activities/ services to periodically *verify* that *procedures* related to the activities/services are in compliance with these *Standards*, the written agreement/contract, and applicable laws and regulations. The inspection/*audit* plan, policies, and *procedures shall* be specified in the *SOPM*.

Documentation that an *audit/inspection* specific for activities or services performed *shall* be maintained by the *tissue bank*. Such documentation *shall* itemize all operational systems that were *verified* to determine compliance with these *Standards*, the agreement/contract and applicable laws and regulations. This itemization of the systems reviewed *shall* be provided to AATB on-site inspectors upon request. For an *audit* tool and requirements to be used for a partner performing *recovery* services, refer to Appendix V.

If, during the course of this contract, agreement, or other arrangement, information suggests that the entity may no longer be in compliance with such requirements, the accredited *tissue bank must* take steps to ensure compliance. If it is determined that the entity will not comply, the contract, agreement, or other arrangement *must* be terminated.

B1.600 Contracted and Non-contracted Laboratory Services for Donor Infectious Disease Testing

Tissue banks that contract laboratory services for donor infectious disease testing *shall* retain in their *records* the name and address of the contracted facility and documentation of the inclusive dates of the contract period. Proof of current laboratory licensure and accreditation *must* be maintained. Additionally, all requirements in the *series of standards* at K1.300 *shall* apply. *Tissue banks* that obtain *donor* infectious disease test results from non-contracted laboratory services (e.g., other *tissue banks*, organ procurement organizations) *shall* maintain the name, address, licensing and accreditation information for each laboratory from which test results are obtained for the purpose of *donor* eligibility or *tissue* suitability assessments. Appropriate *management with executive responsibility shall* ensure a *responsible person* understands the principles of bacteriological and/or infectious disease test *procedures* employed by a laboratory as well as the interpretation of results. *Records* of infectious disease laboratory results used to assess *donor* eligibility *shall* become part of the *donor record*.

NOTE: For international members that do not export *tissues* to the U.S., applicable requirements of the government/competent authority having jurisdiction apply regarding establishment registration, laboratory certification, test kit licensing/approval, and test run record retention.

The *tissue bank must* ensure (and maintain documentation of activities obtained by either paper *audit* or on-site *audit*) that a laboratory performing *donor* infectious disease testing for the *tissue bank* is:

- 1) registered with the FDA as a tissue establishment and lists ‘testing’ as a function;
- 2) using the appropriate FDA-licensed, approved, or cleared *donor* screening tests;
- 3) following manufacturers’ instructions for these tests;

- 4) certified in accordance with the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493, or has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services;
- 5) retaining *donor* infectious disease test run *records* for ten years; and
- 6) aware of the requirement of the *tissue bank* to comply with D4.240.

B2.000 FUNCTIONAL COMPONENTS OF A TISSUE BANK

B2.100 Management Responsibility

B2.110 Quality Policy

Management with executive responsibility shall ensure the establishment of the tissue bank's policy and objectives for, and commitment to, quality, and shall ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

B2.120 Organization

Each tissue bank shall establish and maintain an adequate organizational structure to ensure that all tissue banking activities or services comply with the requirements of these Standards.

B2.121 Responsibilities and Authority

Each tissue bank shall establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality, and provide the independence and authority necessary to perform these tasks in accordance with these Standards. The tissue bank shall ensure that responsibilities and authorities are defined, documented and communicated within the tissue bank.

B2.122 Resources

The tissue bank shall have sufficient resources, including the assignment of trained personnel, for management, performance of work, and assessment activities to meet the requirements of these Standards.

B2.123 Management Representative

Management with executive responsibility shall appoint a member of management who, irrespective of other responsibilities, shall have established authority over and responsibility for ensuring that quality system requirements are effectively established and effectively maintained. The management representative shall periodically report on the performance of the quality system to management with executive responsibility for their review.

B2.130 Management Review

Management with executive responsibility shall review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of these Standards and the tissue bank's established quality policy and objectives. The dates and results of quality system reviews shall be documented.

B2.140 Technical Policies and Procedures

Technical policies and *procedures* utilized in the operation of the *tissue bank must* be established and maintained. The *tissue bank may* adopt current standard *procedures*, such as those in a technical manual prepared by another organization, provided that the *tissue bank has verified* that the *procedures* are consistent with, and at least as stringent as, the requirements of these *Standards* and appropriate for operations.

B2.150 Quality Assurance Program

A *quality assurance (QA) program shall* be established and maintained to ensure that the entire operation is in conformity with the *tissue bank's SOPM*, these *Standards*, and applicable laws and regulations. A documented annual internal review or *audit* to ensure compliance *must* be performed.

B2.200 Medical Director

B2.210 Qualifications

The *tissue bank shall* have a Medical Director who maintains a valid medical license from any state or U.S. territory (or for international members, the physician *must* maintain an equivalent medical license). He/she *should* have training and experience in evaluating and determining *donor* eligibility particularly with regard to infectious diseases, or use a Medical Advisory Committee or consultants to assist in those areas.

B2.220 Responsibilities

The Medical Director *shall* establish, review and approve all policies and *procedures* of a medical nature. See J1.300, J1.400, J1.600.

B2.221 Donor Eligibility Criteria

The Medical Director *shall* be responsible for establishing *donor* eligibility criteria. See the *series of standards* at D4.000 and Appendix II.

The *tissue bank's donor* eligibility criteria *may* be adopted from criteria used by another organization, provided that the Medical Director has *verified* the criteria are consistent with, and at least as stringent as, the requirements of these *Standards* and applicable laws and regulations.

When a *tissue bank* is responsible for determining *donor* eligibility, the Medical Director, or licensed physician designee, *shall* make a determination regarding the eligibility of each *donor* based on a comparison with predetermined *donor* criteria as established in the *SOPM*. This determination *must* occur prior to the

release of *tissue* for *transplantation*. See Section F.

B2.222 Adverse Outcomes

The Medical Director *shall* establish policies and *procedures* regarding *adverse outcomes*. See K4.300.

B2.223 Positive Infectious Disease Test Results

The Medical Director *shall* be responsible for notifying appropriate parties of the availability of positive infectious disease test results, and for reporting positive test results when required, in accordance with D4.232.

B2.300 Technical Staff

B2.310 Qualifications

Staff *must* possess the educational background, experience, and training sufficient to assure assigned tasks will be performed in accordance with the *tissue bank's* established *procedures*. Staff training *shall* be documented in individual employee training files.

B2.320 Responsibilities

Staff *shall* be responsible for implementation of policies and *procedures* as established by the *tissue bank*. Duties of each staff member *shall* be described in written job descriptions. Staff *must* demonstrate *competency* in the operations to which they are assigned.

B2.400 Quality Assurance Program

B2.410 Staff Qualifications

A designated individual, generally familiar with, but not having performed, the specific work being reviewed, *shall* be responsible for each *quality* review.

B2.420 Staff Responsibilities

Quality assurance program personnel *shall* have responsibility for assuring compliance with the *SOPM* regulatory requirements. The individual responsible for the *quality* review *shall* have the responsibility and authority to approve or reject *tissue*, as well as discontinue *processing* and/or release of *tissue* when *deviations* from *SOPM* warrants. *Quality assurance* personnel *shall* be responsible for managing *audits*.

SECTION C RECORDS MANAGEMENT

C1.000 RECORDS MANAGEMENT

C1.100 General

Each *tissue bank shall* develop a *donor* record management system that will allow the detailed documentation of the *tissue banking* process(es) for which it is responsible. Documentation *must* be made concurrent with each significant step and *must* include, but not be limited to:

- 1) information from the *donor referral source*;
- 2) *donor eligibility assessment* information;
- 3) *record of informed consent*, or *document of gift/authorization*;
- 4) *donor physical assessment* or *physical examination*, and donor identification;
- 5) *tissue recovery* or *collection*, transport, and *processing*;
- 6) *quarantine* and infectious disease testing;
- 7) in-process testing;
- 8) *record* review;
- 9) *tissue labeling*, *storage*, release, and *distribution*;
- 10) *quality control*; and
- 11) *services to donor families*.

Such *records shall* indicate the responsible party(ies) and *must* delineate the dates, times, and locations of subsequent *procedures* as well as the individuals performing them in order to facilitate *traceability*. The *records shall* be considered confidential and *shall* be kept in a location with controlled access; precautions for their safety and security *should* be evident.

- (A) *Records shall* include, at a minimum, *donor* identification, and the date and time of *recovery*.
- (R) Names of donors *shall* be encoded; only designated personnel *shall* have the authority to link the *donor's* name to the identification code. No *records shall* exist which link the *anonymous donor* by name to the *recipient*.

C1.110 Required Processing Documentation

Results of laboratory tests used to determine final release of *tissue* for *transplantation* (e.g., *sterility* testing and testing for residual water, ethylene oxide, residual calcium) *shall* be maintained by the *tissue bank* that determines the suitability of the *allograft* for *distribution* (“distributor”). All other *processing records shall* be available to the *tissue bank* within a reasonable amount of time.

C1.120 Electronic Records

If *records* are maintained electronically, there *shall* be an *electronic system* in place to ensure that data integrity of the electronic *records* is maintained, and that information is retrievable, and able to be printed as a hard copy. Compliance with K7.000 is expected.

C1.200 Availability for Inspection

Tissue banking *records shall* be readily accessible for inspection by authorized personnel from accreditation programs and regulatory agencies. Access to *donor* identity and medical, social, travel, and sexual behavior histories *shall* be restricted to *tissue bank* staff with a need for access and to inspectors from accreditation programs and regulatory agencies. Should *records* be maintained electronically, there *must* be a system in place to retrieve information, and print a hard copy for review during inspection or for a period as required by applicable laws and regulations.

C1.300 Retention

Records of the *informed consent*, *documents of gift/authorization*, and *records* pertaining to donor eligibility, *recovery*, *collection*, *acquisition*, *processing*, *storage*, date of *distribution*, *QA*, and identity of person/entity to whom *distributed*, *shall* be retained 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 latest) or longer if required by applicable laws and regulations. *Records shall* be maintained in a manner to preserve their completeness and accuracy over time. *Donor* eligibility *records* of *dura mater donors shall* be retained indefinitely. *Tissue banks* that have their *tissues processed* by another agency *must* assure that *processing* and *QC records* are retained for at least ten years.

(R) The *reproductive tissue bank* should maintain current *donor* and *client depositor* addresses until *tissues* are used or destroyed.

C1.400 Traceability

A *tissue bank's records* management system *shall* identify *tissue* by use of a unique identifier. Each subsequent entity involved in the process of *recovery*, *collection* or *acquisition* through *tissue* dispensing *shall* be required to correlate its *donor* identifier with the *donor* identifier of the entity from which it acquired the *tissue*. *Records shall* also indicate the dates and the identities of the staff involved in each significant step of the operation from the time of *recovery*, *collection* or *acquisition* through final *disposition* of the *tissue*.

Laboratory and *QC* specimens related to a *donor shall* also be *traceable* to the *donor*. *Records shall* indicate which specimens were used for testing and *shall* also permit *tracing* from the *donor* to the specimen and from the specimen to the *donor*.

Whenever an accredited *tissue bank* consigns *tissue* to a non-accredited entity, the accredited *tissue bank shall*:

- 1) require the non-accredited entity to comply with the requirements of this section; and
- 2) impose the requirements of this section on all subsequent *consignees*, up to and including the *tissue dispensing service*.

C1.500 Revisions

Revisions to paper *records shall* be made with a single line drawn through the altered text. The revision *shall* be initialed and dated by the individual making the revision. Additions to a completed *record shall* be initialed and dated by the individual making the additions.

Records revised electronically *must* have an *audit trail* that includes the altered information, date of the revision, and the individual that made the revision. See K7.000.

C2.000 CONSTRUCTION OF RECORDS

Relevant medical records must be reviewed by the *responsible person(s)* at each *tissue bank* involved with *recovery, collection* or *acquisition*, or the determination of *donor* eligibility. The content of *records* that originate or are sourced from outside of a *tissue bank* (i.e., *third party records*) is not under control of the *tissue bank*. The information in these *records* is considered the best available information. *Records* that are produced by *tissue bank* staff *must* be complete, indelible, legible and accurate. *Records must* be in English or, if in another language, *must* be retained and translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document.

Tissue banks shall not utilize documentation related to *informed consent/authorization* or *donor risk assessment interviews* that are obtained by unauthorized parties. Authorized parties *must* be identified in agreements and personnel performing these functions *shall* be qualified, trained, and *competent*.

(A) *Autologous tissue records shall* be maintained either in a separate log, or, if incorporated into general *records*, in such a manner that the *autologous tissue may* not be released for non-*autologous* use.

(C) *Records* additionally *shall* include the following information:

- 1) ABO/Rh, if available;
- 2) date/time of *asystole*;
- 3) date/time of *recovery* of the heart (time when subjected to cold rinse solution);
- 4) date/time of subjection of *cardiac tissue* to *disinfection* solution;
- 5) start and stop times when *tissue* was subjected to *disinfection* solution; and
- 6) date/time:
 - a) when *preservation* began; and
 - b) when placed in final *container*.

(V) *Records* additionally *shall* include the following information:

- 1) ABO/Rh, if available;
- 2) date/time of *asystole*;

- 3) date/time *vascular tissues* subjected to *perfusion solution*;
- 4) date/time *vascular tissues* placed in transport solution and subjected to *wet ice temperatures*;
- 5) date/time of subsection of *vascular tissue* to *disinfection* solution;
- 6) start and stop times when *tissue* was subjected to *disinfection* solution; and
- 7) date/time (a) when *preservation* began and (b) when placed in final *container*.

C3.000 DONOR RECORDS TO BE MAINTAINED

Tissue Banks shall maintain records of their activities in accordance with these Standards.

- (R) *Donor records shall include documentation of informed consent, relevant medical records, results of all laboratory screening tests, and outcome of prior assisted reproductive technology procedures (if known) including number of successful pregnancies and any reports that would affect the donor's eligibility. Records shall also include personal attributes of the donor such as: height, weight, eye color, hair color, complexion, racial group, and/or body type.*

SECTION D
AUTHORIZATION, INFORMED CONSENT, DONOR SCREENING, AND TISSUE
RECOVERY, COLLECTION, AND ACQUISITION

D1.000 GENERAL POLICIES

In addition to the requirements at the *series of standards* at B1.500, all referral arrangements with organ procurement organizations, *donor referral sources* and other *tissue banks* shall be documented.

- (LD) Except for a *reproductive tissue bank*, written *procedures* for interacting with operating room staff, the patient's physician, or other sources/facilities shall be established.

D1.100 Monetary Compensation or Other Valuable Consideration

Monetary compensation or other valuable consideration, including goods or services, shall not be offered to a *donor*, *authorizing person*, the *donor's* estate, or any other third party acting on behalf of the *donor*, except in the following instances:

- 1) the *tissue bank* may reimburse responsible third parties for costs directly associated with a donation; or
 - 2) the *tissue bank* may reimburse *living donors* for costs associated with an acceptable donation, including compensation for restoration of lost earnings when directly attributable to donation, if and as authorized by law.
- (R) The *reproductive tissue bank* may provide monetary compensation to *donors* of *reproductive tissue* if the compensation is compliant with professional standards of practice.

Donors or their families should not be responsible for any expenses related to the *recovery* of *allogeneic tissue*.

D1.200 Tissue for Research

Facilities providing *tissue* for research and other non-*transplantation* purposes shall develop detailed relevant specific policies and *procedures*. *Informed consent* or *authorization* for research and/or education shall be obtained. See the *series of standards* at D2.000 and D3.000.

D1.210 Written Requests

All requests for human *tissue* intended for research use shall be submitted in writing. The request shall indicate the type of *tissue* requested and how it will be used as well as the name, address and affiliation of the principal investigator accepting responsibility for receipt of the *tissue*.

D1.220 Review and Approval

Tissue requests for research purposes shall be reviewed and approved based on legal, ethical, and technical considerations defined in the *SOPM*.

D2.000 AUTHORIZATION

D2.100 Requirements

Authorization to acquire *tissues* and make them available for *transplantation*, therapy, research or education *shall* be obtained from a *donor* or *authorizing person* in accordance with applicable anatomical gift acts and other laws or regulations. This *authorization shall* be expressed in a *document of gift/authorization*, the original or a copy of which *shall* be maintained in the *donor's record* at the *tissue bank* responsible for *recovery*, as well as in the *donor's record* at the *tissue bank* whose Medical Director is responsible for the *donor* eligibility determination. In the case of an electronic or voice recorded *document of gift/authorization*, the original recording *should* be maintained in reproducible form.

NOTE: For international members, terminology used by the government/competent authority having jurisdiction applies regarding lawful authorization for donation of *tissues* for *transplantation*, therapy, research, or education.

D2.200 Conditions

Adequate information concerning the donation and *recovery* of *tissue shall* be presented in a language in which the *authorizing person* is conversant and in terms that are easily understandable by the *authorizing person*. The *donation coordinator* *should* be trained to appropriately answer the questions the *authorizing person* may have. Neither coercion nor inaccurate information *shall* be used in any manner to obtain *authorization*.

D2.300 Signatures and Documentation

D2.310 Document of Gift

In cases where a *donor* has executed a *document of gift* it *may* be acted upon (permits *recovery*) provided it meets applicable laws and regulations. Acceptable documentation *may* include a state driver's license, living will, advanced directive, state ID card, *donor* card, or photocopy thereof, and documentation that the *donor* registered in a *donor registry*.

D2.320 Document of Authorization

When a *document of authorization* is used it *must* contain the following *signatures* and related information:

- 1) the *authorizing person's signature* and:
 - a) name;
 - b) mailing address (NOTE: If requested by the *authorizing person*, only an email address *may* be documented as the address but, in such cases, the *authorizing person* *should* permit its use and *should* be informed that if the email address changes or if email communication is blocked, there *may* be no effective forwarding or receipt of information.);
 - c) phone number; and

- d) relationship to the *donor*;
- 2) the *donation coordinator's signature* and:
 - a) the date; and
 - b) identity of their organization;
- 3) the *signature* of each *witness* if *witnessing* is required by law or regulation;
- 4) documentation that the Core Elements were used; and
- 5) a statement granting *authorization* for *tissue recovery*.

D2.330 Methods of Obtaining Authorization

Legal *authorization* can be obtained using different methods. When *authorization* is obtained:

- 1) **in person**, the *authorizing person* must read and sign the *document of authorization*.
- 2) **by telephone**, the person obtaining the *authorization* shall read to the *authorizing person* the *document of authorization* or, alternatively, shall present each of the Core Elements described in D2.400.

This telephone conversation shall be recorded. There shall be documentation that the *authorization* was obtained by telephone.

A sampling plan must be adopted that verifies that recordings match the content in the written *document of authorization*. This *verification* must be performed by someone other than the *donation coordinator* or *witness*. In the rare event that the telephone conversation cannot be recorded (e.g., equipment failure), and no facsimile or electronic means is feasible for documenting *authorization*, the conversation should be witnessed by a third person. Sampling plans and methods must be established, must be adequate for their intended use, and must be based on valid statistical rationale (e.g., such as the FDA Guide to Inspection of Quality Systems).

- 3) **using a facsimile transmission**, a copy of the *document of authorization* is provided to the *authorizing person*. The *authorizing person* shall return the signed *document of authorization* by facsimile transmission. A *donation coordinator* shall be available to respond to questions posed by the *authorizing person*.

A sampling plan must be adopted that verifies signatures received by facsimile. This *verification* must be performed by someone other than the *donation coordinator* or *witness*. Sampling plans and methods must be established, must be adequate for their intended use, and must be based on valid statistical rationale (e.g., such as the FDA Guide to Inspection of Quality Systems).

- 4) **using an electronic transmission**, a copy of the *document of authorization* is provided to the *authorizing person*. The *authorizing person shall* electronically respond (e.g., by e-mail) that he/she has read the *document of authorization*, is authorized to grant *authorization*, and is granting such *authorization*. A *donation coordinator shall* be available to respond to questions posed by the *authorizing person*.

A *document of authorization* received by electronic transmission *should* be verified pursuant to the relevant law on electronic *signatures*, such as the Uniform Electronic Transactions Act of the relevant state. An electronically transmitted, read-only or otherwise protected *document of authorization may* be used.

D2.400 Core Elements for Authorization

The *document of authorization shall* contain *adequate information*. No *document of authorization* from an *authorizing person shall* be acted upon if it does not contain the following Core Elements. These Core Elements also apply to D2.500.

Core Elements:

- 1) the name of the *Donor*;
- 2) the name, mailing address, and telephone number of the *authorizing person*, and his/her relationship to the *donor* (NOTE: If requested by the *authorizing person*, only an email address *may* be documented as the address but, in such cases, the *authorizing person should* permit its use and *should* be informed that if the email address changes or if email communication is blocked, there *may* be no effective forwarding or receipt of information.);
- 3) an explanation that the *tissue* is a gift, and that neither the *donor's* estate nor the *authorizing person* will receive monetary compensation or valuable consideration for it;
- 4) a description of the general types of *tissue* to be *recovered*;
- 5) a description of the permitted use(s) of the *recovered tissues* (i.e., *transplant*, therapy, research, or education);
- 6) an explanation that *recovery* of *tissue* requires the following actions, and the *document of gift/authorization* thus specifically *authorizes*:
 - a) access to, and required disclosure of, the *Donor's* medical and other relevant *records*;
 - b) testing and reporting for transmissible diseases;
 - c) the removal of specimens which *may* include, but are not limited to blood or *tissue* samples for the purposes of biopsy or other testing necessary for determination of *donor* eligibility;
 - d) the release to the *tissue bank* of any and all *records* and reports of a Medical Examiner, Coroner or Pathologist (e.g., autopsy report); and
 - e) such other requirements as may be applicable for the specific donation or *tissue bank*, such as transport of the *donor's* body, archiving of samples, photographic or other

imaging, etc.

- 7) contact information for the organization represented by the *donation coordinator*; and
- 8) any additional information required by laws or regulations.

The following information *should* be provided to an *authorizing person*:

- 1) a general description of the *recovery* (e.g., timing, relocation of *donor* if applicable, contact information);
- 2) an explanation that costs directly related to the evaluation, *recovery*, *preservation*, and placement of the *tissues* will not be charged to the family;
- 3) an explanation regarding the impact the donation process may have on burial arrangements and on appearance of the *donor's* body; and
- 4) an explanation that the *document of authorization* is available.

Any explanation required by law, such as an explanation that multiple organizations (nonprofit and/or for profit) may be involved in facilitating the gift(s) and/or reference to the possibility that *tissue* may be distributed internationally, *must* be included.

When an Organ Procurement Organization (OPO), or other entity (e.g., hospital), has initiated the process of obtaining *authorization* for a potential organ and *tissue* donation, the *tissue bank* for which the *authorization* is being obtained *shall* request that the OPO or other entity follow the *procedure* and utilize a *document of authorization* that satisfies the requirements of D2.000.

For a *donor* one month (28 days) of age or less, adequate consent pursuant to law *shall* be obtained for collection of blood from the birth mother that will be used for testing.

D2.500 Notification of Gift

In cases where the gift is authorized by a *donor's* own *document of gift* (i.e., first person consent), including a *document of gift* recorded in a *donor registry* (i.e., *donor* designation), and where law mandates *notification*, such *notification shall* be made pursuant to law.

In all other cases, prior to transport of the *donor's* body or *recovery*, the *donation coordinator shall* attempt to *notify* the person who would have been an *authorizing person* had no gift been made during the life of the *donor* or the person who is authorized to make arrangements for final disposition. The information to be provided in the *notification shall* contain, at a minimum, Core Elements of *authorization* but at no time *shall* the *donation coordinator* indicate that the recipient of the information is empowered to revoke or amend the gift made by the *donor*.

The *donation coordinator shall* inquire during the *notification* whether the notified person is aware of any revocation or refusal made by the *donor*.

Notification, if made, *shall* be documented.

Where good faith efforts to *notify* an appropriate person of the gift fail to result in actual

notification within a time frame compatible with the successful *recovery* of the *tissue*, the attempt to notify *shall* be documented, and *recovery may* proceed.

D2.600 Services to Donor Families

Services to donor families or referral to a support system *must* be offered to the *authorizing person*. Subsequent communications and periodic evaluation of services *shall* be documented, maintained, and readily available. See AATB Guidance Document No. 4.

D3.000 INFORMED CONSENT

D3.100 Requirements

Informed consent to acquire *tissues* and make them available for *transplantation*, therapy, research or education *shall* be obtained from a *living donor* or their legal representative, or from a *client depositor* in accordance with applicable laws or regulations. This *informed consent shall* be documented in a *record of informed consent*, the original or a copy of which *shall* be maintained in the *donor's* or *client depositor's record* at the *tissue bank* responsible for *recovery*, *collection* or *acquisition*, as well as in the *donor's record* at the *tissue bank* whose Medical Director is responsible for the *donor* eligibility determination. In the case of an electronic or voice recorded *record of informed consent*, the original recording *should* be maintained in reproducible form.

NOTE: For international members, terminology used by the government/competent authority having jurisdiction applies regarding lawful informed consent for donation of *tissues* for *transplantation*, therapy, research, or education.

D3.200 Conditions

Adequate information concerning the *recovery*, *collection*, or *acquisition* of *tissue shall* be presented in a language in which the *living donor* or their legal representative, or the *client depositor* is conversant, and in terms that are easily understandable by them. The *donation coordinator should* be trained to appropriately answer the questions the *living donor*, their legal representative, or the *client depositor* may have. Neither coercion nor inaccurate information *shall* be used in any manner to obtain *informed consent*.

The potential *donor* or their legal representative *shall* not be under the influence of anesthesia or any drug that could influence his/her ability to give *informed consent*.

Informed consent must be obtained prior to *recovery* or *acquisition*, or when not possible and *recovery* or *acquisition* has already occurred, as soon as practical before use of the *tissue*.

D3.300 Signatures and Documentation

The *record of informed consent must* comply with applicable laws and regulations. It *must* contain, at a minimum,

- 1) the *living donor's signature* or their legal representative's *signature*, or the *client depositor's signature* and:
 - a) name;
 - b) mailing address (NOTE: If requested by the *living donor*, their legal representative, or

the *client depositor*, only an email address *may* be documented as the address but, in such cases, the *living donor*, their legal representative, or the *client depositor* *should* permit its use and *should* be informed that if the email address changes or if email communication is blocked, there may be no effective forwarding or receipt of information.);

- c) phone number;
- 2) the *donation coordinator's signature* and:
 - a) the date; and
 - b) identity of their organization;
- 3) the *signature* of each *witness* if *witnessing* is required by law or regulation;
- 4) documentation that the Core Elements for *informed consent* (see D3.400) were used;
- 5) a statement that the *living donor* or their legal representative, or the *client depositor* understands what has been read or explained and is granting *informed consent* for *tissue recovery, collection, or acquisition*; and
- 6) a statement that the *living donor* or their legal representative, or the *client depositor* has been informed that his/her name and address, as well as required *records*, *shall* be kept on file by the *tissue bank* or *reproductive tissue bank*.

D3.310 Methods of Obtaining Informed Consent

Informed consent can be obtained using different methods, if and as authorized by law or regulation. The methods below appear in preferential order. When *informed consent* is obtained:

- 1) **in person**, the *living donor*, their legal representative, or the *client depositor* *must* read and *sign* the *record* of *informed consent*.
- 2) **by telephone**, the person obtaining the *informed consent* *shall* read to the *living donor*, their legal representative, or the *client depositor* the *record* of *informed consent* or, alternatively, *shall* present each of the Core Elements described at D3.400.

This telephone conversation *shall* be recorded and it *shall* be documented that the *informed consent* was obtained by telephone. A sampling plan *must* be adopted that *verifies* that recordings match the content in the written *record* of *informed consent*. This *verification* *must* be performed by someone other than the *donation coordinator* or *witness*. In the rare event that the telephone conversation cannot be recorded (e.g., equipment failure), and no facsimile or electronic means are feasible for documenting *informed consent*, the *informed consent* *may* be made telephonically and *should* be *witnessed* by a third person. Sampling plans and methods *must* be established, *must* be adequate for their intended use, and *must* be based on valid statistical rationale (e.g., such as the FDA Guide to Inspection of Quality Systems).

- 3) **using a facsimile transmission**, a copy of the *record* of *informed consent* is

provided to the *living donor*, their legal representative, or the *client depositor*. The *living donor*, their legal representative, or the *client depositor* shall return the *signed record of informed consent* by facsimile transmission. A *donation coordinator* shall be available to respond to questions posed by the *living donor*, their legal representative, or the *client depositor*.

A sampling plan *must* be adopted that *verifies signatures* received by facsimile. This *verification must* be performed by someone other than the *donation coordinator* or *witness*. Sampling plans and methods *must* be established, *must* be adequate for their intended use, and *must* be based on valid statistical rationale (e.g., such as the FDA Guide to Inspection of Quality Systems).

- 4) **using an electronic transmission**, a copy of the *record of informed consent* is provided to the *living donor*, their legal representative, or the *client depositor*. The *living donor*, their legal representative, or the *client depositor* shall electronically respond (e.g., by e-mail) that he/she has read the *record of informed consent*, and is granting such *informed consent*. A *donation coordinator* shall be available to respond to questions posed.

A *record of informed consent* received by electronic transmission *should* be verified pursuant to the relevant law on electronic *signatures*, such as the Uniform Electronic Transactions Act, of the relevant state. An electronically transmitted, read-only or otherwise protected *record of informed consent* may be used.

D3.400 Core Elements for Informed Consent

No *informed consent* from a *living donor*, their legal representative, or a *client depositor* shall be acted upon if it does not contain the following Core Elements.

Core Elements:

- 1) the name of the *living donor* or *client depositor*; or
- 2) the identity of the person authorized by law to consent on behalf of the *living donor* or *client depositor* and his/her relationship to the subject including name, address, and telephone number;
- 3) if applicable, an explanation that the *tissue* is a gift, and that the *living donor* or their legal representative will not receive monetary compensation or valuable consideration for it;
- 4) a description of the general types of *tissue* to be *recovered*, *collected*, or *acquired* and any information pertinent to the specific *recovery*, *collection*, or *acquisition* contemplated;
- 5) a description of the permitted use(s) of the *tissues* (i.e., *transplant*, therapy, research, or education);
- 6) a description of the general purposes for which the *tissue* may be used;
- 7) a legally adequate release of the *relevant medical records* of the *living donor*, their legal representative (when applicable), or of the *client*;

- 8) permission to test for disease, if applicable;
- 9) a statement that confirmed positive test results will be reported or disclosed if required by law or regulation (e.g., to the *living donor*, their legal representative, or the *client depositor*, to the attending physician, to appropriate health officials);
- 10) contact information for the organization represented by the *donation coordinator*;
- 11) information concerning possible risks and benefits to the *living donor*, their legal representative, or the *client depositor*, if applicable; and
- 12) any additional information required by laws or regulations.

Any explanation required by law, such as an explanation that multiple organizations (nonprofit and/or for profit) may be involved in facilitating the gift(s) and/or reference to the possibility that *tissue* may be *distributed* internationally, *must* be included.

- (R) In the case of a *client depositor* the *record of informed consent* shall also include details about costs of *tissue cryopreservation, storage, distribution* and *disposition* options.

In the case of an *anonymous donor*, the *record of informed consent* shall also include details about monetary compensation. See D1.100.

D3.500 Services Involving Living Donors

- (BT) Services *shall* be developed that provide answers to questions posed by the birth mother after delivery.

D4.000 DONOR SCREENING AND TESTING

D4.100 Donor Screening

Donor eligibility criteria *shall* be established by the Medical Director and *shall* not conflict with these *Standards*. Each *donor* *shall* be evaluated according to *established* criteria.

- (A) *Donor* eligibility *shall* be documented by a physician caring for the *autologous donor*. It is not necessary to document a *physical examination, a donor risk assessment interview, or medical history and medical record review for autologous tissue* in the *tissue bank records*.
- (BT) Except for *autologous* donations, the health status of the infant(s) *shall* be assessed in regard to information that could affect the *quality or safety* of the *tissue* for *transplantation*. Protocols *shall* be *established* for reviewing information at the time of the infant's delivery. Policies and *procedures* *should* be developed to handle information regarding the health status of the infant reported voluntarily after delivery. Written *procedures* *must* describe how information is evaluated.
- (C) Heart *donors* *shall* also be evaluated for the risk of Chagas' disease.
- (LD) Criteria for accepting *living donors* *shall* be *established* by the Medical Director or licensed physician designee.

- (R) Criteria for accepting *client depositors* and potential *reproductive tissue donors* shall be *established* by the Medical Director or licensed physician designee.
- (S) Potential *donors* shall be evaluated on an individual basis by chart review and visual assessment for size, current medical status, and *skin* condition.

D4.110 Age Criteria

The Medical Director and/or *tissue bank* Medical Advisory Committee shall determine *donor* age criteria.

- (A) There are no age limits for *autologous tissue* donation.
- (BT) There is no age limit for the birth mother, however, policies and *procedures* shall be written regarding gestational age limits.
- (R) *Semen donors* shall be younger than 40 years of age to minimize the risk of genetic anomalies except with the written agreement of the user physician. *Oocyte donors* shall be younger than 35 years, unless an exception has been made by the Medical Director with documented agreement of the user physician.

D4.120 Physical Assessment

Prior to the *recovery* of *tissue* from a deceased *donor*, a *physical assessment* shall be performed by a *responsible person*. This shall be a recent ante-mortem or postmortem *physical assessment* to identify evidence of: high risk behavior and signs of HIV infection or hepatitis infection; other viral or bacterial infections; or, signs of trauma or infection to the body where *recovery* of *tissue* is planned. If any of the following signs are observed or noted in any other available *record*, and are deemed to be an indication of these risks, then the *tissue* shall be rejected:

Note: Each risk type is followed by observational wording in parentheses suggestive of terminology that correlates with each listing. See Appendix III.

- 1) physical evidence for risk of sexually transmitted diseases such as genital ulcerative disease, herpes simplex, chancroid (genital lesions);
- 2) physical evidence for risk of, or evidence of, syphilis (genital lesions, rash, skin lesion [non-genital]);
- 3) for a male donor, physical evidence consistent with anal intercourse including perianal condyloma (insertion trauma, perianal lesions);
- 4) physical evidence of non-medical percutaneous drug use such as needle tracks (and/or non-medical injection sites), including examination of tattoos (which may be covering needle tracks);
- 5) disseminated lymphadenopathy (enlarged lymph nodes);
- 6) unexplained oral thrush (white spots in the mouth);

- 7) blue or purple spots consistent with Kaposi's sarcoma (blue/purple [gray/black] spots/lesions);
- 8) physical evidence of recent tattooing, ear piercing, or body piercing (tattoos/piercings should be described);
- 9) unexplained jaundice, hepatomegaly, or icterus. Note: Hepatomegaly may not be apparent in a *physical assessment* unless an autopsy is performed (enlarged liver, jaundice, icterus);
- 10) physical evidence of sepsis, such as unexplained generalized rash/generalized petechiae, or fever (rash);
- 11) large scab consistent with recent smallpox immunization (scab);
- 12) eczema vaccinatum (lesion, scab);
- 13) generalized vesicular rash, generalized vaccinia (rash);
- 14) severely necrotic lesion consistent with vaccinia necrosum (lesion); and/or
- 15) corneal scarring consistent with vaccinia keratitis (abnormal ocular finding, scarring).

The form and instructions in Appendix III *must* be used to document the *tissue donor physical assessment*.

- (S) The *physical assessment shall* include documentation of findings and conditions that may affect the *quality* or quantity of *skin recovered*.

D4.130 Physical Examination

- (LD) Except for *autologous* and *embryo* donations, prior to the donation of *tissue* from a potential *living donor*, a *physical examination shall* be performed by the Medical Director or licensed physician designee, or by a physician involved with the individual's medical care, or designee as permitted by law. If an examination of a *living donor* was performed for other reasons, review of the findings of such an examination *shall* be performed and documented in the *donor's record*, as well as all other examination findings. After a *donor risk assessment interview* is completed, if any history is suspect, a directed *physical examination shall* be performed. The directed examination *shall* include any of the above applicable items (see D4.120) that would assist with information to determine whether there is evidence of high risk behavior.
- (BT) In addition to the (LD) standard above, a *physical examination* of the birth mother *must* be performed during admission for delivery or within 14 days prior to delivery.
- (R) A *physical examination must* be performed on all *anonymous* and *directed semen* and *oocyte donors*. A repeat *physical examination shall* be performed on *anonymous semen donors* at least every 6 months (180 days) while the *donor* is actively collecting samples in the program.

Semen donors shall not exhibit an infectious skin disease that creates a risk of contamination of the semen.

D4.140 Donor Risk Assessment Interview (DRAI)

A documented dialogue *shall* be conducted with the *donor* (if living) or the deceased *donor's* next of kin, the nearest available relative, a member of the *donor's* household, other individual with an affinity relationship (caretaker, friend, significant life partner) and/or the primary treating physician, using a standardized questionnaire. Questions *shall* be formulated using these *Standards*, current federal regulations and guidance.

Questions *shall* be included that evaluate past medical history for conditions that could constitute a contraindication to the release of *tissue* for *transplantation* (e.g., certain infectious diseases, malignancies, and degenerative neurologic disorders), as defined in these *Standards* (see Appendix II).

For all donors one month (28 days) of age or less, the infant and the birth mother *shall* be screened for risk of *relevant communicable disease agents and diseases* (RCDADs) and the birth mother's blood *must* be tested. Refer to D4.100 (BT) for expectations to obtain the health status of the infant *donor* of *birth tissue*.

The *donor risk assessment interview shall* document the *donor's* name, and the relationship between the *donor* and the interviewee(s) and *shall* indicate the name(s) of the interviewer(s) and interviewee(s). The questionnaire *shall* be maintained as part of the *donor's record*.

- (A) The *tissue bank shall* have a policy for obtaining information from the patient's physician as to whether the *autologous donor* is at high risk for viral hepatitis or HIV infection.
- (BT) The *donor risk assessment interview* of the birth mother *shall* be obtained, or previous *donor risk assessment interview* information *verified*, no more than 14 days prior to delivery. If this interview is performed after delivery it *must* be completed within 14 days of delivery.
- (LD) Interviews *must* be administered by trained staff, or if self-administered, a trained staff member *must* review and *verify* answers with the *donor* in order to facilitate comprehension and provision of accurate answers.
- (R) The donor's risk assessment *shall* include a review of personal alcohol and drug use and sexually transmissible diseases in the *donor* and partner(s). The screening process also *shall* include any history of chemical and/or radiation exposure as well as family medical history and genetic background. An abbreviated *donor* screening *must* be obtained at each repeat donation and reviewed by a *responsible person*. The abbreviated screening *must* determine and document any changes in the *donor's* medical, social, travel, and sexual behavior history (including risk factors) since the previous donation that would make the *donor* ineligible.

D4.141 Family History and Genetic Background

- (BT) If genetic testing has been performed or a genetic history has been

obtained and the information is available, it *should* be considered for the determination of *donor* eligibility.

(R) A minimum of a three-generation family history *shall* be elicited from each prospective *donor*. If a biological family member in the prospective *donor's* family is adopted, Medical Director discretion *must* be made to determine if sufficient family history is provided to determine *donor* eligibility. The genetic history *should* be evaluated by an individual with appropriate clinical genetics education and/or training. Any significant condition in a prospective *donor* or *donor's* family history that would pose a risk of producing an offspring with a serious genetic disease or defect greater than the risk in the general population *shall* disqualify him/her as a *donor*, with the following exceptions:

- 1) *Anonymous donors* whose family history indicates that he/she is at risk for carrying a genetic defect *may* be accepted only if a test to detect carrier status is performed and is negative for the mutation that is known to occur in the family; or
- 2) *Directed gamete donors* and *anonymous* or *directed embryo donors* with any family history indicating he/she is at risk for carrying a genetic defect/condition *may* be accepted, provided the genetic risk to offspring is evaluated in writing and the *recipient(s)* (*R*) has reviewed the evaluation, been offered additional genetic testing, and completed an informed consent.

If indicated by medical history, family history, or ethnic background, *anonymous donors* *should* be screened for Tay-Sachs disease, thalassemia, sickle cell trait, spinal muscular atrophy, and/or cystic fibrosis.

D4.150 Relevant Medical Records Review

Prior to *tissue* donation, a preliminary review of readily available *relevant medical records* *shall* be conducted by a trained individual.

This review *shall* include but *may* not be limited to:

- 1) evidence of significant active infection at the time of donation for *relevant communicable disease agents or diseases* (RCDADs) including signs and/or symptoms of viral and fungal infection, bacteremia or sepsis;
 - 2) risk factors for *relevant communicable disease agents or diseases* (RCDADs) as specified in Appendix II; and
 - 3) additional *tissue donor* specific criteria as documented in the *SOPM* and compliant with written agreements/contracts.
- (A) Except for *skin*, *autologous* donation *should* not be undertaken when the *autologous donor* has, or is being treated for, bacteremia or other significant bacterial infection that can be associated with bacteremia, unless such *tissue* will be secondarily *sterilized* prior to *transplantation* or treated

in such a manner to minimize microbial contamination.

D4.200 Donor Testing

D4.210 Blood Specimens

Except as otherwise specified for certain *reproductive tissue donors*, infectious disease testing of *donor* blood specimens *shall* be performed for each *tissue donor* on a specimen collected at the time of donation or within 7 days prior to or after donation. If the *donor* is one month (28 days) of age or less, a blood specimen from the birth mother *must* be collected within 7 days prior to or after *tissue* donation and tested instead of a specimen from the infant *donor*. There *shall* be written *procedures* for all significant steps in the infectious disease testing process, including blood specimen collection (i.e., documentation of date/time of collection, a *donor* identifier), documentation of the *verification* of specimen *labeling*, and use of appropriate blood specimen types, *labels*, and instructions for specimen handling. *Procedures shall* conform to the test kit manufacturer's instructions for use contained in the package inserts. Specimen collection, storage, and handling *procedures shall* be described in the *SOPM*.

- (R) For *anonymous* and *directed oocyte donors*, the blood specimen *must* be collected within 30 days prior to *oocyte collection*, or within 7 days post donation. Samples for infectious disease testing of *anonymous* and *directed semen donors must* be obtained within 7 days of initial *semen collection*. See D4.360 for testing requirements for *embryo donors*.

D4.211 Plasma Dilution

Tissue from a *donor* who is older than 12 years of age *shall* be determined to be not suitable for *transplantation* if blood loss is known or suspected to have occurred and there has been transfusion/infusion of more than 2,000 milliliters (mL) of blood (e.g., whole blood, or red blood cells) or *colloids* within 48 hours; or more than 2,000 mL of *crystalloids* within one hour; or any combination thereof, prior to *asystole* or the collection of a blood specimen, whichever occurred earlier, unless:

- 1) a pre-transfusion or pre-infusion blood specimen from the *tissue donor* is available for infectious disease testing; or
- 2) an algorithm is utilized that evaluates the volumes administered in the 48 hours prior to collecting the blood specimen from the *tissue donor* to ensure that there has not been *plasma dilution* sufficient to affect test results.

Tissue from a *donor* who is 12 years of age or less who has been transfused or infused at all, *shall* be determined to be not suitable for *transplantation* unless a pre-transfusion or pre-infusion blood specimen from the *tissue donor* is available for infectious disease testing, or an algorithm is utilized that evaluates the volumes administered in the 48 hours prior to collecting the blood specimen from the *tissue donor* to ensure that there has not been *plasma dilution* sufficient to affect test results.

When the fluids transfused are in the “blood” category (alone, or in combination with *colloids* and/or *crystalloids*), a comparison of the total volume of these fluids with the *donor’s* estimated blood volume *shall* be performed, in addition to a comparison of the total volume of *colloids* and/or *crystalloids* with the *donor’s* estimated plasma volume. Since every possible clinical situation cannot be described where *plasma dilution may* affect test results, the *SOPM should* describe how to address additional circumstances when *plasma dilution may* have occurred (e.g., large volumes of transfusions/ infusions administered in the absence of blood loss). It may be necessary to use a pre-transfusion/infusion blood specimen or apply an algorithm in those instances.

Alternative algorithms to evaluate *plasma dilution* can be used if justified.

D4.220 Infectious Disease Testing

Results of initial infectious disease and/or confirmatory testing *shall* be used as one component of determining *donor* eligibility. Testing used for *donor* eligibility *shall* be performed by laboratories that are registered with FDA as a tissue establishment for testing and are either certified to perform such testing on human specimens in accordance with Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) and 42 CFR part 493, or that have met equivalent requirements as determined by the Centers for Medicare and Medicaid Services.

NOTE: For international members that do not export *tissues* to the U.S., applicable requirements of the government/competent authority having jurisdiction apply regarding establishment registration, laboratory certification, and test kit licensing/approval.

FDA-licensed, approved, or cleared **donor screening** tests *must* be used, except when testing for *Chlamydia* or *gonorrhea* in which case, an FDA-licensed, cleared or approved diagnostic test *must* be used.

A new test *shall* be implemented when AATB and/or FDA issues notification to that effect. Prior to that time, use of the new test, even if FDA-licensed, approved, or cleared for *donor* screening, is voluntary. Tests specifically labeled for use with specimens collected after the *donor’s* heart has stopped beating instead of a more generally labeled test *shall* be used when applicable and when available.*

A list of *donor* screening tests that have been licensed for use with specimens collected after the *donor’s* heart has stopped beating can be accessed at the FDA/CBER website.

*See AATB Bulletin No. 06-45 “Intent of Update to Standard D4.353.” (Note: this standard is currently D4.220)

Rapid antigen and/or antibody testing for infectious disease *may* be performed in addition to the required tests. Results of these tests *must* be evaluated (see F1.140) and shared (see D4.300) in accordance with policies and *procedures*.

If a laboratory that performs organ *donor* testing performs the initial testing in duplicate or triplicate, the *tissue bank must* obtain and review the results of all individual tests performed. Individual test results *shall* be shared in accordance with B1.510, D4.300, and K1.100.

All *tissue* from *donors* who test repeatedly reactive on a required screening test *shall* be *quarantined* and *shall* not be used for *transplantation*. There *shall* be written *procedures* for all significant steps in the infectious disease testing process that *shall* conform to the manufacturer's instructions for use contained in the package inserts for required tests. These *procedures shall* be readily available to the personnel in the areas where the *procedures* are performed unless impractical. The manufacturer's instructions *shall* be followed in regard to acceptable *donor* specimens and their handling. *Donor* sample testing *shall* be performed and test results interpreted according to the manufacturer's instructions in the package insert for the particular infectious disease marker.

Additional testing to confirm or supplement infectious disease test results *may* be performed at the discretion of the Medical Director using FDA-licensed, confirmatory test kits when commercially available. Results of infectious disease testing *shall* be evaluated prior to disclosure of availability of positive test results (see D4.232).

D4.230 Required Infectious Disease Tests

Excluding *autologous*, *embryo donor*, and *client depositor tissue*, all human *tissue* intended for *transplantation shall* be from *donors* who are tested and found to be negative for:

- 1) antibodies to the human immunodeficiency virus, type 1 and type 2 (anti-HIV-1 and anti-HIV-2);
- 2) nucleic acid test (NAT) for HIV-1;
- 3) hepatitis B surface antigen (HBsAg);
- 4) nucleic acid test (NAT) for the hepatitis B virus (HBV);
- 5) total antibodies to hepatitis B core antigen (anti-HBc—total, meaning IgG and IgM);
- 6) antibodies to the hepatitis C virus (anti-HCV);
- 7) nucleic acid test (NAT) for HCV; and
- 8) syphilis (a non-treponemal or treponemal-specific assay *may* be performed).

Donors of viable leukocyte-rich *tissue* (e.g., *semen*, certain (CT)) *shall* also be tested and found to be negative for antibodies to human T-lymphotropic virus type I and type II (anti-HTLV-I and anti-HTLV-II). Note: HTLV testing of *donors* of other *tissue* types *may* be required by law and/or regulation, including, where applicable, foreign laws and/or regulations.

All test results *shall* be documented in the *donor's record*.

- (R) In addition to the infectious disease tests listed above, all *anonymous* and *directed semen* and *oocyte donors shall* undergo testing for *Neisseria gonorrhoea* and *Chlamydia trachomatis*. The manufacturer's requirements for specimens

must be met. If the reproductive *tissue* is *collected* by a method that ensures freedom from contamination of the *tissue* by infectious disease organisms that may be present in the genitourinary tract, then these tests are not required.

All *anonymous* and *directed semen donors* shall also be tested for total antibody to cytomegalovirus (anti-CMV—total, meaning IgG and IgM).

Required tests for *anonymous* and *directed embryo donors* are listed in D4.231.

Client depositors who deposit *semen*, testicular fluid or *tissues*, *oocytes* or ovarian *tissue*, or *embryos*, shall be tested prior to use for:

- 1) antibodies to the human immunodeficiency virus, type 1 and type 2 (anti-HIV-1 and anti-HIV-2);
- 2) hepatitis B surface antigen (HBsAg); and
- 3) antibodies to hepatitis C virus (anti-HCV).

D4.231 Repeat Testing of Living Donors

(R) All donated *semen* from *anonymous donors* shall be frozen and *quarantined* for at least 6 months. After such time and prior to release of *semen*, the *donor* shall be retested for anti-HIV-1, HIV-1 NAT, anti-HIV-2, HBsAg, anti-HBc, HBV NAT, anti-HCV, HCV NAT, anti-HTLV-I, anti-HTLV-II, syphilis, and for anti-CMV. *Anonymous donor semen* shall not be made available for use unless results of all tests, excluding CMV and syphilis, are negative or nonreactive. Results of all testing performed *must* be interpreted as in F1.140. All tests for infectious diseases shall be repeated at least every 6 months while the *semen donor* remains an active participant in the *donor* program and after any lapse exceeding 6 months.

Oocyte donor tissue is not subject to *quarantine* and the *donor* is not subject to repeat testing.

For *directed* or *anonymous donation* of *embryos* created by sexually intimate *client depositors*, the *embryos* shall be *quarantined* (stored) for at least 6 months from the date of creation. After the 6-month *quarantine* and prior to release of the *embryo(s)* for *transfer*, appropriate measures *should* be taken to test the sexually intimate *client depositor* male and female for anti-HIV-1 anti-HIV-2, HBsAg, anti-HBc, anti-HCV, and for HIV-1 NAT, HBV NAT, HCV NAT, and syphilis. In addition, the male *should* be tested for anti-CMV, anti-HTLV-I, and anti-HTLV-II.

For *directed* or *anonymous donation* of *embryos* created using one *anonymous* or *directed egg* or *sperm donor*, *embryos* shall be *quarantined* (stored) for at least 6 months from the date of creation. After such time and prior to release of the *embryo(s)* for *transfer*, appropriate measures *should* be taken to test the *client depositor* for anti-HIV-1, anti- HIV-2, HBsAg, anti-HBc, anti-HCV, and for HIV-1 NAT,

HBV NAT, HCV NAT, and syphilis. If the *client depositor* is male, he *should* also be tested for anti-CMV, anti-HTLV-I, and anti-HTLV-II. A *Summary of Records* for the *gamete donor* must be provided prior to release.

For *directed* or *anonymous donation* of *embryos* created using both an *anonymous* or *directed* egg and sperm donor, a *donor summary of records* must be obtained for both donors.

“Appropriate measures” means using available resources to accomplish the testing. If the *client depositor* cannot be tested due to death or inability to locate the person, *directed* or *anonymous donation* of the *embryos* can still be completed.

D4.232 Disclosure and Availability of Positive Infectious Disease Test Results

The *donor*, if living, *shall* be provided test results as required by applicable law or regulation. For deceased *donors*, the *authorizing person* *should* be contacted regarding the availability of infectious disease test results that may be of medical significance as determined by the Medical Director or licensed physician designee. Contact *should* include the means by which available test results *should* be requested. If a *document of gift* was used (i.e., there is no *authorizing person*), contact regarding the availability of infectious disease test results *should* be made to the person who would have been the *authorizing person* had no gift been made during the life of the *donor*, or to the person authorized to make arrangements for final disposition of the body. These *records* *should* be provided upon written request as permitted by law or regulation. Positive test results *shall* be reported to state and/or local health department(s) as required by law or regulation.

Contact regarding availability and/or disclosure of test results *shall* be documented.

D4.240 Archived Samples

A serum or plasma sample from each *donor* *shall* be archived if any sample remains after testing. A policy *shall* be established to collect and archive serum, plasma, or hematopoietic *tissue* samples from *donors*. Samples *shall* be retained for ten years after the *recovery*, *collection*, or *acquisition* date. If a *donor* is determined to be unsuitable, archived serum, plasma, or hematopoietic *tissue* samples *should* still be retained for use for possible unforeseen future investigational purposes (e.g., emerging infectious diseases, medical/legal, blood borne pathogen exposure, etc.).

- (DM) Appropriate brain *tissue* specimens (i.e., formalin-fixed brain *tissue*, histological sections from examination of brain, *donor* serum) from each *donor* of *dura mater* *shall* be archived under appropriate storage conditions, and for the appropriate duration.
- (R) Archived serum or plasma from *reproductive donors* whose *tissue* has been *stored* but subsequently destroyed and never *distributed* does not require retention.

D4.250 Semen Analysis

(R) **Semen Donors:** Prior to enrollment of a *donor* in the sperm *donor* program, his *semen shall* be tested for sperm quality and found acceptable for such parameters as sperm motility, concentration, and post-thaw motility. *Donors shall* be excluded unless the specimen meets criteria set by the Medical Director and, when appropriate, the Medical Advisory Committee. Criteria for *directed donors* may differ from those for *anonymous donors*. Sperm quality tests *shall* be repeated at a frequency determined by the *tissue bank*.

Client Depositors: A *semen* analysis, that includes sperm concentration and motility, at a minimum, *shall* be performed. The *reproductive tissue bank shall* make pertinent test results available to the *client depositor's* physician.

D4.300 Information Sharing

The *tissue bank* that recovers *tissues* must have a *procedure(s)* for receiving, investigating, evaluating, and documenting *donor* information as well as how they will share *records* with all establishments who are known to have also *recovered tissues*, or to have received *recovered tissues*, from the same *donor*:

- 1) *record* sharing *should* occur as new information is received and this *must* be documented and included in the *records*;
- 2) relevant *records* that could affect eligibility determinations *must* be sent without delay to *tissue banks* that will determine *donor* eligibility of *recovered tissues* and/or the *donor*;
- 3) the *tissue bank* that recovers *tissue* must share *tissue recovery* culture (*pre-sterilization/ pre-disinfection culture*) information with all *tissue banks* to which *tissue* from shared *donors* was sent. If defined in a written agreement, an eye bank can choose not to receive *pre-sterilization/pre-disinfection culture* results; and
- 4) if any *tissue bank* determines a *donor* to be ineligible, this determination *must* be communicated in writing to the *tissue bank* that *recovered tissues*, and the *tissue bank* that *recovered tissues* *must* share this information with all establishments that are known to have *recovered tissues*, or to have received *recovered tissues*, from the same *donor*.

Written *procedures* *must* describe how this information is received, evaluated, and disseminated in a timely fashion.

Any *tissue* testing performed after it has been *disinfected* or subjected to *processing* (e.g., *in-process* testing, *post-processing* microbiological testing, final cultures) is not considered relevant *donor records* for the *tissue bank* that *recovered tissues* and, if such results are reported, would not be expected to be shared with *tissue banks* who received *recovered tissues* from a shared *donor*.

D5.000 RECOVERY, COLLECTION, AND ACQUISITION

Policies and *procedures* *shall* be established for the *recovery*, *collection*, or *acquisition* of *tissue* in accordance with *Standards*. Reagents, supplies, materials, and equipment *shall* be of appropriate grade for intended use, and approval for use *shall* be documented. All *tissue* *must* be uniquely identified and

traceable to the *donor* from *recovery*, *collection*, or *acquisition* through transport and receipt at the *processing* or storage facility. The environment in which *tissue* can be obtained, and techniques that *should* be used, *shall* be specified. *Recovery*, *collection*, *acquisition* and *preservation* *shall* occur within a time interval appropriate for retention of *tissue quality* and *shall* be compatible with intended use of the *tissue*. Detailed *records* of the *tissue* donation *shall* be maintained that include information regarding relevant packaging, transportation, and, when applicable, *donor* reconstruction steps.

D5.100 Reagents, Supplies, Materials, and Equipment

All *critical* supplies, reagents, materials, and equipment approved for use for *recovery*, *collection*, or *acquisition* *shall* be identified and specifications (e.g., *sterile* where applicable) documented. A *record* *shall* be made of all reagents, supplies, and materials following receipt including, as applicable, the type, quantity, manufacturer, *lot* number, date of receipt, and expiration date or manufacturing date (as applicable). Inspection *shall* be documented, including identification of the staff performing the inspection. The *tissue bank* *shall* maintain *records* of all supplies, reagents, materials, and equipment from receipt through period of time used. All reagents, supplies, materials and equipment *shall* be used and stored in accordance with manufacturers' instructions, unless qualified/*validated* for intended use or storage.

All non-disposable surgical instruments and parts of mechanical/ electrical equipment which come in contact with *tissue* *shall* be properly cleaned, *decontaminated*, and *sterilized* prior to use for *recovery*, *collection*, or *acquisition* according to written *procedures* prepared to prevent contamination or *cross-contamination*. *Records* *shall* be maintained that document sterilization steps. All reagents, supplies, and materials *shall* be used and stored in accordance with manufacturers' instructions unless qualified/*validated* for intended use or storage.

D5.110 Stock Rotation

Reagents, supplies, and materials with expiration dates or production dates *shall* be stored in a manner to facilitate inventory rotation. Items not bearing an expiration or production date *shall* be labeled with the date of acquisition and stored in a manner to facilitate inventory rotation. Older items *should* be used first and not used if expired or quality has been compromised.

D5.200 Donor Identification

Each *donor* *shall* be assigned a unique *donor* identifier to facilitate *tracing* of the *tissue* from the *donor* and to final *disposition* of each *tissue*.

D5.210 Verification Procedures

D5.211 Confirmation

Prior to *recovery* or *collection*, staff *shall* confirm that in the case of a deceased *donor*, *authorization* for donation has been obtained and documented in a *document of gift/authorization*. In the case of a *living donor*, *informed consent* *must* be obtained and documented prior to the initial *collection*. If *informed consent* was not obtained prior to *recovery* (e.g., *autologous tissue*, *surgical bone*) or *acquisition*, it *must* be obtained as soon as practical after *recovery* or *acquisition*.

D5.212 Donor Identity

Prior to initiation of *tissue recovery, collection, or acquisition* the potential donor's identification shall be verified with the donor's name as stated on the record of informed consent or document of gift/authorization. Donor identity verification shall be documented in the donor record prior to *tissue recovery, collection, or acquisition*. Records shall indicate the staff member(s) involved and include the source of the verification information (e.g., hospital wristband, medical examiner number, driver's license, or government issued identification with photograph).

(A, SB) Identification of the donor shall be the responsibility of the hospital staff involved with the *recovery*.

(BT) Identification of the birth mother shall be the responsibility of the hospital staff, or the *tissue bank* staff member involved with *acquisition*.

D5.300 Tissue Recovery, Collection, and Acquisition

Recovery, collection, or acquisition shall be performed using aseptic or clean techniques appropriate to the specific *tissue* type and intended use. *Tissue* must be labeled using a donor identifier and a description according to the *SOPM* (see G1.100).

D5.310 Recovery

Recovery shall be performed using aseptic or clean techniques appropriate to the specific *tissue* recovered and intended use of the *tissue*. The *SOPM* shall specify the time limits for the postmortem *recovery* of *tissue* consistent with *tissue*-specific standards, where applicable. If *recovery* is to be delayed for a deceased donor, the donor's body should be refrigerated/cooled as specified in the *tissue*-specific standards. To prevent *cross-contamination* or mix-ups, *recovery* from one donor shall be the exclusive activity taking place at one time at a *recovery site*. Other activities (e.g., embalming, autopsy, another *tissue donor recovery*) cannot occur simultaneously in the same room as *recovery*. *Tissue recovery* shall not occur after embalming procedures have begun (i.e., injection of embalming fluid, application of drying agents either internally or topically).

(LD) Methods for *recovery* of perioperative *tissue* shall be safe, aseptic, and ensure accurate identification of *tissue*.

D5.320 Collection

(R) *Collection* of anonymous donor semen shall be made at the reproductive *tissue bank* using a sterile *collection* container. If the *tissue* requires transportation to the processing laboratory, it should be transported within a reasonable time period as specified in the *SOPM*, so as to maintain the utility of the *tissue*. The *collection* container shall be labeled with the date of *collection* and the donor's identification or, in the case of *client depositors or directed donors*, the name. The time of *collection* shall also be recorded.

D5.330 Acquisition

(BT) Methods for *acquisition* of *birth tissue* shall be safe, aseptic, and ensure accurate identification of *tissue* post delivery.

Birth tissue shall be *packaged* post-delivery using a *sterile* receptacle/transport package in a controlled environment. Prior to *acquisition*, the *birth tissue* receptacle/transport package shall be *labeled*.

D5.340 Pooling

Pooling tissue from multiple *donors* shall not occur during *recovery*, *collection*, *acquisition* or *storage*.

D5.400 Time Limits for Postmortem Tissue Recovery

When *recovery* of *tissue* has begun, subsequent *recovery* steps *must* proceed without delay.

(C, V) *Cardiac tissue* and *vascular tissue* *recovery* and *processing* time limits (i.e., *warm* and *cold ischemic time*, *disinfection time*, and the *perfusion time* [specific to *vascular tissues*]) shall be established by each individual *tissue bank*; however, the following upper time limits for initiation of *recovery* of specific *tissue* types shall not be exceeded.

(C) *Warm ischemic time* (C) shall not exceed 24 hours from *asystole* if the *donor's* body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of *asystole*. The time limit shall not exceed 15 hours if the *donor's* body was not cooled or refrigerated. If the *donor's* body is cooled for a period of time then not cooled for a period of time, the time period the *donor's* body is not cooled cannot exceed 15 cumulative hours.

(V) 1) *Perfusion time* shall not exceed 12 hours from *asystole*; and

2) *warm ischemic time* (V) shall not exceed 24 hours from *asystole* if the *donor's* body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of *asystole*. The time limit shall not exceed 15 hours if the *donor's* body was not cooled or refrigerated. If the *donor's* body is cooled for a period of time then not cooled for a period of time, the time period the *donor's* body is not cooled cannot exceed 15 cumulative hours.

(MS, OA, S)

The *skin prep* shall begin within 24 hours of *asystole* provided the *donor's* body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of *asystole*. The *skin prep* shall begin within 15 hours of death if the deceased *donor's* body has not been cooled or refrigerated. If the *donor's* body is cooled for a period of time then not cooled for a period of time, the time period the *donor's* body is not cooled cannot exceed 15 cumulative hours.

For expectations when evaluating cooling of a *donor's* body, refer to Guidance Document No. 7.

D5.500 Recovery Environment

All *tissue shall be recovered* in an aseptic or clean fashion using standard surgical preparation with *sterile* packs, instrumentation, and technique. Prior to *recovery*, the *recovery site must* be evaluated for suitability using pre-established criteria designed to control contamination and *cross-contamination* (see Appendix IV). The *recovery site evaluation must* be documented, however, if the *recovery site* is an operating room in a health care facility, no documented site evaluation is required.

D5.510 Recovery Site Suitability Parameters

These *must* address the control of:

- 1) size/space;
- 2) lighting;
- 3) plumbing and drainage for the intended use;
- 4) the physical state of the facility (i.e., state of repair);
- 5) ventilation;
- 6) cleanliness of room and furniture surfaces;
- 7) pests;
- 8) traffic;
- 9) location;
- 10) other activities occurring simultaneously;
- 11) sources of contamination; and
- 12) the ability to appropriately dispose of biohazardous waste and handle contaminated equipment.

D5.520 Recovery Cleansing and Preparation

Environment:

An evaluation of the *recovery site must* be performed to identify potential sources of contamination (see Appendix IV). All working surfaces (e.g., back table, Mayo stand, recovery table) used during *recovery must* be *decontaminated* using a bactericidal/antimicrobial agent. All cleansing and disinfecting events performed by *tissue bank* personnel *shall* be documented. For guidance, refer to Guideline for environmental cleaning in Guidelines for Perioperative Practice. Denver, CO: AORN, Inc. (current edition).

Technician:

Technician gowning, gloving, and movement *shall* be accomplished with the same diligence as used routinely for operative procedures. Aseptic technique *shall* be

followed. For guidance, refer to AORN's Guideline for sterile technique (current edition). Persons performing the surgical *recovery shall* perform a surgical scrub or wash of their hands and forearms prior to *recovery*. For guidance, refer to AORN's for hand hygiene (current edition). A head cover, eye shields and mask *shall* be worn at the time of scrub, and a *Sterile* gown and gloves *shall* be donned after the scrub/wash. For guidance, refer to AORN's Guideline for surgical attire (current edition).

Donor:

Cleansing, preparing (i.e., *skin prep*), and draping the *skin shall* be accomplished with the same diligence as used routinely for operative procedures. Agents used *shall* be antimicrobial *skin* preparation products, as specified in the *SOPM*, and *shall* be used in accordance with manufacturers' guidelines/instructions. For guidance, refer to AORN's Guideline for preoperative patient skin antisepsis (current edition).

D5.530 Recovery Technique

Specific *tissue recovery* operations that control contamination and *cross- contamination* (e.g., sequencing of the *tissue recovery*, use of well-defined zone *recovery* techniques, and isolation draping in the presence of trauma; see Appendix IV *shall* be implemented. Areas of *skin* that have abrasions or puncture wounds *should* be avoided. All *tissue shall* be *recovered* using aseptic technique.

D5.531 Cultures Obtained at Recovery

(MS, OA, S, SB)

If performed, the technique used to obtain cultures of *recovered tissues shall* be appropriate for the *tissue* type, and performed according to written instructions.

D5.600 Delivery Environment and Cultures Obtained Prior to Acquisition

D5.610 Delivery Environment

(BT) If the delivery location is an operating room in a health care facility, no documented site evaluation is required, however, any other location of delivery *must* meet the requirements at D5.500 and D5.510. Such an evaluation *must* be documented.

D5.620 Cultures Obtained Prior to Acquisition

(BT) If performed, the technique used to obtain cultures prior to *acquisition shall* be appropriate and performed according to written instructions.

D5.700 Records

D5.710 Recovery Records

For *allogeneic tissue*, details of the *tissue* donation *shall* be documented in the *recovery record*. *Recovery records shall* include, but not be limited to:

- 1) name, and address of the *recovery* agency;
- 2) date, time and staff involved in all significant steps performed during the *recovery*

(documentation *shall* be as per C1.100);

- 3) location and assessment of the suitability of the *recovery site*;
- 4) documentation of the *physical assessment* or *physical examination*;
- 5) documentation of any *errors, accidents, or deviations* that occurred;
- 6) *donor* name, age, and sex;
- 7) the type, *lot* number, manufacturer, and expiration date of *critical* reagents, supplies and materials, and the identification of equipment, used to *recover, rinse, and/or transport tissue*; and
- 8) specific *tissue recovered*; and
- 9) other available *relevant medical records*.

The *tissue bank* or agency *recovering* the *tissue shall* provide a *record* of the *tissue* recovered, date of *recovery*, name and address of the *recovery* agency, and name of the *donor* to the *recovery site* facility.

- (A) The following information regarding *autologous tissue recovery shall* be documented:
 - 1) name and address of the institution in which the *autologous tissue* was *recovered*;
 - 2) date and time the *autologous tissue* was *recovered*;
 - 3) name of the physician *recovering* the *autologous tissue*;
 - 4) *donor* name, age, sex, and hospital medical record number and/or social security number; and
 - 5) type of *tissue recovered*.

D5.720 Delivery and Post-Delivery Records

Details of the delivery and post-delivery time period through *acquisition shall* be documented in the *donor's record*. These *records shall* include, but not be limited to the:

- 1) birth mother's name;
- 2) infant *donor's* gestational age;
- 3) name and address of the health care facility and the identification of the delivery environment/location;
- 4) date and time of the delivery;

- 5) the physician or other authorized practitioner involved with the delivery, or designee as permitted by law;
- 6) information to allow tracking of *critical* reagents, supplies and materials provided by the *tissue bank*;
- 7) specific *tissue(s) acquired*;
- 8) other available *relevant medical records*; and
- 9) documentation of any *errors, accidents, or deviations* that occurred.

D5.800 Packaging, Labeling, and Transport

D5.810 Post-Recovery Packaging and Labeling

Immediately following *recovery* of each individual *tissue* at the *recovery site*, *recovered tissue shall* be individually and aseptically wrapped or enclosed and *shall* be immediately *labeled* with the unique *donor* identifier and the description according to the *SOPM* (see G1.100). *Tissue shall* be maintained at defined environmental temperatures until the time of transport to the *processing* center. Maintenance of such temperatures *shall* be documented. The receptacle/transport package *must* be designed to prevent contamination of the contents and allow for aseptic presentation of the *tissue* at the time of *processing*.

- (A) Immediately following *recovery* of the *autologous tissue*, *it shall* be individually and aseptically wrapped. The package *shall* be *labeled* immediately with definitive *autologous donor* identifying information such as the patient's name, hospital registration number, security number, birth date, etc., and *shall* be prominently labeled "FOR AUTOLOGOUS USE ONLY."
- (C) *Recovered cardiac tissue shall* be rinsed and *packaged* in an isotonic, *sterile* solution such as normal saline, lactated Ringer's solution, PlasmaLyte®, transplant organ perfusate (e.g., Belzer's UW solution, Collin's solution) or tissue culture media, immediately following *recovery*. The volume of the transport solution *should* be adequate to cover the entire heart, including the vessels and valves. The type, *lot* number, manufacturer, and expiration date *shall* be documented.
- (V) Immediately following *recovery*, *vascular tissue shall* be gently flushed and packaged in an isotonic *sterile* solution such as tissue culture media. Normal saline solution *should* not be used. The type, *lot* number, manufacturer, and expiration date of all reagents used for *recovery* and *packaging shall* be documented.
- (S) *Recovered skin tissue shall* be *packaged* in a *sterile* solution immediately following *recovery* or *packaged* by another method that maintains the integrity of the *tissue* for its intended use (e.g., decellularized dermis). If in solution, the volume of transport solution *must* be adequate to cover the entire *skin*. The type, *lot* number, manufacturer, and expiration date(s) *shall* be documented.

D5.820 Post-Delivery Packaging and Labeling

- (BT) Following delivery, *tissue shall* be aseptically contained. *Labeling* that includes a unique *donor* identifier and the description according to the *tissue bank's SOPM* (see G1.100) *shall* be performed prior to transport. The receptacle/transport package *must* be designed to prevent contamination of the contents and allow for aseptic presentation of the *tissue* at the time of *processing*.

Tissue shall be maintained at defined environmental temperatures until the time of transport to the processing center. Maintenance of such temperatures *shall* be documented.

D5.830 Tissue Transport

Tissue shall be transported in a manner established by the *tissue bank* that permits required environmental conditions for the duration of transport necessary to maintain the integrity of the *tissue* for its intended use. Transportation temperatures do not require monitoring if the *packaging* and transport conditions have been *validated* to maintain the required environmental conditions, including temperatures. The receptacle/*transport package must* indicate that “DONATED HUMAN TISSUE” is enclosed and *must* include the name and address of the originating agency and *processing* center (if different). All human *tissue processed* or shipped prior to determination of *donor eligibility must* be under *quarantine*, accompanied by *records* assuring identification of the *donor* and indicating that the *tissue* has not been determined to be suitable for *transplantation* (e.g., “Quarantine”; “Donor Eligibility Has Not Been Completed”; and “Not Suitable for Transplant in its Current Form”).

- (A, LD, CT)

When *wet ice temperatures* would be injurious to the *tissue recovered*, it may be transported at appropriate temperatures and within time limits that maintain the *quality* of the *tissue* for its intended use.

- (C, V) The transport *package shall* be transported at *wet ice temperatures*. Time of acceptance of the *tissue* into the *processing* center *shall* be documented. *Cardiac tissue* and *vascular tissue shall* be received at the *processing* location within sufficient time following *recovery* to allow for the start of *disinfection* within the *established cold ischemic time* limit.

- (MS) The *recovered tissue shall* be wrapped in an aseptic fashion with at least one moisture barrier and *shall* be transported at *wet ice temperatures* or colder. The maximum time that *recovered tissue shall* remain at *wet ice temperatures*, prior to either *processing* or freezing, *shall* be no longer than a time limit *established* by a *validated procedure* that maintains *tissue quality*.

- (OA) The *recovered tissue shall* be transported at *wet ice temperatures*. The maximum time that *recovered tissue shall* remain at *wet ice temperatures* prior to *processing shall* be no longer than a time limit *established* by a *validated procedure* that maintains *tissue quality*.

- (S) If the *tissue* is to be *cryopreserved*, the *skin transport package shall* be transported at *wet ice temperatures* or *packaged* by another method that

maintains the *quality* of the *tissue* for its intended use.

D5.900 Reconstruction of a Deceased Donor's Body

Unless there is a specific request from a medical examiner, pathologist, or a funeral home, the surgical incision(s) *shall* be closed in an aesthetic fashion and the deceased *donor's* body prepared for the next portion of the *recovery* or for transportation to an appropriate facility. The *donor's* body *shall* be reconstructed in accordance with the *SOPM*. Reconstruction *should* employ techniques consistent with funeral home guidelines and/or medical examiner or pathologist requests. Documentation of *donor* reconstruction (if applicable) and disposition of the *donor's* body *shall* be maintained in the *donor's record*.

D6.000 STORAGE OF TISSUE

Storage, including temporary *storage*, of *recovered*, *acquired*, or *collected tissue* *shall* be in conformance with *storage* temperature and monitoring expectations provided by the *tissue bank* that will *process* the *tissue*. See C1.300, E3.330, E3.331, and E3.340.

D6.100 Quarantine Areas

Quarantine tissue storage areas including *storage* areas within freezers, refrigerators or other *tissue storage* equipment, *shall* be physically separated and clearly labeled as “*quarantine*.”

D6.200 Segregation

The *SOPM* *must* address when the segregation of *tissue* during *storage* is indicated and how it will be appropriately segregated to avoid contamination, *cross-contamination* and mix-ups.

Considerations for assessment of risk include, where applicable:

- 1) *donor* infectious disease test results are unavailable or this testing will not be performed;
- 2) the intended use of the *tissue* is primarily for *transplantation* or is restricted to research or education;
- 3) *autologous tissue* is segregated from *allogeneic tissue*;
- 4) the *donor* has been determined to be ineligible;
- 5) the ability of *packaging* and *labeling* to withstand *storage* temperatures, and/or
- 6) the ability to *decontaminate storage* equipment or the *storage* area should an accident occur.

Appropriate segregation *must* include considerations above and *storage* *must* be in clearly defined and labeled areas (shelves or compartments) of the *storage* equipment or *storage* area.

D6.300 Storage Equipment

Freezers and refrigerators used for *storing tissue shall* be regularly maintained, calibrated, and monitored according to written *QC procedures*. See the *series of standards* at J5.000.

SECTION E PROCESSING AND STORAGE

E1.000 RECEIPT OF TISSUE AT PROCESSING/STORAGE FACILITY

Approval or rejection of the receipt of *tissue* into the *processing* or *storage* facility *must* be documented. The receipt and movement into *storage*, to immediate *processing* or to removal, *shall* be documented, including, at a minimum:

- 1) the condition of the transport *package*;
- 2) confirmation each *tissue* is *labeled* with a *tissue identification number*, or other *traceable* unique identifier;
- 3) evidence proper environmental conditions were maintained (e.g., presence/absence of ice/coolant). Refer to H3.300;
- 4) the date and time of receipt and movement; and
- 5) personnel involved.

E1.100 Tissue Identification

Except for *reproductive tissue*, each unit of *tissue* *shall* be assigned a *tissue identification number*, which *shall* serve to relate the *tissue* to the *donor* from whom it was *recovered* or *acquired* and the associated *records* at any phase (e.g., *quarantined*, unprocessed, processed inventory) of the operation. *Tissue* units *shall* be assigned the same *tissue identification number* only if they are identical and processed as a *lot*.

- (R) *Reproductive tissue donors* and *client depositors* *shall* be assigned a unique identifier, which *shall* be used to identify the *tissue* during steps of *collection*, *processing*, *storage*, and *distribution*. The unique identifier can be a *directed donor's* or a *client depositor's* name. For *donors* and *client depositors* giving multiple specimens, a secondary code *shall* be used to distinguish between dates of *collection*. The *reproductive tissue bank* that *collects* and *processes* the *reproductive tissue* *shall* be identified by name, code, or other identifier on the final *container*.

E1.200 Pooling

Tissue from multiple *donors* *shall* not be *pooled* during *processing*, *preservation*, or *storage*.

E2.000 PROCESSING

Processing and *preservation* methods *shall* be *established* in accordance with *Standards* and applicable laws and regulations. All *tissue* *shall* be *processed*, *preserved*, *quarantined*, and/or *stored* pursuant to such methods so as to render them suitable for clinical use.

- (A) If *autologous tissue* is not to be *processed*, it *should* be retained in its original wrapping.
- (C, V) *Processing* *shall* include a *disinfection* period followed by rinsing, packaging, and *preservation*.

E2.100 Tissue Evaluation

Written criteria for evaluation and assessment of *tissue quality* must be established.

(C, V, OA)

A standardized evaluation and classification system is required that describes the attributes of each *allograft*. A detailed description of the condition of the *allograft* shall be recorded in the permanent *donor processing records*. The *allograft* evaluation system shall be made available to the implanting surgeon.

E2.200 Processing Environment

Except for *reproductive tissue*, when *tissues* are exposed to the environment during *processing*, these activities shall be consistent with the requirements of *aseptic processing*. There shall be demonstrated and documented evidence that the chosen environment achieves the *quality* and *safety* required for the type of *tissue*, *processing*, and intended use.

Without a subsequent *validated* microbial inactivation process, *aseptic processing* shall be performed in a certified and qualified bacteriologically and climate-controlled environment.

E2.210 Environmental Control and Monitoring

Where environmental conditions could reasonably be expected to cause contamination or *cross-contamination* of *tissue* or equipment, or accidental exposure of *tissue* to communicable disease agents, there must be adequate *environmental control* and monitoring of viable and non-viable particles under *dynamic* as well as *static* conditions. Effectiveness of these controls shall be *validated*. See AATB Guidance Document No. 5.

Adequate control is defined by justifying and documenting the following:

- 1) type and frequency of *environmental monitoring*;
- 2) when the samples are to be taken (e.g., during or at the conclusion of operations);
- 3) sampling locations and number of sites to be sampled;
- 4) sample duration;
- 5) sample size (e.g., surface area, air volume);
- 6) action and alert levels for test results; and
- 7) potential *corrective actions* when alert and/or action levels are exceeded.

E2.300 Tissue Contamination

Written *procedures* shall be prepared, *validated*, and followed for control and prevention of contamination or *cross-contamination* by *tissue* during *processing*.

E2.400 Reagents, Supplies, Materials and Equipment

All *critical* supplies, reagents, materials, and equipment approved for use for *processing* and *preservation* shall be identified and specifications (e.g., *sterile* where applicable) documented. It is expected that the *tissue bank* has the ability to link all supplies, reagents, materials, and equipment to *tissue processed* over the period of time they were in use.

A *record* shall be made of all reagents, supplies, and materials following receipt including, as applicable, the type, quantity, manufacturer, *lot* number, date of receipt, and expiration date or manufacturing date (as applicable). Inspection shall be documented, including identification of staff performing the inspection. All reagents, supplies, materials and equipment shall be used and stored in accordance with manufacturers' instructions.

All non-disposable surgical instruments and mechanical/electrical equipment used in *tissue processing* shall be cleaned, *decontaminated*, and, where applicable *sterilized*, between use for *tissue* from different *donors* according to written *procedures*. For non-disposable surgical instruments and mechanical/electrical equipment deemed *critical*, written *procedures* must be prepared and methods shall be *validated*, to prevent contamination or *cross-contamination* during *processing*.

E2.410 Stock Rotation

Reagents, supplies, and materials with expiration dates or production dates shall be stored in a manner to facilitate inventory rotation. Items not bearing an expiration or production date shall be labeled with the date of acquisition and stored in a manner to facilitate inventory rotation. Older items should be used first and not used if expired or quality is compromised.

E2.420 Containers

E2.421 Physical Properties

The *container* shall maintain its integrity, withstand *sterilization* and *storage* conditions, not produce toxic residues during *storage*, and maintain *tissue quality* through the *labeled* expiration date. *Containers* shall not interfere with the effective use of appropriate agents applied to *sterilize* or *disinfect* the *tissue*.

If ethylene oxide is used to *sterilize processing* or *packaging* components that come in contact with the *allografts* (e.g., *disinfection* jars or *packaging* pouches), residues of ethylene oxide, ethylene glycol, and ethylene chlorohydrin should be evaluated. Refer to ISO 10993-7.

(C, V) Final packaging *containers* shall be adequate for use at defined *storage* temperatures and documented to remain stable and impervious to microbial particles under normal environmental conditions at the specified temperature and throughout the recommended thawing regimen.

E2.422 Receipt of New Shipments

Containers shall be stored under *quarantine* until the *containers* have been tested, sampled, or examined, as appropriate, and released for use. *Containers* not meeting specifications shall not be used.

E2.423 Storage

Unused *containers shall* be handled and stored to maintain integrity.

E2.424 Integrity and Sterility

Sterilized containers shall be handled in a manner to preclude contamination.

E2.425 Visual Inspection

Each *container shall* be examined visually for damage or evidence of contamination prior to use and immediately after filling. *Containers* not meeting visual criteria *shall* not be used.

E2.500 Processing Methods

Tissue shall be processed using *validated* methods to prevent contamination and *cross-contamination*.

E2.510 Temperature Limits

- (C, V) Methods *shall* be employed that maintain the *tissue* at desired *processing* temperatures as required by reagents used and as described in written *procedures*.
- (S) If additional warm ischemia and potential cellular or matrix damage caused by temperature cycling impact *quality* for intended use (e.g., *cryopreserved*), methods *shall* be employed that maintain the *tissue* or solutions above 10°C for no longer than 2 hours. The methods/equipment *shall* be qualified to maintain the appropriate temperatures.

E2.520 Time Limits for Pre-processing, Processing and Preservation Phases

Time limits and/or other valid *process control* end points or limits for the completion of each phase of *processing* and *preservation shall be established* and *validated* with reference to *tissue quality*. Additionally, a time limit and temperature for *pre-processing quarantine storage* that address *tissue quality must be established* and justified.

- (C, V) *Disinfection of cardiac and vascular tissue shall* be accomplished via a time-specific, *validated process (disinfection time)*. The *total ischemic time shall* not exceed 48 hours.
- (R) After *collection*, analysis *shall* be performed within an appropriate time period, and *processing*, if performed, *shall* be initiated within a time period appropriate for retention of functional *quality*, as specified in the *SOPM*.
- (S) When *preservation* of cellular viability is desired, *processing of skin shall* be initiated within 10 days of *recovery*, provided the *skin* is placed in tissue storage media that is replaced at least every 72 hours. If the media is not changed, *processing shall* be initiated within 96 hours of *recovery*.

E2.530 Prevention of Matrix Deterioration

(C, V, OA, S)

To prevent drying and possible cellular and extracellular matrix deterioration, the *tissue shall* be kept moist at all times during *processing* using a *sterile* solution/medium. If drying does not impact *quality* for intended use (e.g., decellularized dermis), the requirement to prevent drying is not applicable.

E2.540 Additives

When applicable, the type, amount, concentration, and method of incorporation/addition of all media, *cryoprotectants*, and any other additives used in *processing shall* be specified in the *SOPM*. This information about the *allograft shall* be made available to the implanting/*transplanting* physician, upon request.

E2.600 In-Process Controls

In-process controls shall be applied as necessary and according to the *SOPM* during *processing* and packaging to ensure that each process meets requirements specified in the *SOPM*. The *tissue bank shall* determine when, which, and how controls are to be performed (e.g., residual moisture testing, microbial cultures of *tissue*, solutions, packaging, equipment, pH measurements, or post-thaw sperm *quality*). Sampling for *in-process controls shall* be designed to be representative of the materials to be evaluated.

Process control procedures shall be designed to assure that *tissue* has the identity, characteristics, and *quality* intended. *Procedures* and any changes in these *procedures shall* be reviewed to ensure that such changes are *verified*, or where appropriate *validated*, before implementation.

E2.610 Tolerance Limits of Processed Tissue

Tissue banks that process tissue shall include in their *SOPM* a description of the final types of *tissue*, any specifically required or specifically prohibited dimensions or characteristics, and the means used to assess these characteristics. At or near the end of *processing, tissue shall* be evaluated according to these *procedures* to determine whether it is in conformance with the *SOPM*. Relevant *tissue* dimensions or characteristics *shall* be *recorded*. All *tissue* deemed to be out of conformance *shall* not be released for *transplantation*.

This inspection, the staff involved, and the *disposition* of each *tissue* unit *shall* be documented.

E2.611 Tissue Measurement

Tissue measurement *shall* be performed and documented and *must* include the quantity or other characteristics of the *tissue* expressed as applicable (e.g. volume, weight, dimensions, cell density, number of viable cells or a combination of these).

(C) *Allograft* heart valve grafts *shall* be inspected, evaluated, and sized by internal valve annulus diameter, and *recorded* in millimeters (mm).

The length of the aortic conduit, main pulmonary artery, and the left and right pulmonary arteries *shall* be *recorded* in millimeters (mm) or

centimeters (cm).

- (V) *Vascular tissue* grafts shall be inspected, evaluated, and sized by diameter and *recorded* in millimeters (mm).

The length of the vascular segment shall be *recorded* in centimeters (cm).

(MS, OA)

Radiographic techniques *may* be used as needed.

E2.612 Calcium Residuals: Demineralized Bone

- (MS) Unless bone is treated by a *validated* process to reduce minerals, representative samples of each *lot* shall be tested for residual calcium by a standard method.

Residual calcium content for bone *labeled* as demineralized shall not exceed 8% by a standard method.

For bone that has been subjected to a demineralization process with a residual calcium content target that exceeds 8% when tested, the *tissue* must not be *labeled* as demineralized and *should* be labeled as partially demineralized to describe the extent of demineralization.

E2.620 In-House Laboratory Testing

If the *tissue bank* performs laboratory tests and results are used to determine acceptability of *tissue* for *transplantation*, the requirements at K2.100 and K2.200 shall apply.

E2.621 Laboratory Records

Records of in-house laboratory testing shall include, at a minimum:

- 1) sample source and quantity;
- 2) *tissue identification number*;
- 3) test date and identification of the person performing the test;
- 4) assay methods;
- 5) calculations, graphs, and charts, if used;
- 6) test results as well as interpretation of results;
- 7) testing or standardization of reference standards, reagents, or standard solutions; and
- 8) *record* review by an individual other than the operator generating the *records* to ensure compliance with *Standards*.

E2.700 Tissue Preservation

E2.710 Lyophilization

Validated procedures for lyophilizing tissue shall be established and described in the SOPM. Each lyophilization cycle shall be monitored and recorded for shelf temperature, condenser temperature, and vacuum. Residual moisture measurement shall not exceed a limit linked to tissue quality. The analytical method selected must be validated for its intended use. The final container shall maintain these moisture requirements for the indicated expiration period.

E2.720 Dehydration/Desiccation

Validated procedures for dehydration or desiccation of tissue shall be established and described in the SOPM. Quality control parameters shall be established and verified for each batch.

If a residual moisture limit has been established for *finished tissue*, the *container shall* maintain the limit for the duration of the expiration period. The residual moisture level *shall* not exceed a limit linked to *tissue quality*. The analytical method selected *must be validated* for its intended use.

E2.730 Freezing Tissue

Procedures for freezing tissue shall be established and documented to maintain tissue quality.

E2.740 Cryopreservation

Except for *reproductive tissue*, *tissue to be cryopreserved must be frozen at a controlled and monitored, predetermined rate with compensation for heat of crystallization/latent heat of fusion to a predetermined end-point. Documentation of the concentrations of cryoprotectant and nutrient or isotonic solutions in the cryopreservative solution shall be maintained. When applicable, procedures for cryopreservation shall be established and the method controlled to maintain tissue quality.*

(R) *Procedures for cryopreservation of reproductive tissue shall be established and documented. If a controlled rate chamber is being utilized, the thermal profile for each cryopreservation cycle shall be logged with the specimen records.*

E2.741 Control-Rate Freezing: Surrogate Packages

If surrogates are used for monitoring the freezing program, the packaging *shall* be regularly inspected and solutions and *tissue* changed when indicated. Monitoring for deterioration of the packaging *shall* be performed. The *processing center shall* have a procedure describing the assembly of such surrogates and a means for monitoring their integrity.

E2.742 Termination of Freezing Program

Upon termination of the freezing program, the *cryopreserved tissue shall* immediately be placed in *storage*. Temperature fluctuation and cycling *should* be avoided.

E2.743 Freezing Profile

If a programmed control-rate freezing method is employed, a *record* of the freezing profile *shall* be evaluated and approved and become a permanent part of the *processing records*.

E2.750 Chemical Preservation

(BT, MS)

Procedures for the *preservation* of *tissue* by chemical means *shall* be *validated* and documented. When chemical *preservation* has been used, the *package insert shall* so indicate.

E2.800 Sterilization/Disinfection of Tissue

Individual *processing* facilities *shall* *establish, validate,* and document *disinfection* or *sterilization* regimens and microbial surveillance methods. The *SOPM shall* *establish* a list of organisms that necessitate discard, *sterilization* and/or *disinfection* of *tissue*. The list *shall* be based upon not only the category type of *tissue* but also the method by which the *tissue* was *processed* (e.g., *cryopreserved MS tissues* that cannot be *sterilized* and can only be *disinfected* and rendered culture negative).

The following are considered to be pathogenic, highly virulent *microorganisms* that *shall* result in tissue discard unless treated with a *disinfection* or *sterilization process validated* to eliminate the infectivity of such organisms:

(C, V, CT)

- 1) *Clostridium*;
- 2) fungi (yeasts, molds); and
- 3) *Streptococcus pyogenes* (group A strep.).

(MS, OA)

- 1) *Clostridium*; and
- 2) *Streptococcus pyogenes* (group A strep.).

(S)

- 1) *Clostridium*;
- 2) *Enterococcus* sp.;
- 3) fungi (yeasts, molds);
- 4) gram negative bacilli;
- 5) *Staphylococcus aureus*; and
- 6) *Streptococcus pyogenes* (group A strep.).

E2.810 Non-Terminal Irradiation

A dose is selected to reduce or eliminate *bioburden*. The selected dose *shall* be justified and any *claims* made *must* be supported by data. The type of irradiation *shall* be indicated on the *container label* or *package insert* of all *tissue* exposed to *non-terminal irradiation*.

E2.820 Terminal Sterilization by Irradiation

The most common sources of ionizing radiation are Cobalt 60, electron beam, and X-ray. Identification of the irradiation source, the dosimetry, and completed certificate of irradiation *shall* be documented in the *processing record*. The *sterilization* dose used *must* be *validated* and supported by data. A *sterility assurance level* (SAL) *shall* be selected and the *sterilization* dose *must* be shown to be capable of achieving that SAL.

Validation methods generally are *bioburden*-based methods (e.g., AAMI/ISO 11137), but other methods can be justified. The type of irradiation *shall* be indicated on the *container label* or *package insert* of all *tissue* exposed to irradiation.

E2.830 Sterilization by Other Methods

Tissue sterilization by other methods (other than by irradiation) *shall* be documented in the *processing record*. This includes the type of *sterilization*, the *processing* parameters, and certification of *sterilization*. The *process* utilized to *sterilize* the *tissue* *must* be *validated* and supported by data. A *sterility assurance level* (SAL) *shall* be selected and the method *must* be shown to be capable of achieving that SAL. *Validation* methods generally are *bioburden*-based methods (e.g., AAMI/ISO 11137), but other methods can be justified. The type of *sterilization* method used *shall* be indicated on the *container label* or *package insert* of all *tissue* exposed to the method.

Following ethylene oxide *sterilization*, *procedures* *shall* be *established* to ensure appropriate aeration has eliminated residual ethylene oxide and/or its breakdown products.

Residual Level in Parts per Million			
Tissue Size/Weight	Ethylene Oxide	Ethylene Chlorohydrin	Ethylene Glycol
Very Small (<100 mg)	2,500	2,500	5,000
Small (<10 grams)	250	250	5,000
Medium (10–100 grams)	100	100	2,000
Large (>100 grams)	25	25	500

E2.840 Disinfection by Chemical Agents

(MS) Iodophors, ethanol, and other solvent/detergent combinations *may* be used as *disinfectants* of bone in a *validated processing procedure*. In any instance where a chemical *disinfectant* or antibiotic agent is used, the *container label* or the *package insert* *shall* identify presence of possible trace residuals. Refer to G3.120.

E2.850 Other Disinfection Agents

(BT, MS)

Other agents such as heat, ultraviolet radiation, or exposure to antibiotics *may* be used as *disinfection agents*. *Procedures* for *processing* with such agents *shall* be documented and *validated* to ensure consistency in *tissue processing*.

E2.900 Processing and Preservation Records

A *record shall* be created to document the *processing* and *preservation* of *tissue*. *Processing* and *preservation records shall* include the following:

- 1) *processing* dates and responsible *processing* personnel;
- 2) *tissue identification number(s)* and type(s) of *tissue* being *processed*;
- 3) *tissue* measurements (e.g., weight, dimensions, volume), as appropriate;
- 4) expiration, where applicable;
- 5) type and quantity of *tissue* sampled for *in-process controls*;
- 6) final *disposition* of each *tissue* obtained and/or *processed*; and
- 7) the type, *lot* number, manufacturer (unless *recorded* in other *records*), and expiration date, where applicable, of *critical* reagents, supplies and materials, and the identification of *critical* equipment, used to *process* and/or *preserve tissue*.

E3.000 STORAGE

E3.100 Quarantine

E3.110 Quarantine Areas

Quarantine tissue storage areas including *storage* areas within freezers, refrigerators or other *tissue storage* units, *shall* be physically separated and clearly *labeled* to distinguish *quarantine tissues* from *tissues* not suitable for *transplant* and from *tissues* available for *distribution*.

E3.120 Situations Requiring Quarantine

Human *tissue shall* be *quarantined* until the *tissue* is either determined to be suitable for *processing*, *transplantation* or another appropriate *disposition* is accomplished. All *tissue shall* be *quarantined* until the following criteria for *donor* eligibility are satisfied:

- 1) all required infectious disease testing has been completed, reviewed by the *responsible person*, and found to be negative or non-reactive; and
- 2) *donor* screening has been completed, reviewed by the *responsible person*, and determined to indicate freedom from risk factors for and clinical evidence of HIV, hepatitis B, and/or hepatitis C infection.

Tissue shall be *quarantined* at any phase of the operation when its release could affect the

safety, effectiveness, or *quality* of the *tissue*, and subsequently, the health of the *recipient*.

The following *tissue shall be quarantined*:

- 1) *tissue* that is pending completion of *processing*, packaging, *preservation*, or *labeling* and final-release-approval *signature*;
- 2) *tissue recovered, collected, or acquired* from *donors* not meeting *established donor eligibility criteria*, including unacceptable test results;
- 3) *tissue* involved in a *recall* pending investigation, documentation, and *resolution*;
- 4) *tissue* failing to meet technical or *quality assurance* specifications;
- 5) *tissue* pending discard as medical waste; and
- 6) *tissue* returned by a *consignee*, pending evaluation.

E3.130 Labeling Quarantined Tissue

All human *tissue processed* or shipped prior to determination of *donor eligibility must be under quarantine*. Such *tissue shall be accompanied by records* assuring identification of the *donor* and indicating that the *tissue* has not been determined to be suitable for *transplantation*. *Tissue* determined to be unsuitable for *transplantation* and intended for release for other purposes *shall be identified accordingly*.

E3.140 Quarantine Records

Quarantine records for tissue quarantined post-release shall indicate the reason for quarantine and the final disposition of the tissue. Release dates or disposal dates *shall be indicated as well*.

E3.200 Segregation of Tissue

The *SOPM must address whether the segregation of tissue during storage is indicated and how it will be appropriately segregated to avoid contamination, cross-contamination and mix-ups*.

Except for *reproductive tissue*, considerations for assessment of risk include, where applicable:

- 1) *donor* infectious disease test results are unavailable or this testing will not be performed;
- 2) the intended use of the *tissue* is primarily for *transplantation* or is restricted to research or education;
- 3) *autologous tissue* is segregated from *allogeneic tissue*;
- 4) the *donor* has been determined to be ineligible;
- 5) the ability of *packaging and labeling* to withstand *storage* temperatures; and/or
- 6) the ability to *decontaminate storage equipment or the storage area* should an *accident* occur.

Appropriate segregation *must include considerations above and storage must be in clearly defined*

and labeled areas (shelves or compartments) of the *storage* equipment or *storage* area.

- (R) *Cryopreserved reproductive tissues* from untested *client depositors* shall be stored in a physically separate area clearly defined from those of tested *client depositors*. *Tissues* from *client depositors* known to be reactive on tests for anti-HIV-1, anti-HIV-2, anti-HCV, or HBsAg or any other test excluding CMV without subsequent negative confirmatory testing as approved by the *reproductive tissue bank's* Medical Director shall be stored in a physically separated area clearly identified from *tissue* of seronegative *client depositors*. See F2.200 for documentation required for release.

E3.300 Storage Temperatures

Each *tissue bank* shall establish acceptable temperature-range limits for the *storage* of *tissue* before and after *processing* in accordance with these *Standards*, applicable laws and regulations and in consideration of *tissue quality* and the *packaging* system for the *tissue*.

- (A) *Storage* temperatures and conditions shall be the same as for comparable *allogeneic tissue*. Any exception shall require written approval of the Medical Director of the *tissue bank*.

E3.310 Frozen and Cryopreserved Tissue

(MS, OA)

Procedures for storing processed frozen and *cryopreserved tissue* to ensure graft safety and quality shall be written. *Processed* frozen or *cryopreserved musculoskeletal tissues* shall be stored at temperatures of -40°C or colder. Temporary *storage* of *processed* frozen or *cryopreserved musculoskeletal tissue* between -20°C and -40°C is limited to six months total.

(C, V) *Cryopreserved cardiac tissue* and *vascular tissue allografts* shall be maintained at temperatures of -100°C or colder.

(R) *Reproductive tissues* shall be stored either in liquid nitrogen or in the vapor phase of liquid nitrogen.

(S) Frozen or *cryopreserved skin* shall be stored at ultra-low (-40°C or colder) temperatures.

E3.320 Lyophilized/Dehydrated/Desiccated Tissue

Lyophilized, dehydrated, or desiccated tissue must be stored at ambient temperature or colder.

E3.330 Monitoring Storage Temperatures

A temperature monitoring system shall be utilized to document temperatures and to alert staff when temperatures have strayed outside acceptable limits. *Procedures* shall be in place for reviewing temperatures. Documentation of such review shall be indicated with the reviewer's initials and the date. If temperature *recording* charts are used, they shall be initialed and dated when placed on and also when removed from the *storage* unit. Completed charts shall be retained for the duration specified in C1.300. If *storage* utilizes liquid nitrogen, either liquid nitrogen levels or temperature shall be monitored and documented at an interval specified in the *SOPM*.

E3.331 Storage Conditions for Commonly Transplanted Human Tissue

Storage Conditions for Commonly Transplanted Human Tissue		
Human Tissue	Storage Conditions	Temperature (°C) *
<i>Birth tissue (BT)</i>	Frozen, refrigerated, cryopreserved, lyophilized, dehydrated, desiccated	<i>Established by the tissue bank</i>
<i>Cardiac (C), vascular tissue (V)</i>	Frozen, cryopreserved	-100°C or colder
<i>Cellular tissue (CT)</i>	Refrigerated	Above freezing (0°C) to 10°C
	Frozen, cryopreserved	<i>Established by the tissue bank</i>
<i>Musculoskeletal tissue (MS), osteoarticular graft (OA)</i>	Refrigerated	Above freezing (0°C) to 10°C
	Frozen, cryopreserved (temporary storage for 6 months or less)	-20°C or colder to -40°C (this is warmer than -40°C but colder than -20°C)
	Frozen, cryopreserved (long term storage)	-40°C or colder
	<i>Lyophilized, dehydrated, desiccated</i>	Ambient **
<i>Reproductive tissue (R)</i>	Frozen, cryopreserved	LN ₂ (Liquid or Vapor Phase)
<i>Skin (S)</i>	Refrigerated	Above freezing (0°C) to 10°C
	Frozen, cryopreserved	-40°C or colder
	<i>Lyophilized, dehydrated, desiccated</i>	Ambient **
* Warmest target temperature unless noted to be a range		
**Ambient temperature monitoring not required for <i>lyophilized, dehydrated, or desiccated tissue</i>		

E3.340 Emergency Transfers

Policies and *procedures shall* be developed for the emergency transfer of *tissue* to designated alternative *storage* facilities and for alternative monitoring methods in the event of mechanical failure or loss of coolant. These *shall* include specification of *tolerance limits* or temperatures and time limits after which the initiation of the emergency transfer is required. Actions to be taken when limits have been exceeded *shall* also be specified in the *SOPM*.

E3.400 Expiration Date/Storage Period

The maximum *storage* period for *tissue shall* be appropriate to the type of *tissue*, method of *preservation*, required *storage* temperature, *packaging*, and *processing*, as well as to its intended application. Expiration dates *shall* be qualified to demonstrate that the *packaging* system or *container* is suitable to maintain *tissue quality* (e.g., sterility, moisture content) through the expiration date.

- (A) The implanting physician *shall* be informed of any expiration dates.

E3.410 Refrigerated Tissue

- (A) *Autologous skin* that has not been *processed* or *preserved* should be stored refrigerated for no longer than 14 days.

SECTION F TISSUE RELEASE

F1.000 TISSUE RELEASE

Prior to release of *tissue for transplantation*, the Medical Director or licensed physician designee *shall* determine *donor* eligibility. All necessary information *shall* be complete and compiled in a standardized format prior to final review and determination of *donor* eligibility and *tissue* acceptability for *transplantation*. Each *donor record* *shall* contain a *disposition/release* statement and *signature* of both the Medical Director or licensed physician designee who is assuming responsibility for *donor* eligibility determination and, if different, the individual(s) responsible for reviewing all technical and *quality control* specifications. If *processing* was performed, there *shall* be documentation of a review by designated personnel of all technical and *quality control* specifications. An *SOPM* *shall* clearly define the responsibilities of each reviewer.

F1.100 Donor Eligibility Review

The eligibility of each *donor* *shall* be determined by the Medical Director or licensed physician designee upon review of all *records* as specified below and in accordance with the *SOPM*.

Although the *donor risk assessment interview* may be preliminarily reviewed by technical staff to evaluate acceptability for *recovery, acquisition, collection, or processing, tissue* *shall* not be released for *transplantation* without determination of *donor* eligibility by the Medical Director or licensed physician designee.

F1.110 Records for Review

The Medical Director or licensed physician designee *shall* determine *donor* eligibility based on a review and evaluation of the *donor's relevant medical records* or a summary of these generated by a trained individual. The determination of eligibility *shall* be based on the *SOPM*, these *Standards* and applicable laws and regulations. The *donor* eligibility review *shall* include, but is not limited to these *records*:

- 1) acceptability of the *authorization* or *informed consent*;
- 2) suitability of the *recovery site*, delivery environment, or where *collection* took place;
- 3) pertinent information from the medical *records* generated at the time of death, including any pathology and laboratory reports, physician summaries, and transfusion/infusion information;
- 4) *the donor risk assessment interview*;
- 5) all results of laboratory testing relevant to *donor* eligibility;
- 6) any *plasma dilution* calculations used to determine the acceptability of the blood sample used for testing;
- 7) all relevant culture results up to and through the completion of *recovery*

(e.g., blood cultures, if performed; *pre-sterilization/pre-disinfection cultures*, if available);

- 8) applicable time limits for *tissue recovery*;
- 9) pertinent circumstantial and *donor* screening information relayed to *tissue bank* staff;
- 10) results of the *physical assessment* or *physical examination*;
- 11) the autopsy report, or a summary of findings, if an autopsy was performed; and
- 12) any other information gathered for the purposes of disease screening as required by *Standards* and applicable laws or regulations.

In the case of pediatric *donors* who have been breastfed within the past 12 months and/or are 18 months of age or less, the birth mother's risk for transmissible disease *shall* be evaluated for HIV, HBV, HCV and other infectious agents when indicated. See Appendix II.

For all *donors* one month (28 days) of age or less, the infant and the birth mother *shall* be screened for risk of *relevant communicable disease agents and diseases* (RCDAD) and the mother's blood *must* be tested. Refer to D4.100 (BT) for expectations to obtain the health status of the infant *donor* of *birth tissue*.

Once the determination is made, the *donor* eligibility statement *shall* be documented, dated, and signed by the Medical Director or licensed physician designee.

F1.111 Absence of Third Party Records

When no *third party records* are available that can be used to establish a likely cause of death, and if no autopsy was performed, a *certified copy* of the death certificate *must* be included in the *donor record*. If it is not possible to obtain a *certified copy*, a *verified copy* of the death certificate *must* be included in the *donor record*.

When *third party records* are available that can be used to establish a likely cause of death, or if an autopsy was performed, obtaining a *certified copy* or *verified copy* of the death certificate is voluntary.

F1.112 Autopsy Report

If an autopsy was performed, the *tissue bank's* Medical Director or licensed physician designee *shall* review the autopsy report or a summary of findings prior to the release of *tissue* to inventory. If a copy of the autopsy report is not available for the *donor's record*, the cause of death and other pertinent autopsy findings *shall* be documented in the *donor's record*.

If it is determined that an autopsy was not performed due to infectious disease risk or, if an autopsy was performed, if any special precautions were taken that would suggest risk of a communicable disease in the *donor*, this information *should* be considered.

In the case of suspected Sudden Unexpected Infant Death (SUID), an autopsy *should* be performed and results reviewed to confirm the cause of death.

(DM) After the *dura mater* has been *recovered*, a qualified pathologist *shall* perform an examination of the *donor's* brain. Following fresh examination, the brain *should* be fixed and sliced, gross examination of the entire brain *should* be conducted (including multiple cross sections), and multiple specimens of *tissue should* be obtained (from different parts of the brain, e.g., frontal and occipital lobes) for histological examination. The gross and histologic findings *must* be assessed for any evidence suggestive of transmissible spongiform encephalopathy (TSE).

F1.120 Infectious Disease Risk Review

Tissue shall not be *distributed* from a *donor* who, or a *donor* whose birth mother, has engaged in behaviors defined as high risk for transmission of *relevant communicable disease agents or diseases* (RCDADs). This information *shall* be obtained via a *donor risk assessment interview, physical assessment or physical examination*, and by review of other available *relevant medical records*.

The Medical Director or licensed physician designee *shall* not determine an *allogeneic donor* eligible with any of the following findings:

- 1) evidence of significant active infection at the time of donation for *relevant communicable disease agents or diseases* (RCDADs). These include, but are not limited to: septicemia, viral disease (e.g., HIV, viral hepatitis, West Nile virus, rabies, Ebola virus disease, Zika virus infection, etc.), human transmissible spongiform encephalopathies, untreated syphilis, clinically active tuberculosis, leprosy (Hansen's disease) or systemic mycosis; and/or
 - 2) risk factors for *relevant communicable disease agents or diseases* (RCDADs) as specified in Appendix II.
- (R) *Semen donors shall* not exhibit an infectious skin disease that creates a risk of contamination of the *semen*. For all *reproductive tissue donors*, there *shall* not be evidence of infection within the past twelve months with *Chlamydia trachomatis* and/or *Neisseria gonorrhoea* unless the *reproductive tissues* are *collected* by a method that ensures freedom from contamination of the *tissue* by infectious disease organisms that may be present in the genitourinary tract.

F1.130 Other Medical Conditions

In addition to the infectious disease risk review, the Medical Director *shall* establish criteria and evaluate *tissue donors* for conditions that may adversely affect the *safety* or utility of the specific types of *tissue processed* and/or *distributed* by the *tissue bank*. Such conditions include, but are not limited to:

- 1) history of autoimmune diseases;
- 2) current or prior diagnosis of malignancy and the evaluation *shall* include the type of malignancy, clinical course, and treatment prior to acceptance;
- 3) ingestion of, or exposure to, toxic substances;

- 4) genetic, metabolic, traumatic, or infectious diseases that may adversely affect the *quality* of specific *tissues*;
- 5) previous surgery; and
- 6) diseases of unknown etiology.

F1.140 Interpretation of Infectious Disease Test Results

Disposition of allogeneic *tissue shall* be based upon the interpretation of all infectious disease test results and *shall* be as follows:

- 1) Human *tissue shall* be determined not to be suitable for *transplantation* if from a *donor* whose specimen has tested repeatedly reactive on an FDA-licensed, approved, or cleared *donor* screening test for anti-HIV-1, anti- HIV-2, HBsAg, anti-HBc, or anti-HCV. When a birth mother's specimen is used for testing, these same rules apply.
- 2) Viable leukocyte-rich *tissue* (e.g., semen) *shall* be determined not to be suitable for *transplantation* if from a *donor* whose specimen has tested repeatedly reactive (RR) on an FDA-licensed, approved, or cleared *donor* screening test for anti-HTLV-I or anti-HTLV-II.

The eligibility of other human *tissue* for *transplantation* from *donors* whose specimens test RR for anti-HTLV-I or anti-HTLV-II *shall* be determined by the Medical Director.

Note: Law and/or regulation, including, where applicable, foreign laws and/ or regulations, may differ in regard to a RR HTLV antibody test result and how this impacts the suitability of the *donor's tissues* for *transplantation*.

- 3) Human *tissue shall* be determined not to be suitable for *transplantation* if from a *donor* whose specimen had a final test result of positive, repeat reactive, or repeatedly reactive on a screening test using a NAT assay. When a birth mother's specimen is used for testing, these same rules apply.
- 4) If a laboratory that performs organ *donor* testing performs the initial testing in duplicate or triplicate, the *tissue bank must* obtain and review the results of all individual tests performed. If any one of those initial tests is reactive or positive, the *tissue shall* be determined not suitable for *transplantation*.
- 5) *Tissue* from a *donor* reactive for syphilis using an FDA-licensed, cleared, or approved **non**-treponemal screening assay *may* be used for *transplantation* only if the sample is found to be negative using an FDA-licensed, cleared or approved treponemal-specific confirmatory assay. If initial testing was performed using an FDA-licensed, cleared, or approved treponemal-specific assay and was reactive, the *tissue shall* not be used for *transplantation*.
- 6) If results of additional infectious disease testing are received for tests that are not required, such test results *must* be included in the *donor's record* and any results from those tests *must* be considered when determining *donor* eligibility.

Procedure(s) *shall* be established for the interpretation of additional infectious disease test results.

NOTE: For international members that do not export *tissues* to the U.S., applicable requirements of the government/competent authority regarding test kit licensing/approval apply.

- (A) Determination of the final *disposition* of *tissue* in which a *donor's* blood sample tests positive is the responsibility of the *autologous donor's* physician. If *tissue* from a *donor* who tests positive is to be *stored* in a *tissue bank*, refer to E3.200.
- (R) Determination of the use of *client depositor* and/or *directed donor reproductive tissues* in cases where required test results are positive or repeatedly reactive *must* be documented according to protocols described at F2.200 (see note for CMV below).

Tissue from an *anonymous semen donor* who tests reactive for an active, acute infection with cytomegalovirus (CMV) *shall* not be deemed suitable for use. *Tissue* from an *anonymous semen donor* determined to be in a latent CMV status *may* be acceptable. Each *reproductive tissue bank* *shall* develop a *procedure* for determining eligibility for both *anonymous* and *directed donors*. *Procedures* *must* also include provisions for communicating CMV status to the *end-user* physician such that a decision can be made regarding use of *tissue* from a CMV positive (total IgG plus IgM) *donor*.

Tissue from a *donor* testing positive for *Chlamydia* or *Gonorrhea* *shall* not be suitable for use.

F1.200 Technical Review

Tissue *may* be released for *transplantation* only with notation in *processing records* by *responsible persons* that *tissue* produced meets technical specifications set forth in the *SOPM* (e.g., dimensions, quality) and that *processing* was performed according to the *SOPM*. There *must* be a *signature* by technical staff indicating that all technical elements were reviewed.

For contractual *processing* arrangements, *tissue* *shall* be released for *transplantation* by the distributing *tissue* bank only with a *signature* and written *disposition*/release statement or equivalent documentation from the *processing* center indicating that all *quality* measures were reviewed and determined to be acceptable according to the written *SOPM*. The written *disposition*/release statement or equivalent documentation *shall* indicate that the following conditions, at a minimum, have been met:

- 1) review of *tissue* processed for consistency with specific *tissue* requirements;
- 2) review of all *processing* and packaging bacteriologic testing results for completeness and acceptability;
- 3) review for completeness and acceptability of any test or environmental testing results generated;

- 4) review of all *lot* numbers and expiration dates *recorded* for *verification* of completeness and that all were within acceptable ranges (e.g., recovery kits, culture media, *processing* solutions);
- 5) review of all *processing records* for completeness and accuracy, and *verification* that *tissue* was *processed* in accordance with the *SOPM* and met defined specifications;
- 6) review and comparison of *tissue* obtained and units produced from each *tissue* for *verification* that the *disposition* of each *tissue* *recovered, acquired, or collected* is *traceable*;
- 7) *verification* that all (if any) *error* and *accident* reports potentially related to the *safety* or quality of the *tissue* to be released are resolved and *corrections* made where appropriate;
- 8) *verification* that all *processing* was accomplished within time limits specified in the *SOPM* and within applicable technical specifications in the *SOPM* (e.g., acceptable residual moisture, irradiation exposure limits, temperatures, and freezing curves); and
- 9) if *tissue* was recovered or collected by another entity, *verification* that the shipment was acceptable when it arrived at the *processing* center (e.g., with respect to temperature and time limits).
 - (A) If *autologous tissue* is *processed*, the *autograft* may be released for *clinical use* only upon notation in *processing records* by technicians or their supervisor that *processing* was performed according to the *SOPM*. There *must* be a *signature* by technical staff indicating that all technical elements were reviewed.

F1.300 Quality Review

Except for *reproductive tissue*, *tissue* shall not be released for *transplantation* without a *signed disposition/release* statement from the *responsible person(s)* at the site of *distribution*, indicating that, at some time prior to release, all *quality* measures were performed and found acceptable according to the written *SOPM*. The written *disposition/release* statement or equivalent documentation shall indicate that the following conditions, at a minimum, have been met:

- 1) review of *tissue processed* for consistency with specific *tissue* requirements;
- 2) review and comparison of *tissue* obtained and grafts produced from *tissue* for *verification* that the *Disposition* of *tissue* recovered is *traceable*;
- 3) *verification* that all (if any) *error* and *accident* reports, potentially related to the *safety* or quality of the *tissue* from each *donor*, are resolved and *corrections* made where appropriate;
- 4) *verification* that all *processing* was accomplished within time limits specified in the *SOPM* and within applicable technical specifications in the *SOPM* (e.g., acceptable residual moisture, irradiation exposure limits, temperatures, and freezing curves);
- 5) if *tissue* was *recovered* by another entity, *verification* of the acceptability of the shipment upon arrival at the *processing* center (e.g., with respect to temperature and time limits);
- 6) *verification* that the Medical Director or licensed physician designee has made a

decision regarding *donor* eligibility and that all directives of the Medical Director regarding the *donor* were implemented; and

- 7) *verification* that final *labeling* of *tissue* was performed in accordance with *SOPM* and *Standards*.
- (R) *Reproductive tissue shall* not be released for clinical use without a *signed*, written *disposition/release* statement of the person responsible for authorizing release, at the site of *processing*, indicating that all *quality* measures were reviewed and found acceptable according to the written *SOPM*. This includes, but is not limited to:
 - 1) review of *donor* age and of *tissue processed* for consistency with specific *tissue* requirements;
 - 2) *record* and *verification* that all *lot* numbers and expiration dates were complete and that all were within acceptable ranges (e.g., *cryopreservation* media);
 - 3) review of all *processing records* for completeness and accuracy and *verification* that the *tissue* was *processed* in accordance with the *SOPM* and meets defined technical specifications;
 - 4) review of *tissue* obtained and specimens produced from each *collection* for *verification* that the *disposition* of each *tissue* specimen is *traceable*;
 - 5) *verification* of *resolution* of all *error* or *accident* reports (if any) potentially related to the *safety* or *quality* of the *tissue*;
 - 6) *verification* that all *processing* was accomplished within time limits specified in the *SOPM* and within applicable technical specifications in the *SOPM* (e.g., ejaculate volume, sperm motility, concentration, morphology, and post-thaw motility);
 - 7) if *reproductive tissue* was collected by another entity, *verification* of the time of receipt at the *reproductive tissue bank* and condition of the sample upon receipt; and
 - 8) *verification* that the Medical Director has made a decision regarding *donor* eligibility and that all directives of the Medical Director regarding the *donor* were implemented.

F1.310 Review of On-Site Processing Records

If *processing* was performed on site, there *shall* also be written documentation that all *quality* measures were performed and acceptable according to the written *SOPM*. This includes but is not limited to:

- 1) review of all *processing* and packaging bacteriologic testing results for completeness and acceptability;
- 2) review of all test or environmental testing results generated for completeness and acceptability;
- 3) review of all *lot* numbers and expiration dates *recorded* (e.g., materials such as recovery kits, culture media, *processing* solutions) for *verification* that all were

within acceptable ranges; and

- 4) review of all *processing records* for: completeness and accuracy; *verification* that *tissue* was *processed* in accordance with the *SOPM*; and conformance to defined technical specifications.

F2.000 OTHER RELEASE

F2.100 Tissue Release Based on Tissue Utility

Pre-established release criteria based on *tissue* utility *must* be developed. If *tissue* other than *reproductive tissue* is *distributed* or dispensed for *transplantation*, there *shall* be in each instance, documentation of:

- 1) *donor* eligibility and *tissue processing* information available at the time of release. All *donor* eligibility requirements in F1.100 *must* be met with the exception of a review of the autopsy report (if applicable) and pending culture results;
- 2) Medical Director or licensed physician designee review of all relevant information present;
- 3) approval of the release by the Medical Director or licensed physician designee;
- 4) a written statement issued to the *end-user* physician indicating what information required by the *SOPM* and/or these *Standards* is available and what information is not available for review, and when it is expected that the information will be available; and
- 5) a statement from the *end-user* physician indicating his/her understanding that the *tissue* is being released using available information.

Relevant final results *shall* be forwarded promptly to the *end-user* physician upon completion of testing. Documentation of the release based on *tissue* utility *shall* be maintained in the *donor record*. These *records shall* be maintained together or summarized in a log.

F2.200 Special Circumstances in Release of Reproductive Tissues

(R) Release of *reproductive tissue* may be considered in the special cases of:

- 1) *reproductive tissues* from *client depositors* known to be reactive on tests for anti-HIV-1, anti-HIV-2, anti-HCV, HBsAg, or any other test, excluding CMV, without subsequent negative confirmative testing as approved by the Medical Director; or
- 2) *reproductive tissues* from *client depositors* that have not been tested or do not meet current *Standards*; or
- 3) *directed donors* who have completed all required testing and screening according to *Standard* but:
 - a) had reactive test results; or
 - b) are determined ineligible according to screening criteria.

In the case of release for one of the three circumstances listed above, the following documentation is required (refer to G3.210 and G3.220 for *labeling* requirements):

- 1) a written statement *signed by a responsible person at the reproductive tissue bank* disclosing the *deviation(s)* from *Standards* and description of potential risks to the *recipient*; and
- 2) acknowledgement from the medical provider indicating he/she:
 - a) has received the written statement from the *reproductive tissue bank* and acknowledges the *deviation(s)* from *Standards*;
 - b) has had ample opportunity to discuss the implication(s) with a *responsible person* at the *reproductive tissue bank* and other medical authorities;
 - c) agrees to fully explain the implication(s) to the *recipient* and provide her ample opportunity to ask questions and consult with experts of her choice; and
 - d) will document *informed consent* from the *recipient*.

F2.300 Shipping Reproductive Tissue in Quarantine

If *donor reproductive tissue* is to be released before completion of the *donor eligibility assessment*, the *tissue must* be kept in *quarantine* during shipment. The labeling *must* include a statement that the *donor eligibility assessment*, has not yet been completed. It *must* also include a statement indicating the *reproductive tissue must* not be *transplanted* or *transferred* until the *donor eligibility assessment*, is complete.

F3.000 TISSUE FAILING REVIEW PROCESS

Tissue failing any portion of the review process *shall* be maintained in *quarantine* pending *resolution* or disposal and *shall* not be released for *transplantation*. Unexplained discrepancies or *deviations* from specifications *shall* be fully investigated and documented.

F3.100 Ineligible Donors

If a *donor* is deemed ineligible as a result of *donor eligibility assessment* or disease screening procedures, the finding *shall* be specifically stated in the *donor record* and in the release/*disposition* decision statement, and this determination *must* be described and communicated in writing in a timely manner to the *tissue bank* that *recovered tissue*. If the *tissue* is to be made available for nonclinical purposes from a *donor* who has been determined to be ineligible based on the results of required testing and/or screening, it *must* be *labeled*:

- 1) “For Nonclinical Use Only”; and
 - 2) with the biohazard legend.
- (SB) Permanent and temporary deferrals of living *surgical bone donors* and the reason(s) for such deferral *shall* be documented in the *donor record*.

F3.200 Technical or Quality Assurance Assessments

If *tissue* is deemed unsuitable for release for *transplantation* for reasons other than *donor eligibility*, the *processing* and release/*disposition* decision *records shall* specifically describe the reason(s) for the determination. If this *tissue* is to be made available for nonclinical purposes it

must be labeled “For Nonclinical Use Only.”

F4.000 TISSUE TRANSFER

F4.100 Transfer to Distribution Inventory

Before *tissue* is transferred to *distribution* inventory, appropriate release documentation *shall* be *verified*. *Tissue* for *transplantation* may then be placed in *distribution* inventory. The identification of the *tissue* transferred, date of transfer, and staff performing the *verifications* and transfer *shall* be documented.

F4.200 Transfer to Other Inventory Locations

Disposition of *tissue* that is transferred *shall* be documented (e.g., discard, research, further *processing*). Date of transfer, staff involved, and *verification* of *tissue* identity *shall* also be documented.

SECTION G LABELING

G1.000 LABELS AND LABELING

G1.100 Nomenclature

Nomenclature used to describe *tissue*, cultures, blood specimens and other *donor* specimens (e.g., lesions, lymph nodes) *shall* be specified in the *SOPM* and be applied consistently. For *finished tissue*, units of measurement and the *processing* that *tissue* has received *shall* also be specified in the *SOPM*.

G1.200 Label List

A list of *labels* used *shall* be maintained, as well as an example of every *label* that is utilized by the *tissue bank*. Dates of use (start and discontinuance) *shall* be *recorded*. Changes pertaining to *labels* and communicating changes *shall* be expected from *tissue banks* that supply *labels* to other *tissue banks* and *tissue distribution intermediaries*.

G1.300 Labeling Integrity

Labels shall be designed and *qualified* to be legible, indelible, and affixed firmly to the *container* under anticipated *storage* conditions for length of use. See K1.200. *Labels* applied by *tissue bank* staff *shall* not be removed, altered, or obscured except to correct *labeling errors*. When applicable, this also applies to *labeling materials*. Suppliers of *labels* deemed *critical* are responsible for *establishing* specifications.

G1.400 Claims

All *labeling claims shall* be clear, accurate, substantiated, and not misleading.

G2.000 LABELING PROCESS

G2.100 General Requirements

There *shall* be *SOPs* established and followed to ensure that approved *labels, labeling, and packaging* materials are used for *tissue*. *Tissue labeling shall* be documented at each step (e.g., *unprocessed, in-process, quarantined, rejected, released*).

G2.200 Relabeling

If *tissue* is to be *re-labeled* for any reason, such as *label* detachment or to correct a *labeling error*, the *tissue bank shall* establish a *relabeling procedure* delineating the methods to be utilized, conditions under which *tissue may* be *re-labeled*, and the staff authorized to perform such activities. The reasons for, and events surrounding, the *relabeling of tissue shall* be documented in the *records*. *Relabeling methods shall* consider *storage* conditions and *label* integrity (see G1.300).

G2.300 Controls

Labeling control procedures *shall* be *established* to ensure *label* integrity, legibility and accuracy, and the *establishment* of checks to prevent transcription and other *labeling errors*. Electronic *labeling* systems *shall* possess adequate controls to prevent the erroneous *labeling* of *tissue*. *Labeling* reviews and checks *shall* be documented and *shall* be included in the *records*. If a sampling plan is used, it *must* follow a statistically valid method, such as ANSI/ASQ Z1.4: Sampling Procedures and Tables for Inspection by Attributes. The *labeling* area *shall* be inspected prior to the start of *labeling* activities to ensure that all *labels* and *packaging* materials from previous *labeling* have been removed. The inspection of the area *shall* be documented and included in the *records*.

G2.310 Label Inspection

Labels *shall* meet written specifications and be approved by *quality assurance* staff prior to release for use by a designated person. *Labels* not meeting such specifications *shall* be discarded. Date of receipt, date of inspection, and the names of the staff involved in receipt and inspection *shall* be documented.

G2.320 Label Storage

The storage area for *labels* and *labeling materials* *shall* be clearly identified. Access *should* be restricted to authorized personnel only. This is not applicable to *labels* included in *tissue recovery* packs.

G2.330 Labeling Process Controls—Obsolete Labels

Procedures *shall* be *established* to retrieve obsolete and/or outdated *labels* and *labeling materials* from all *labeling* areas and inventory locations. As each type of *label* is removed from inventory, one *label* *shall* be retained for the archives and the surplus *labels* *shall* be discarded. The *label* list and the *SOPM* *shall* be updated accordingly.

G2.340 Tissue and Container Visual Inspection

Prior to *labeling* a unit of *processed tissue*, the *container* *shall* be inspected for evidence of impurities, defects, broken seals, or contamination that could compromise the *quality*, or *safety* of the *tissue*. A sufficient area of the *container* *shall* remain uncovered to permit inspection of the contents whenever possible. Any *tissue* or *container* suspected of not meeting specifications *shall* be *quarantined* immediately pending further investigation and *resolution* following *established procedures* in the *SOPM*. This review *shall* be documented.

G3.000 LABELING INFORMATION

G3.100 Container Labels

G3.110 Design

Container labels *shall* be designed to facilitate the use of uniform *labeling* techniques for each type of *tissue*.

G3.120 Content

Except for *autologous tissue* and *reproductive tissue*, *container labels shall* include:

- 1) the *tissue identification number*;
- 2) descriptive name of the *tissue* and other information necessary for selection or use (e.g., size, right/left, medial/lateral, anterior/posterior);
- 3) expiration date (if applicable), including the month, day, and year or, if only the month and year are used, the expiration date *must* be clearly described in *labeling* as occurring at the beginning or the end of the month;
- 4) *storage* conditions, including recommended *storage* temperature and/or *storage* temperature range;
- 5) quantity or other characteristics of *tissue* expressed as applicable (e.g., volume, weight, dimensions, cell density, number of viable cells or a combination of these);
- 6) a reference to the *package insert*.

The following information *shall* be included on the *container label* unless space limitations require use of a corresponding insert:

- 1) *disinfection* or *sterilization procedure* utilized (if applicable);
- 2) *preservative* (if utilized) and/or method of *preservation* (if applicable);
- 3) potential residues of *processing* agents/solutions (e.g., antibiotics, ethanol, ethylene oxide, dimethylsulfoxide); and
- 4) name(s) and address(es) of *tissue bank(s)* responsible for determining *donor* eligibility, *processing* and *distribution*. Should more than two *tissue banks* be involved, the name of all *tissue banks* are required but the address is only required for the *tissue bank* determining *donor* eligibility.

(A) The following information *shall* be included on the *container label* for *autologous tissue* unless space limitations require use of a corresponding insert:

- 1) the *donor* classification statement “AUTOLOGOUS DONOR”;
- 2) definitive *autologous donor* identifying information such as the patient’s hospital identification number, social security number, birth date, etc.;
- 3) a *label* or attached tag “FOR AUTOLOGOUS USE ONLY”; and
- 4) if infectious disease testing or *donor* screening is not complete or has not been performed, a *label* indicating “NOT EVALUATED FOR INFECTIOUS SUBSTANCES” is required; or
- 5) if infectious disease testing was performed and any results were positive, or if *donor* screening was performed and risk factors identified, then *labeling*

with a “BIOHAZARD” *label* is required.

- (R) Cryocontainers (e.g., vials, straws or ampules) *shall* be *labeled* so as to identify:
- 1) *donor* or *client depositor* unique identifier and/or other code that can be used by the *reproductive tissue bank* to identify the date the specimen was *cryopreserved* and the stage of development at *cryopreservation*, where applicable; and
 - 2) name, initials, or other code that can be used to identify the *reproductive tissue bank* at which the specimen was *processed*.

G3.200 Summary of Records and Package Insert

Tissue determined to be suitable and released for *transplantation* *shall* be accompanied by a *summary of records* and *package insert*. A *summary of records* is not required if a *donor* eligibility determination is not required (i.e., *autologous tissue* and certain types of *reproductive tissue*).

G3.210 Summary of Records Content

A *summary of records* is required when *donor eligibility assessment* has been completed and *shall* include:

- 1) a statement that the *tissue* was prepared from a *donor* determined to be eligible based on the results of screening and testing. All results of relevant communicable disease tests performed on specimens from the *donor* and used for release of *tissue* *shall* be listed. Relevant tests include those tests that are required (see D4.230). For example, the CMV test result used *must* be listed for *reproductive tissue*. If a test for anti-HTLV I and/or anti-HTLV II was performed it *must* be reported;
- 2) the name and address of the establishment that made the *donor eligibility assessment*; and
- 3) a statement that the communicable disease testing was performed by a laboratory registered with *FDA* to perform *donor* testing and certified to perform such testing on human specimens in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493, or that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services (CMS).

NOTE: For international members that do not export *tissues* to the U.S., applicable requirements of the government/competent authority having jurisdiction apply in regard to required *labeling* involving *donor* infectious disease test results.

- (R) A statement noting the reason for the determination of ineligibility in the case of *tissue* from a *directed donor* who is ineligible based on screening and/or testing.

G3.220 Package Insert Content

The *summary of records* may be included in the *package insert*. The *package insert* shall contain the following information:

- 1) a statement limiting use to specific health professionals (e.g., physicians, dentists, and/ or podiatrists);
- 2) a statement that the *tissue* is intended for use in one patient, on a single occasion only, or as is applicable for *reproductive tissue*;
- 3) known contraindications (if any) to the use of the *tissue*;
- 4) warnings and list of known possible significant adverse reactions;
- 5) a statement that *adverse outcomes* potentially attributable to the *tissue* must be reported promptly to the *tissue* supplier;
- 6) presence of known sensitizing agents (if any);
- 7) a statement that indicates that the *tissue* may transmit infectious agents;
- 8) a statement, if applicable, that the *tissue* may not be *sterilized* or *re-sterilized*.
- 9) dosage information (if applicable);
- 10) description of how the *tissue* was supplied (e.g., frozen, *lyophilized*, irradiated, demineralized or partially demineralized, see E2.612);
- 11) type of antibiotics present (if applicable);
- 12) concentration of *preservative(s)* and/or *cryoprotectant(s)* in final package solution (if applicable);
- 13) instructions for opening the *package* and/or *container*;
- 14) instructions for preparation of *tissue* for *transplantation*;
- 15) expiration time of *tissue* following reconstitution (upon preparation for use);
- 16) instructions indicating that once a *container* seal has been compromised, the *tissue* shall be either *transplanted*, if appropriate, or otherwise discarded;
- 17) acceptable *storage* conditions and *tolerance limits*;
- 18) special instructions required for the particular *tissue*, when applicable (e.g., “DO NOT FREEZE,” “DO NOT X-RAY,” “DO NOT IRRADIATE”);
- 19) a statement that it is the responsibility of the *tissue dispensing service*, *tissue distribution intermediary*, and/or *end-user* clinician to maintain *tissue* intended for *transplantation* in appropriate *storage* conditions prior to further *distribution* or *transplant* and that *recipient records* must be maintained for the purpose of *tracing*

tissue post-transplantation;

20) a statement that the *tissue* is “DONATED HUMAN TISSUE,” when applicable;
and

21) effective date or other traceable version identifier.

NOTE: Except for *client depositors, directed donors of reproductive tissues, and autologous tissues*, the accompanying *records* required by this section *must* not contain the *donor’s* name or other personal information that might identify the *donor*.

(C, V) Inserts for *cardiac tissue* and *vascular tissue* shall contain the following additional information:

- 1) warning against using a graft if there is evidence that the *container* has broken or the contents have thawed;
- 2) statement that the *end-user* may not subject the *tissue* to *sterilization* (e.g., DO NOT STERILIZE the *allograft* by any method. Exposure of the *allograft* and the *packaging* to irradiation, steam, ethylene oxide, or other chemical sterilants will render the *allograft* unfit for use);
- 3) *donor* age (and blood type, if available);
- 4) date of dissection or *preservation*;
- 5) *tissue warm ischemic time*;
- 6) *tissue cold ischemic time*;
- 7) graft sizes (e.g., diameter and length);
- 8) graft physical descriptions and evaluations, including description of imperfections and evaluation criteria;
- 9) the type of *cryoprotectant* (if applicable) and clear statement regarding the possibility of residuals;
- 10) a description of the temperature-sensitive nature of the grafts; and
- 11) instructions for preparation of *tissue* for use.

Center-specific protocols shall be established for control of proper thawing, removal of *cryoprotectant*, and restoration of isotonic balance within the *cryopreserved tissue*. These protocols shall be provided with each cardiovascular *allograft* distributed for *transplantation*.

The preparation instructions shall be sufficiently detailed and unambiguous to allow operating room personnel of average skill to follow and complete the *procedure* successfully.

(R) See F2.200 for additional requirements that may be applicable in certain *directed*

donor or client depositor situations.

Reproductive tissue in the following categories require additional information in *package inserts* as listed below:

- 1) If the intended *recipient* is the sexually intimate partner of the *gamete* provider(s):

Note: a *Summary of records* is not required for this category.

- a) For all *reproductive tissue*, include the statement: “For use by Sexually Intimate Partner Only.”
 - b) For all reproductive *client depositors* who were not tested or screened using all parameters required for either a *semen* or egg *donor*, including the required tests and time limits for *donor* testing, include the statements:
 1. “Not evaluated for Infectious Substances”; and
 2. “WARNING: Advise Recipient of Communicable Disease Risks.”
 - c) For all reproductive *client depositors* who have reactive or positive test results:
 1. biohazard symbol; and
 2. “WARNING: Reactive test results for (insert name of test).”
- 2) If the intended recipient is NOT the sexually intimate partner of either *gamete* provider, the following *labeling* is required in addition to a *summary of records*:
 - a) *Directed donors (semen, oocyte, and/or embryo)* with reactive test results:
 1. biohazard symbol;
 2. “WARNING: Reactive test results for (insert name of test)”; and
 3. “WARNING: Advise Recipient of Communicable Disease Risks.”
 - b) *Directed donors (semen, oocyte, and/or embryo)* determined to be ineligible based upon risk factors for or clinical evidence of relevant communicable disease agents or diseases, including the *physical examination*:
 1. biohazard symbol; and
 2. “WARNING: Advise Recipient of Communicable Disease Risks.”

- 3) If the intended *recipient* is NOT the sexually intimate partner of either *gamete* provider, and the *tissue* is from *anonymous* or *directed embryo donors* in cases where the *gamete* provider(s) was (were) not initially tested as *donors*, but were re-tested following 6-month *quarantine*, include the statement: “Advise *recipient* that screening and testing of the *donor(s)* were not performed at the time of *cryopreservation* of the *reproductive tissue*, but have been performed subsequently.”

(Note: A *summary of records* is not required for this category, however, a summary of the test results *must* be included.)

- 4) If the intended *recipient* is NOT the sexually intimate partner of a *gamete* provider who initially *cryopreserved reproductive tissue* as a *client depositor* but was subsequently screened and tested as a *directed donor* in cases where additional *collections* are unavailable, include the statement: “Advise *recipient* that screening and testing of the *donor(s)* were not performed at the time of *cryopreservation* of the *reproductive tissue*, but have been performed subsequently.”

- 5) *Reproductive tissue* intended for research:

- a) *Client depositor reproductive tissue* when *gamete* provider(s) were not tested or screened using all parameters required for either a *semen* or *egg donor*, including the required tests and time limits for *donor* testing, or *donor (anonymous or directed) tissue* has not completed 6-month *quarantine* release requirement:

1. “For Non-Clinical Use Only”; and
2. “Not evaluated for Infectious Substances.”

- b) *Anonymous donor tissue* that has completed 6-month *quarantine* release requirement:

1. “For Non-Clinical Use Only.”

- c) *Client depositor* or *donor (anonymous or directed) tissue* from *gamete* provider(s) who had reactive test results OR have been determined to be ineligible:

1. biohazard label;
2. “For Non-Clinical Use Only”; and
3. if applicable, “WARNING: Reactive test results for (insert name of test).”

G3.300 Transport Package Label Content

G3.310 Domestic Shipments

The transport *package label* shall include the following information:

- 1) name, address and telephone number of the *distribution* facility;
- 2) name and address of the destination;
- 3) prominent identification of contents as “DONATED HUMAN TISSUE.” Note: If the *reproductive tissue* in the shipment was *collected* from a *client depositor*, prominent identification as “HUMAN TISSUE”;
- 4) recommended *storage* conditions;
- 5) *validated* expiration date/time of the transport *package* when the *storage* temperature *must* be controlled;
- 6) type and quantity (when the quantity is applicable) of refrigerant or other hazardous materials enclosed-in the transport *package*; and
- 7) any special handling instructions, when applicable (e.g., “DO NOT FREEZE,” “DO NOT X-RAY,” “DO NOT IRRADIATE”).

G3.320 International Shipments

Labels for international shipments *shall* contain all of the information required for domestic shipments; however, information *may* be modified to meet requirements of the federal government and those of the receiving country.

SECTION H DISTRIBUTION AND DISPENSING

H1.000 DISTRIBUTION AND DISPENSING

There *shall* be *SOPs* for the following: receipt of *tissue* orders, unit selection, final *container*, and/or *package* inspection, shipping, and transportation of *tissue* for *transplantation*.

H1.100 Tissue Distribution and Dispensing Restrictions

Provision of *tissue* for *transplantation* *shall* be restricted to hospitals, free-standing medical facilities, *tissue banks*, *tissue dispensing services*, and *end-users* (e.g., physicians, dentists, podiatrists or other medical professionals) for use in *recipients* with the *veterinary use* exception that follows. Human *tissue* for *transplantation* *shall* not be offered, *distributed* or dispensed for *veterinary use* unless such use is specifically granted in a *document of gift/authorization* or in a *record of informed consent*. If *tissue* is provided to a *tissue distribution intermediary*, the *tissue distribution intermediary* *shall* meet the requirements of Section M of these *Standards*. Controls *must* exist to ensure distribution restrictions are met such as those found on the *document of gift/authorization* or in a *record of informed consent*. *Distribution* restrictions *must* be communicated to distributors. Periodic *verification* of activities performed by the *tissue distribution intermediary* *shall* be documented (e.g., a paper *audit*, on-site *audit*, on-site inspections, etc.). See B1.520.

H1.110 Client Depositor Authorization

- (R) *Reproductive tissue* *shall* be released for use by the *client depositor* or the *client depositor's* sexually intimate partner only. Prior to release of the specimens, a statement containing a *verified signature* from the *client depositor* *shall* be obtained indicating the relationship between the intended *recipient* and the *client depositor*.

Reproductive tissue for potential therapeutic insemination, use in another *assisted reproductive technology procedure*, or for other specified *disposition* *shall* be released as per written authorization of the *client depositor*, if of legal age or, if not, by that of parent, legal guardian, or his/her legally appointed designee.

H1.120 Reproductive Tissue Distribution Restrictions

- (R) A *client depositor* who requests that his/her *reproductive tissue* be *distributed* to a *recipient*, who is not the *client depositor* or who is not the sexually intimate partner of the *client depositor*, *shall* be treated as a *directed donor(s)*. All *directed donor(s)* *must* be fully tested and screened in a manner consistent with *donor* protocols and these *Standards*. If additional *collections* of *reproductive tissue* are unavailable due to the infertility or health condition of the now *directed donor*, appropriate measures *should* be taken to screen and test the *directed donor* prior to *distribution* (excluding testing for *Neisseria gonorrhoea* and *Chlamydia trachomatis*). Alternatively, the *client depositor* *reproductive tissue* may be *distributed* in *quarantine* with proper *labeling* to clearly identify the *donor* eligibility assessment is not yet complete. See F2.300.

Reproductive tissue shall not be distributed to private individuals unless the request is in the form of a physician's written order for such distribution.

H1.130 Donor Conceived Offspring Limitations

- (R) A written policy addressing limitation of the number of offspring by a *gamete donor shall be established*. The policy shall include the upper limits deemed acceptable to the *reproductive tissue bank* and shall describe the methods that will be used to comply.

H1.200 Distributing Tissue to Other Tissue Banks/Dispensing Services

When a *tissue bank distributes tissue* obtained from another *tissue bank* or *tissue distribution intermediary*, all accompanying original *labeling materials* or other enclosures shall be distributed with the *tissue*.

H1.210 Consignment Inventory Management

If *tissue* is provided on *consignment*, the *distributing tissue bank shall maintain procedures* to ensure *traceability* and that appropriate *storage* conditions are maintained during *consignment*, transfer or return.

H1.300 Requests for Donor Status and Tissue Processing Information

Donor risk assessment, tissue-related information, and tissue processing details shall be made available to the end-user upon request, except such information that may infringe upon the confidentiality of donor information.

H1.400 Distribution Records

Records shall be maintained by the tissue bank that distributes tissue (including unfinished or as yet unreleased tissue) to other entities. These records shall be designed to permit tissue to be traced from the donor to a consignee or end-user, and from a consignee or end-user back to the donor. Tissue distribution records shall include:

- 1) date of order placement;
- 2) name and address of *consignee*;
- 3) name of individual placing the order;
- 4) type and quantity of *tissue* ordered;
- 5) information pertaining to *tissue* shipped including:
 - a) identification number(s) of *tissue(s)*;
 - b) *collection* and/or expiration date of *tissue*;
 - c) date of shipment;
 - d) type of refrigerant, and quantity of refrigerant when applicable, in the shipment;

- e) mode of transportation and/or courier; and
 - f) name of the staff member filling the order.
- 6) identifying information, if available, about the intended *recipient*.

H1.410 Responsibility

The *tissue bank shall establish recipient* follow-up data collection protocols, and *procedures* to evaluate information received.

H2.000 TISSUE FOR RESEARCH

Facilities providing *tissue* for research and other non-transplantation purposes *shall* develop detailed relevant specific policies and *procedures*. *Informed consent* or *authorization* for research and/or education *shall* be obtained. See the *series of standards* at D2.000 and D3.000.

H2.100 Written Requests

All requests for human *tissue* intended for research use *shall* be submitted in writing. The request *shall* indicate the type of *tissue* requested and how it will be used as well as the name, address and affiliation of the principal investigator accepting responsibility for receipt of the *tissue*.

H2.200 Review and Approval

Tissue requests for research purposes *shall* be reviewed and approved based on legal, ethical, and technical considerations defined in the *SOPM*.

H3.000 PACKAGING AND SHIPPING

H3.100 Solutions

Any specifically required solutions not readily available to the *end-user* that are needed to prepare the *tissue* for use *shall* be made available to the utilizing facility.

H3.200 Integrity

Packaging shall be designed to ensure *tissue* quality and prevent contamination of the contents of the final *container(s)*.

H3.300 Tissue Storage Environment

Maintenance of defined environmental conditions during transit *shall* be required. Specific environmental conditions *shall* be in accordance with the *SOPM*, these *Standards* and applicable laws and regulations.

H3.400 Validation and Expiration of Transport Package

If *tissue* to be shipped requires specific environmental conditions other than ambient temperature, the capability of the transport *package* to maintain the required environmental

conditions *shall* be demonstrated and documented in a *validation* study. The length of time that these conditions can be maintained by the transport *package shall* also be determined and documented. Expiration dates (and time if applicable) of the transport *package shall* be noted on the outside of the transport *package*.

H3.500 Quality Control of Reusable Shipping Packages

If *tissue* to be shipped requires specific environmental conditions other than ambient temperature, and the transport *package* can be reused, *QC* monitoring of *the* transport *packaging must* be performed according to the *SOPM* to verify package integrity has been maintained. These *QC* checks *shall* be documented.

H3.600 Pre-shipping Inspection

Prior to shipping, *packages shall* be *inspected* to ensure the external *packaging* and *labels* are undamaged, the *tissue* is not expired and the *tissue* being shipped is consistent with the *tissue* requested. The exterior of the transport *package shall* be inspected to *verify* that requirements in G3.310 are met. These inspections *shall* be documented, including identification of staff conducting inspections.

H3.700 Transportation

The mode of transportation selected *shall* be determined by any special shipping and handling requirements of the *tissue* and/or shipping refrigerants, by shipping restrictions of commercial carriers, and the urgency of the *tissue* request.

H4.000 RETURN OF TISSUE

A *tissue bank shall* establish a policy authorizing or prohibiting the return of *tissue* in its original, unopened *container*. If returns are permitted, the integrity of the *container*, *package*, and *labeling shall* be examined for evidence of contamination or tampering. If there is any evidence of contamination, tampering, mishandling, or failure to maintain required *storage* temperatures, *tissue shall* not be returned to *distribution* inventory. Information pertaining to the return of *tissue shall* be *recorded* in the *disposition records* for that shipment of *tissue* as follows:

- 1) documentation of *package* and/or *container* examination;
- 2) documentation of *end-user* handling, *storage*, and shipping conditions;
- 3) reason for the return;
- 4) *disposition* of the returned *tissue(s)*; and
- 5) date and name of the staff member authorized to evaluate and determine the *disposition* of the *tissue(s)*.

H4.100 Temperature Records

For *tissue* that requires controlled environmental temperatures, at a minimum, documentation is required that attests the *tissue* was maintained at required *storage* temperatures.

H5.000 FIELD CORRECTIONS AND REMOVALS

Tissue banks shall have specific written policies and procedures for the initiation and performance of a field correction or removal, if applicable. Procedures shall include, but are not limited to, the following:

- 1) evaluation and determination by a *responsible person(s)*;
- 2) timely identification and management of affected inventory;
- 3) assessment of associated health risk;
- 4) field communications (e.g., *field notification*);
- 5) types of *field corrections* or *removals* (e.g., *recall, market withdrawal*) and *stock recovery*;
- 6) reporting requirements;
- 7) evaluation of effectiveness;
- 8) termination or closure;
- 9) documentation and *record* requirements; and
- 10) review by *management with executive responsibility*.

Tissue banks not directly responsible for conducting field corrections or removals, but that perform activities that could lead to the need for a field correction or removal (e.g., tissue recovery, donor screening, donor testing) shall have policies and procedures for the timely notification of all affected parties regarding information related to tissue safety or regulatory requirements.

H5.100 Circumstances That May Require Field Correction or Removal

The need to perform a *field correction* or *removal* may be identified as a result of a *complaint, adverse outcome, accident, error, deviation, audit*, or by any other means. An evaluation to determine if *field correction* or *removal* is warranted *should* be made whenever *distributed tissue* may not meet specifications related to *safety, quality, traceability*, identification, function and/or use. This evaluation *must* consider both risk to health posed by the *tissue* and applicable regulatory requirements, and be documented.

H5.200 Notification Responsibilities

Upon discovery of the need for *field correction* or *removal*, the *tissue bank* shall promptly notify all entities to which affected *tissue* was *distributed* or dispensed as well as the *tissue bank* that *recovered* the *tissue*, if applicable.

H5.300 Handling of Tissue

All *tissues* not already *transplanted*, which are subject to *field correction* or *removal*, shall be located and *quarantined* pending *resolution* of the issue.

H5.400 Reporting Requirements

Tissue banks shall comply with all field correction and removal reporting requirements for

applicable federal, state and international government/competent authorities under which they operate or *distribute tissue*.

For additional information, refer to FDA Guidance for Industry: Product Recalls, Including Removals and Corrections at:

<http://www.fda.gov/safety/recalls/industryguidance/ucm129259.htm>

H5.500 Field Correction and Removal Records

All information relating to the *field correction* or *removal* of *tissue* and resulting communications *shall* be documented and retained on file at least 10 years beyond the date of *distribution*, the date of *transplantation* (if known), *disposition*, or expiration of the *tissue*, whichever is latest. The file *shall* include the following information:

- 1) events precipitating the *field correction* or *removal*;
- 2) identification and location of affected *tissue*, including *quarantine* steps;
- 3) associated risk assessment;
- 4) type of *field correction* or *removal* (e.g., *recall*, *market withdrawal*) and *stock recovery*;
- 5) steps taken to correct or retrieve *tissue*;
- 6) documentation of all related communications (e.g., phone calls and/or written correspondence, including copies of *field notifications* or letters and a list of those to whom notice was sent);
- 7) final *disposition* of the *tissue*;
- 8) copies of reports to regulatory authorities, accreditation organizations and certification bodies, if required;
- 9) *corrective actions* recommended and implemented; and
- 10) documentation of review; if of a medical nature, review by the Medical Director or licensed physician designee.

SECTION J GENERAL OPERATIONS

J1.000 STANDARD OPERATING PROCEDURES MANUAL (SOPM)

Each *tissue bank shall* develop written detailed policies and *procedures* in a standardized format, which *shall* be collected into a *standard operating procedures manual (SOPM)*. These *shall* be available at all locations for which they are designated, used, or otherwise necessary, and *shall* be utilized to ensure that all *tissue* released for *transplantation* is in compliance with these *Standards* and applicable laws or regulations.

J1.100 Identification and Control

Policies and *procedures shall establish* a document control system for *procedures* and forms including requirements for:

- 1) approval prior to use for intent and compliance to relevant regulatory requirements and standards;
- 2) reviewing revisions and re-approval as needed;
- 3) identification of the current revision status and of changes to previous revisions;
- 4) distribution to points of use (i.e., all locations where access to *procedures* is needed);
- 5) legibility and ease of identification; and
- 6) prevention of the unintended use of obsolete documents and suitable identification controls for archived documents.

J1.200 Contents

The *SOPM shall* specifically include, but *shall* not be limited to policies and *procedures* for:

- 1) *informed consent* or *authorization*, *donor* eligibility criteria, *donor* screening methods, time limits for *tissue recovery*, notification of confirmed positive test results, information sharing, construction of *records*, and, if applicable, reconstruction and final disposition of a deceased *donor's* body (*series of standards* at C2.000, D2.000, D3.000, D4.000 and D5.000);
- 2) *tissue collection*, *recovery*, *acquisition* and handling, including *recovery site* assessment, *recovery*, materials management/supplies management, *processing*, packaging, *quarantine*, *labeling*, *storage*, *donor* eligibility review, and ~~for~~ release of *tissue* (*series of standards* at D5.000, D6.000 and Sections E, F and G);
- 3) laboratory tests performed in-house, including establishment of appropriate specifications, standards, and test *procedures* to assure that *tissue* is safe and *quality* is addressed; and for contracted laboratory testing defining which tests *shall* be performed and how test results *shall* be received, reviewed, interpreted, and managed (B1.600, *series of standards* at D4.200, *series of standards* at F1.100, F1.200, F1.300 and F2.000, *series of standards* at K1.300, *series of standards* at K2.000);

- 4) purchasing controls, order receipt, *finished tissue* selection, final *container* inspection and packaging and shipping of *tissue*, as well as criteria for returning and reissuing *tissue* (K1.300, *series of standards* at M3.000, M4.000, M5.000 and Section H);
- 5) external audits for services, suppliers, contractors, and consultants, when indicated (*series of standards* at K6.000, and K1.300 and B1.520);
- 6) record management to maintain *traceability*, retain records, and facilitate (if necessary) *field corrections* and *removals*, and *recipient* notification by documentation of each step of *tissue* production from the point of *collection*, *recovery* and identification to final *distribution* of the *tissue* (*series of standards* at C1.000, H5.000, L4.000, M6.000 and M7.000);
- 7) *quality assurance* and *quality control* of supplies, equipment, instruments, reagents, *labels*, and processes employed in *tissue collection*, *recovery*, *acquisition*, *processing*, packaging, *labeling*, *storage*, *distribution*, and preparation of *tissue* for *transplantation*, including policies or *procedures* for:
 - a) labeling of cultures, blood specimens and other *donor* specimens (e.g., lesions, lymph nodes) (D4.350, *series of standards* at D5.000, and Section G);
 - b) monitoring *storage* temperatures, for defining *tolerance limits*, and for describing what, when, and how *corrective actions* are to be taken for implementing emergency transfers and determining alternative *storage* and monitoring methods for *tissue* and reagents (F4.200, *series of standards* at E4.000 and M2.000);
 - c) investigating, documenting and reporting *accidents*, *errors*, *complaints*, and *adverse outcomes* (*series of standards* at K4.000);
 - d) performing *field corrections*, *removals*, and *stock recoveries*, if applicable, and ~~of~~ the timely notification of affected parties regarding information related to *tissue* safety or regulatory requirements (*series of standards* at H5.000, L6.000 and M6.000);
 - e) of notifying *management with executive responsibility* of any *field corrections*, ~~or~~ *removals*, *stock recoveries*, investigations, inspection reports, or regulatory actions (*series of standards* at H5.000 and K4.000);
 - f) supplies, reagents, materials and equipment and identifying those that are considered *critical* (D5.100, E2.000, E2.400, J5.100);
 - g) maintaining equipment management programs that include inspection, maintenance, repair and calibration for the purpose of maintaining equipment (*series of standards* at J5.000);
 - h) describing the receipt, identification, storage, handling, sampling, testing, and subsequent approval or rejection of *containers*, packaging materials, *labels*, reagents, and supplies (*series of standards* at D5.000, E1.000, and E2.000, J5.500 and Section G); and
 - i) monitoring *in-process controls* and managing events such as failed test runs and failure of a *lot* to meet established specifications (Section K).

- 8) assigning time limits and temperature for pre-*processing quarantine storage, processing*, and expiration dates (E2.520, E3.400, H3.400 and K1.200);
- 9) handling requests for research *tissue (series of standards* at D1.200, H2.000);
- 10) disposing of medical waste and other hazardous waste (*series of standards* at J3.000);
- 11) covering emergency and safety including reporting of staff injuries and potential exposure to blood-borne pathogens (*series of standards* at J3.000);
- 12) maintaining the sanitation of facilities and describing the cleaning schedules, methods, equipment and materials to be used (*series of standards* at J4.000 and J5.000);
- 13) describing the design or arrangement of the physical plant to meet operational needs such as designation of spaces, environmental monitoring, and security (*series of standards* at J4.000);
- 14) describing manual methods for tissue banking activities in the event of electronic or equipment malfunction (*series of standards* at K7.000);
- 15) describing training program requirements for technical and *QA* staff (*series of standards* at J2.000); and
- 16) identifying and controlling *procedures* and forms including requirements (J1.100, J1.400).

J1.300 Implementation

The *SOPM* and associated *process validation* studies *shall* be reviewed and approved by appropriate individuals as dictated by content. All policies and *procedures* of a medical nature *shall* be reviewed and approved by the Medical Director. Upon implementation, all portions of the *SOPM* *must* be followed as written. Minor *deviations* from the *SOPM* *may* be authorized in writing by the Medical Director, or *QA* designee provided the *deviation* is in compliance with these *Standards*.

J1.400 Modifications

The *SOPM* *shall* be updated to reflect modifications or changes, and *shall* include a description of the change, justification for the change, identification of the affected documents, the *signature* of the approving individual(s), the approval date, and when the change becomes effective.

Prior to implementation, each modification shall be approved by appropriate individuals or the Medical Director, as dictated by content, and training *shall* be provided to pertinent staff. Implementation dates *shall* be recorded for all affected *procedures*. Obsolete documents *shall* be promptly removed from all points of use or otherwise prevented from unintended use.

J1.500 References

Copies of publications cited in support of policies or procedures *shall* be maintained at the *tissue bank*.

J1.600 Annual Review

An annual review of the *SOPM*, and the safety manual if separate, *shall* be performed and documented:

- 1) the Medical Director *shall* review relevant policies and procedures of a medical nature (e.g., *donor eligibility, adverse outcomes*);
- 2) *management with executive responsibility*, or a *responsible person* designee, *shall* review policies and *procedures* to ensure adequacy in regard to current practice, and applicable standards, laws or regulations; and
- 3) staff *shall* review policies and *procedures* for which they have been trained and are currently responsible.

J1.700 Staff Access and Review

Current copies of the *SOPM* applicable to specific staff functions *shall* be in designated locations and available to the staff at all times. New and revised policies and *procedures shall* be reviewed by applicable staff prior to implementation. Documentation of review and any associated training *shall* be maintained at least 16 years after termination of employment or as required by applicable laws or regulations, whichever is longer.

J1.800 Inspections

The *SOPM shall* be made available for inspection upon request by the AATB or authorized regulatory agencies.

J1.900 Archives

A file of archived *SOPs shall* be maintained in historical sequence for 16 years after discontinuation. The *records shall* indicate the inclusive dates that each policy and/or *procedure* (including forms, letters, *labels*, and other specific documents) was in use.

J2.000 TECHNICAL AND QUALITY ASSURANCE STAFF—TRAINING/CONTINUING EDUCATION

J2.100 Training

Training *shall* be conducted for technical and *QA* staff to maintain *competency* in *procedures* and familiarity with applicable regulations and AATB *Standards*. Training *shall* encompass the following areas, as applicable: new employee orientation; the *SOPM*; technical training; *QA*; *electronic systems*; and continuing education. All training activities *shall* be documented. Training *records shall* be retained for 16 years after termination of employment or as required by law, whichever is longer.

- 1) Personnel *shall* be made aware of their designated functions and of the consequences of the improper performance of their designated functions.
- 2) Personnel performing *verification* and *validation* activities *shall* be made aware that *accidents* and *errors may* occur during the performance of their designated functions.

(SB) Training *shall* be conducted to maintain *competency* in *procedures* and familiarity with appropriate regulations and AATB *Standards*. Training *shall* be conducted for all staff whether they are employees of the *tissue bank*, contracted employees, or other individuals (e.g., hospital staff) who are responsible for determining *donor* eligibility, or recovering, or packaging the tissue.

J2.200 Competency

Technical staff *must* demonstrate *competency* for their designated functions (including a thorough understanding of relevant policies, *procedures*, *process controls*, and regulatory requirements).

J2.300 Continuing Education

Technical staff *shall* participate in continuing education, which may include training courses, technical meetings, and any other educational programs pertaining to designated functions. Such participation *shall* be documented.

J2.400 Training Records

Training *records shall* be maintained for each employee with documentation of the following:

- 1) delineation of functions that each employee is authorized and trained to perform;
- 2) initial training of new employees;
- 3) initial training of newly designated functions of existing employees;
- 4) review and training prior to implementation of new and/or revised sections of the *SOPM*;
- 5) annual review of policies and procedures for the employee's designated functions, including safety *procedures* (see J1.600);
- 6) annual safety training; and
- 7) attendance at workshops, seminars, meetings, or other continuing education programs.

J3.000 SAFETY PRACTICES

J3.100 Work Environment

Each *tissue bank shall* provide and promote a safe work environment by developing, implementing, and enforcing safety *procedures*. These *procedures shall* be incorporated into the *SOPM* or reside in a specific Safety Manual which is referenced by the *SOPM*.

Procedures shall be written in accordance with applicable Occupational Safety and Health Administration (OSHA) regulations, guidelines established by the CDC, and applicable laws or regulations. All safety *procedures shall* be reviewed annually.

J3.200 Procedures

Safety *procedures shall* include, but are not limited to, the following:

- 1) instructions for contacting emergency personnel and the establishment of evacuation routes and *procedures* in the event of fire or disaster;
- 2) *procedures* for management of worker injury including possible exposure to hazardous materials or blood-borne pathogens. Such *procedures shall* require a written report of the incident, including documentation of medical care received, management notification, and actions to prevent recurrence;
- 3) delineation of Universal Precautions as defined by the CDC;
- 4) *procedures* specifying the proper storage, handling, and utilization of hazardous materials, reagents and supplies, including pertinent Safety Data Sheets; and
- 5) *procedures* outlining the steps to be followed in cleaning bio-hazardous spills.

J3.300 Hazardous Materials Training

A training program *shall* be designed to inform employees about chemical, biological, and, if applicable, radioactive hazards of the workplace as well as the use of personal protective equipment to reduce the risk of exposure to these hazards.

J3.400 Universal Precautions

Universal Precautions, as defined by the CDC, *shall* be implemented and enforced to reduce the potential exposure of staff to communicable diseases.

J3.500 Immunization

Hepatitis B vaccination *shall* be offered free of charge to all non-immune personnel whose job-related responsibilities involve the potential exposure to blood-borne pathogens. Personnel files *shall* include documentation of receipt of vaccination or refusal of immunization with hepatitis B vaccine.

J3.600 Hazardous Waste Disposal

Biohazardous human *tissue*, medical waste, and other hazardous materials *shall* be disposed of in accordance with applicable laws or regulations in such a manner as to minimize environmental impact and exposure to personnel. Medical waste and hazardous material tracking *records shall* be maintained in accordance with the regulations of the regulatory agency charged with management oversight.

J3.700 Personnel

J3.710 Attire

Personnel engaged in the *Recovery, Processing, Preservation*, or packaging of tissue shall be suitably attired. Attire shall include personal *protective equipment* to minimize the spread of transmissible pathogens among and between *donors, tissue*, and staff.

J3.720 Infections

Any staff member shown (either by medical examination or supervisory observation) to

have a serious infectious condition (e.g., an apparent illness or open lesion) that *may* adversely affect the *safety* of the *tissue shall* be excluded from the *recovery, processing, preservation, or packaging* of *tissue* until the condition is determined to be resolved. All staff members *shall* be instructed to report, to supervisory personnel, any health conditions that *may* have an adverse affect on *tissues*.

J4.000 FACILITIES

J4.100 General

The physical plant *shall* be designed or arranged to meet operational needs. The premises *shall* be maintained in a clean, sanitary, and orderly manner with adequate plumbing, drainage, lighting, ventilation, and space. Adequate, clean, and convenient hand washing facilities *shall* be available for personnel and for *donors* when applicable. Specific suitability parameters for the *recovery site* (see D5.500), or where *collection* of anonymous *semen* donation takes place, *shall* be evaluated. Areas of the facility where *donor* screening and/or obtaining *authorization* or *informed consent* takes place *should* be arranged to prevent *errors* and maintain confidentiality of information discussed.

J4.200 Designated Space

To prevent *errors* and/or *cross-contamination* of tissue, the following critical procedures shall be performed in designated areas of adequate size:

- 1) *donor* screening;
- 2) obtaining *authorization* or *informed consent*;
- 3) *processing*;
- 4) *quarantine* storage of *in-process materials*;
- 5) other *quarantining*;
- 6) *labeling*;
- 7) *storage* of *distributable* inventory;
- 8) *quality assurance/control* functions;
- 9) receipt and storage of *containers, container labels, supplies, and reagents*;
- 10) storage of medical waste;
- 11) irradiation and other *sterilization procedures*; and
- 12) final product inspection and *distribution* activities.

J4.210 Routine Decontamination and Record Retention

Facilities used for *collection, recovery, processing, or preservation, or for other* activities where there is potential for *cross-contamination* of *tissue* or exposure to

blood-borne pathogens, *shall* be subjected to routine, scheduled, documented *decontamination* (sanitation) *procedures*. Cleaning events performed by *tissue bank* personnel *shall* be documented and retained for three (3) years after their creation.

J4.300 Environmental Monitoring

Environmental monitoring procedures shall be established, where appropriate, as part of the *QA program*. Monitoring *procedures may* include, but are not limited to, *static* and *dynamic* particulate air samplings (e.g., air bacterial content assays) equipment and personnel monitoring where *tissue* contact occurs, and work-surface cultures. Frequency of sampling *shall* be based on *related industry guidelines*, the results of prior samplings or suitable justification. *Procedures shall* include *tolerance limits* and *corrective actions* to be implemented in the event that *limits* are exceeded. Each monitoring activity *shall* be documented and results trended.

Environmental monitoring at the *recovery site* is not required, however pre-established parameters designed to prevent contamination and *cross-contamination must* be met (see D5.500).

Rooms used for storage of liquid nitrogen tanks *should* be periodically monitored for oxygen levels if not appropriately ventilated.

J4.400 Security

Tissue banks shall maintain adequate physical security to safeguard *tissue* inventory and *records* as well as to prevent the entry of unauthorized individuals. Such security *may* be in the form of personnel, electronic or mechanical devices or barriers, or configuration of the physical plant. Limited access areas *shall* be established as appropriate, permitting entry of only those personnel (including auditors and inspectors) who are authorized by supervisory personnel.

J5.000 EQUIPMENT AND INSTRUMENTS

J5.100 Selection

Equipment and instruments *should* be of appropriate quality for their intended function and use. Equipment used in the *recovery, processing, preservation, packaging, or storing of tissue shall* be appropriately sized, designed, and located to facilitate use, cleaning, *decontamination*, and maintenance. Equipment *shall* be constructed so that surfaces contacting *tissue shall* not alter the *safety or quality* of the *tissue*. See E2.400.

J5.200 Operation

Equipment *shall* be operated according to manufacturer's recommendations unless it is demonstrated that modifications to operating procedures will not adversely affect either the *quality of tissue* or personnel safety. Use of instruments *shall* be appropriate for the task.

J5.300 Qualification and Maintenance

Equipment, instruments, apparatus, gauges, and recording devices *shall* be *qualified* and routinely calibrated, maintained, inspected, monitored, cleaned, *decontaminated, sterilized* (when applicable), and repaired at appropriate intervals in accordance with the *SOPM* and established equipment schedules. Calibration procedures *shall* include specific directions and limits for accuracy and precision. When accuracy and precision limits are not met, there *shall* be

provisions for remedial action to reestablish the limits and to evaluate whether there was any adverse effect on *quality*. Where appropriate, *tolerance limits shall* be specified.

J5.310 Requalification/Recalibration

Following repairs and system upgrades, equipment *should* be requalified or recalibrated according to procedures in the *SOPM* that have been designed to be in compliance with the manufacturer's requirements and recommendations.

J5.400 Decontamination

Equipment and instruments *shall* be cleaned, or *decontaminated*, and *sterilized* (when applicable) at appropriate intervals in accordance with the *SOPM* to prevent malfunction, contamination, *cross-contamination*, or accidental exposure of *tissue* or staff to blood-borne pathogens. *Procedures shall* be established to track *critical* instruments that are cleaned and *decontaminated* with any other instruments. Reusable basins or bath units used for instrument soaks/washes/rinses *must* be cleaned and *decontaminated* between uses. See recommendations in AATB Guidance Document No. 3.

Instruments used to *recover* and/or *process dura mater*, vertebrae, or ocular *tissue* that are known to have come in contact with *tissue* from a *donor* suspected or confirmed to have a prion-associated disease, *must* be removed and destroyed. *Tissues* from other *donors* for which those instruments were subsequently used for *recovery* or *processing shall* be identified, *quarantined*, withdrawn and/or *recalled* pending further evaluation.

J5.500 Sterilization

Equipment and instruments *shall* be *sterilized* if they are intended to come into contact with *tissue* or if they have the potential of contaminating *tissue*, if not *sterilized*. *Sterilization must* be performed in a manner that is consistent with applicable industry standards.

To ensure that *sterilization* is successful during routine processing of equipment and instruments, it is important that the following be performed at required or recommended intervals:

- 1) Regular maintenance of the *sterilization* equipment: The *sterilization* equipment manufacturer's maintenance recommendations *must* be met.
- 2) Use of routine *lot* release controls: Routine *lot* release controls *must* be performed according to the specifications, and at the intervals, outlined in the following table.
- 3) Performance of efficacy monitoring: The specifications and intervals for required efficacy monitoring are outlined in the following table. In addition to the specifications found in the table, additional efficacy monitoring *may* be necessary, such as leak testing, dynamic air removal testing (DART test), and Bowie-Dick testing, and process challenge device (PCD) testing. Guidance on efficacy monitoring *may* be found in *sterilization* equipment manuals, consulting with the *sterilization* equipment manufacturer, or can be found in applicable industry standards:
 - a) steam *sterilizers*: ANSI/AAMI ST79; or
 - b) ethylene oxide *sterilizers*: ANSI/AAMI ST41.

In the event that routine *lot* release controls indicate failure of the load to achieve necessary *sterilization* conditions, the *sterilizer* load contents *must* be exposed to a subsequent successful *sterilization* cycle. Frequent *sterilization* failures are often indicative of a process problem and *should* be investigated to determine the cause of failures. Investigation *may* need to include increased efficacy monitoring.

All *sterilization* accessories, to include but not limited to biological indicators, commercially available PCDs, wrappers, pouches, and *sterilization* containers, *must* be used in a manner consistent with the accessory manufacturer’s instructions for use or be *validated* appropriately for the use.

Table of Common Sterilization Methods, Cycle Parameters, Controls & Monitoring					
Method (other methods may be used)	Cycle Parameters	Routine Release Controls (for each load)		Efficacy Monitoring	
		Required	Recommended	Required	Recommended
Steam	Use the recommended parameters (e.g. exposure times, temperatures, pressures, drying times, weight and geometric complexity of load, etc.) specified in the sterilizer manufacturer’s operator’s manual, or <i>validate</i> other cycle parameters in accordance with industry standards.	<i>Verify</i> cycle parameters were met	1. Utilize internal and external chemical indicators 2. Utilize appropriate PCD and <i>verify</i> as negative prior to release of load	Weekly: Utilize appropriate PCD*	Daily: Utilize appropriate PCD
Ethylene Oxide (EO)					
Vaporized Hydrogen Peroxide (VHP)					
Irradiation (i.e. Gamma, x-ray, electron beam)	Use <i>validated</i> cycle per ISO 11137	<i>Verify</i> cycle parameters were met	N/A	Bioburden testing, dose audits and dose mapping per ISO 11137	N/A
Other (e.g., novel, nontraditional)	Follow manufacturer’s instructions for method selected. <i>Validation</i> is expected if manufacturer’s instructions are not followed.				

* Weekly use of a PCD is not required if a PCD is already being used in each load as recommended for “Routine Release Controls.”

J5.600 Storage Equipment

Equipment used for *storage of tissue shall* be identified to facilitate monitoring of temperature and location of *in-process, quarantine, and distribution* inventory. Equipment *shall be labeled* with the general nature of the contents.

Storage equipment used for *storing tissue*, reagents, media, refrigerants, or other laboratory solutions *shall not be utilized* for the storage of food and/or liquids for human consumption and *shall be marked accordingly*.

J5.700 Record Retention

Documentation of equipment and instrument cleaning, *decontamination, sterilization, qualification, calibration, and maintenance shall* be maintained in records for 10 years after their creation. Such *records shall* also include documentation of repairs, rejection, return, and/or disposal of defective equipment.

SECTION K
QUALITY ASSURANCE

K1.000 QUALITY ASSURANCE PROGRAM

All tissue banks shall have a *QA program*.

K1.100 Basic Elements

The *QA program* shall include, at a minimum:

- 1) designating and managing *quality control* functions, including:
 - a) environmental monitoring at designated intervals;
 - b) performing periodic equipment and facility inspections and documenting in maintenance *records* or logs;
 - c) reviewing equipment monitoring *records* for maintenance within specified *tolerance limits*, and reviewing *records* of other equipment or *processing* functions that have specified *tolerance limits*;
 - d) inspecting and monitoring *in-process control* results, including collection and testing of representative samples;
 - e) performing *qualification* of reagents, supplies, materials, instruments, or equipment when deemed *critical* or applicable; and
 - f) monitoring laboratory performance, if applicable.
- 2) performing *process validation* studies when the results of a process cannot be fully *verified* by subsequent inspection and test. Each *tissue bank* shall establish and maintain *procedures* for monitoring and controlling process parameters for *validated* processes to ensure that the specified requirements continue to be met. Each *tissue bank* shall ensure that *validated* processes are performed by qualified individual(s). For *validated* processes, each *tissue bank* shall document the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process and the major equipment used. When changes or process deviations occur, the *tissue bank* shall review and evaluate the process and perform *revalidation* where appropriate, and shall document these activities.
- 3) performing equipment *qualification studies* as necessary;
- 4) establishing purchasing controls;
- 5) establishing procedures for implementing *corrective action* and *preventive action* and taking action when appropriate. The *procedures* shall include requirements for:
 - a) analyzing processes, work operations, concessions, *quality audit reports*, *quality records*, *errors*, *accidents*, *complaints*, returns, and other sources of *quality data* to identify existing and potential causes of *nonconforming tissue*, or other *quality*

- problems. Appropriate statistical methodology *shall* be employed where necessary to detect recurring *quality* problems;
- b) investigating the cause of *nonconformities* relating to *tissue*, processes, and the *quality system*;
 - c) identifying the action(s) needed to correct and prevent recurrence of *quality* problems;
 - d) *verifying* or *validating* the *corrective action* and *preventive action* to ensure that such action is effective and does not adversely affect the *finished tissue*;
 - e) implementing and *recording* changes in methods and *procedures* needed to correct and prevent identified *quality* problems;
 - f) ensuring that information related to *quality* problems is disseminated to those directly responsible for assuring the *quality* of *finished tissue* or the prevention of such problems; and
 - g) submitting relevant information on identified *quality* problems, as well as *corrective action* and *preventive actions*, for management review;
- 6) reviewing, as applicable at each *tissue bank* involved, *donor screening*, *informed consent* or *authorization*, *recovery*, *acquisition*, or *collection*, and *processing records*;
 - 7) approving, as applicable, all *processing records* and *relevant medical records* prior to release of *tissue* for *transplantation*;
 - 8) *auditing*;
 - 9) documenting formal conclusions of all *accident*, *error*, *complaint*, *adverse outcome*, and *field correction*, *removal*, or *stock recovery* incidents;
 - 10) maintaining documentation including, but not limited to:
 - a) master copy of current *SOPM*;
 - b) *records* of names, *signatures*, initials or identification codes and inclusive dates of employment for those authorized to perform or review tasks (e.g., onsite or at a central location);
 - c) reports and conclusions of process *validation* and *equipment qualification studies*;
 - d) *records* of supply and reagent acceptance or rejection;
 - e) archived documents; and
 - f) master lists of preprinted *labels*.
 - 11) evaluating training of personnel and, where required, the *competency* of personnel, and requiring that staff are appropriately oriented and trained concerning any modifications to the *SOPM*;

- 12) maintaining *labeling* controls, including all brochures, pamphlets, and promotional materials; and
- 13) establishing a process for sharing information with other *tissue banks* that are known to have *recovered* and/or received *tissue* from the same *donor*.

K1.200 Qualification, Verification, and Validation Requirements

Each *tissue bank* shall:

- 1) develop, document, and implement protocols for the *qualification, verification, or validation* of significant components of:
 - a) facilities;
 - b) processes;
 - c) equipment;
 - d) reagents;
 - e) *labels*;
 - f) *containers*;
 - g) packaging materials;
 - h) *electronic systems*; and
 - i) *donor* eligibility criteria.
- 2) perform process *validations* for processes whose results cannot be fully *verified* by subsequent inspection and test;
- 3) assess process changes and perform *revalidation* as appropriate; and
- 4) evaluate parameters tested and determine the adequacy of the study to demonstrate necessary outcomes.

Elements or items that *must* be *qualified, verified, or validated* shall be determined from a risk assessment that has been approved by the *tissue bank's quality* department and the frequency of these activities will be determined by the risk assessment and results of the initial and follow up *validations*.

K1.210 Validation Methods

Where *validation* is required or desired, evidence supporting *validation* must be demonstrated. Acceptable methods to demonstrate *validation* are:

- 1) studies conducting challenges such as temperature, time, with indicator organisms, as appropriate, and/or other factors determined by the risk assessment that potentially affect *tissue quality*, as well as studies demonstrating consistency when the steps are

repeated lot to lot; or

- 2) identification of an established *procedure* or process known to be effective, with implementation of the same *procedure* or process, without modification; such *procedure* or process *shall* be *verified*, as specified in K1.230. [For example, the implementation of a literature based *disinfection* process *shall* include conducting at least method suitability testing (Bacteriostasis/Fungistasis testing) per USP <71> prior to implementation (see AATB Guidance Document No. 5)]; If any steps are modified, all such modifications *shall* undergo documented evaluation (e.g., through a risk assessment) for potential impact, and a potential result may be that a *re-validation* is necessary per method 1 of this section.

K1.220 Packaging Qualification and Transport/Shipping Validation

Packages used to transport *recovered tissue*, to ship tissue in-process, or to *distribute finished tissue* *shall* be *qualified*. The method(s) used *shall* be *validated* to demonstrate that the *packages* can maintain the required conditions to meet the *finished tissue quality* at the end of its stated expiration date.

K1.230 Verification Methods

Where *verification* is required or desired, evidence supporting *verification* *must* be produced by one or more of the following methods:

- 1) review, examination, inspection, or testing of a defined number of samples (the justification of the number of samples *must* be documented) in order to establish and document that the *tissue*, service or system meets specified regulatory or technical standards;
- 2) *verification* of the implementation of an established, previously *validated*, *procedure* or process without modification; *such verification* *shall* be conducted using a defined number of samples/processing events (the justification of the number of samples/processing events *must* be documented); or
- 3) a documented review such as when a *tissue recovery* program *must verify* that a *processor's donor* eligibility criteria is compliant with federal regulations, state law, and AATB *Standards*.

K1.300 Purchasing Controls

Each *tissue bank* *shall* establish and maintain *procedures* to ensure that all purchased or otherwise received products and services, including testing services, conform to specified requirements. Each *tissue bank* *shall* establish and maintain the requirements, including *quality* requirements that *must* be met by suppliers, contractors, and consultants. Each *tissue bank* *shall*:

- 1) evaluate and select potential suppliers, contractors, and consultants on the basis of their ability to meet specified requirements, including quality requirements. The evaluation *shall* be documented;
- 2) define the type and extent of control to be exercised over the product, services, suppliers, contractors, and consultants, based on the evaluation results; and

- 3) establish and maintain *records* of acceptable suppliers, contractors, and consultants. Each *tissue bank shall* establish and maintain data that clearly describe or reference the specified requirements, including *quality* requirements, for purchased or otherwise received product and services. Purchasing documents *shall* include, where possible, an agreement in which the suppliers, contractors, and consultants agree to notify the *tissue bank* of changes in the product or service so the *tissue bank* can determine whether the changes *may* affect *quality*.

For contracted services involving *donor* screening, *donor* eligibility, *tissue recovery*, *acquisition*, *collection*, *processing*, *storage*, and/or *distribution*, refer to B1.500 for additional requirements. Also refer to specific information at B1.600 for contracted and non-contracted laboratory services for infectious disease testing.

K1.310 Contracted Testing Services

Contracted testing services *may* be performed remotely at the contracted laboratory or on-site at the *tissue bank*, and evaluation of testing services is expected.

K1.311 Types of Testing Services

Examples of contracted testing services include, but are not limited to, the following:

- 1) donor infectious disease testing (also see B1.600);
- 2) microbiology testing (e.g., cultures on *tissue*, bioburden determination);
- 3) *environmental monitoring*;
- 4) *sterilization validation*;
- 5) irradiation dose auditing;
- 6) *lot* release testing (e.g., residual moisture, residual calcium, endotoxin levels);
- 7) calibration services (e.g., pipettes, temperature monitoring devices, equipment); and
- 8) cleanroom certification.

K1.312 Evaluation of Testing Services

Each *tissue bank* utilizing outside testing services *shall* ensure the testing facility and test methods are adequate for the intended use of the test results. This evaluation *may* include, but is not limited to, the following:

- 1) FDA registration, if required;
- 2) applicable state licenses, certifications and accreditations;
- 3) maintenance of an adequate *quality assurance program* to ensure the validity of results (e.g., test sample integrity, *quality control* samples, personnel *competency*, equipment maintenance, materials management);

- 4) participation in a laboratory *proficiency testing* program, if available;
- 5) adherence to relevant standards (e.g., CAP, ISO, ASTM, AAMI, USP);
- 6) follow manufacturers' instructions (e.g., package inserts, equipment manuals, electrical, and/or environmental conditions);
- 7) appropriate test method selection and *validation/qualification*;
- 8) use of traceable reference materials and calibration standards, where applicable; and
- 9) results from a paper, virtual, or on-site *audit*.

K2.000 QUALITY CONTROL PROGRAM

The *QA program shall* establish and maintain *QC procedures* that include the following:

- 1) *environmental monitoring*;
- 2) equipment maintenance and monitoring;
- 3) *tolerance limits*;
- 4) *in-process controls* monitoring;
- 5) reagent and supply monitoring; and
- 6) laboratory performance monitoring.

K2.100 Laboratory Proficiency Testing

Laboratories *shall* participate in relevant *proficiency testing* programs for all analytes, if available. *Proficiency testing shall* be conducted in accordance with the laboratories' normal testing and reporting procedures, unless otherwise specified in the instructions from the proficiency test provider.

Procedures shall incorporate a plan for *corrective action* for poor performance on *proficiency testing*.

K2.200 Laboratory Quality Assurance Program

Laboratories *shall* establish and maintain a *quality assurance program* adequate to ensure the validity of test results. The laboratory *quality assurance program shall* include, but is not limited to, the following:

- 1) appropriate test method selection and *validation/qualification*;
- 2) monitoring/trending internal *quality control* samples;
- 3) test sample specifications and integrity (e.g., identification, transportation, type, quantity, rejection criteria, preparation, storage);

- 4) personnel qualification, training and *competency*;
- 5) equipment selection, *validation/qualification*, calibration and maintenance;
- 6) use of traceable reference materials and calibration standards, where applicable;
- 7) follow manufacturers' instructions (e.g., package inserts, equipment manuals, electrical and/or environmental conditions);
- 8) materials management;
- 9) adherence to relevant standards (e.g., CAP, ISO, ASTM, AAMI, USP);
- 10) result *verification*, review and release; and
- 11) *records*/data management.

K2.300 Microbiological Tissue Cultures

K2.310 Pre-Sterilization/Pre-Disinfection Cultures

Except for *reproductive tissue banks* and *skin* (S), each *tissue bank* shall establish appropriate *pre-sterilization/pre-disinfection culture* methods and sampling strategies to represent all *tissues* received from a particular *donor*. The *pre-sterilization/pre-disinfection culture* results shall be documented in the *donor's record*. See AATB Guidance Document No. 5 for expectations.

If tissue *sterilization* or *disinfection* will not occur a *pre-sterilization/pre-disinfection culture* is not required, however, refer to culture requirement at K2.320.

The Medical Director or his/her physician designee [see exception that follows for (S)] shall review these *pre-sterilization/pre-disinfection culture* results prior to release of *tissue* for *transplantation*.

(MS, OA, SB)

Tissues with *pre-sterilization/pre-disinfection cultures* positive for *Clostridium*, *Streptococcus pyogenes* (group A *strep.*), or any other *microorganisms* determined by the *processor* to be virulent or difficult to eliminate, shall be discarded unless treated with a *disinfection* or *sterilization process validated* to eliminate the infectivity of such organisms. Other individual *tissues* from the same *donor* that were *recovered* under conditions that could result in *cross-contamination* must be discarded unless they will be treated with a *disinfection* or *sterilization process validated* to eliminate the infectivity of such organisms.

(BT, C, V, CT)

E2.800 applies.

(S) Cultures shall be obtained prior to *processing*. Culture methods shall be *validated* to ensure the suitability of the culture method selected. Inhibitory substances (e.g., *skin prep* solution(s), transport media, antibiotics, etc.) that may be added to unprocessed *skin* during *recovery* or for transport must not

interfere with culture results. (i.e., produce false negative results).

Culture results *shall* be documented in the *donor's record*. Cultures positive for *microorganisms* considered pathogenic, highly virulent *must* be discarded unless the *tissue* can be *disinfected/sterilized* with a *validated* process (see E2.800). The Medical Director or designee *shall* review all available pre-processing *skin* culture results prior to releasing the *tissue* for *transplantation*. *Skin recovery shall* be performed as a separate zone from other *tissue* types so that culture results can be independently reviewed.

K2.320 Final/Pre-Packaging Cultures

Except for *autologous* and *reproductive tissues*, all *tissue* to be released for human *transplantation shall* have representative microbiological cultures obtained which includes testing to detect bacteria and fungi. The results *must* be documented in the *donor record*, unless *dosimetric release* has occurred by a *validated* process according to E2.820. Appropriate final packaging cultures (aerobic and anaerobic) *shall* be obtained and the results *shall* meet established parameters defining acceptable final packaging cultures before *tissue* is released for *transplantation*. All culture results *shall* be reviewed prior to release of *tissue* for *transplantation*. Any variance in the culture results from established parameters *shall* be reviewed and approved by the Medical Director or his/her designee prior to release. Except as described for *skin* (S) below, no *allografts* contained within the *processing batch may* be released for *transplantation* if post-*processing* final sterility test results show organism contamination. *Allograft* rework is permitted with an established program *validated* to eliminate the organism identified.

(A) Except for *skin*, if *autologous tissue* is being *processed*, microbiologic cultures, which includes testing to detect bacteria and fungi, *should* be obtained immediately prior to *processing*.

(C, V) Representative *cardiac tissue* and *vascular tissue* samples *shall* be cultured for fungal growth.

(MS, OA, SB, C, V, CT)

Microbiologic testing of *processed tissue*, which includes testing to detect bacteria and fungi, *shall* be performed on each donor *lot*.

(S) Representative fresh or *cryopreserved skin* samples *shall* be cultured for the presence of fast-growing fungal organisms. Fresh or *cryopreserved skin shall* not be used for *transplantation* if any one of the following is detected at final culture:

- 1) *Staphylococcus aureus*;
- 2) *Streptococcus pyogenes* (group A strep.);
- 3) *Enterococcus* sp.;
- 4) gram-negative bacilli;
- 5) *Clostridium*; and

6) fungi (yeasts, molds).

K2.400 Testing for Residues

(C, V) Initially, and as required at K1.200, each *tissue bank shall* thaw, rinse and prepare representative samples from *processed tissue* as if for use and test them to evaluate the concentration of residual *cryoprotectant(s)* (if applicable).

K2.500 Other Quality Control Procedures

K2.510 Lyophilized/Dehydrated/Desiccated Tissue

QC programs for monitoring performance of either a lyophilizer, a dehydrator or desiccator *shall* be established and *verified* for each *batch*. When a residual moisture limit has been established, a representative sample that demonstrates the worst-case scenario for that *batch shall* be tested and *shall* not exceed the limit. Refer to E2.710 and E2.720.

K2.520 Annual Calibrations

Each *tissue bank shall* ensure at least annual calibration of mechanical devices used for *storage* with a National Institute of Standards and Technology-traceable thermometer. The overall *QA program shall* include maintenance of calibration *records*.

K3.000 MICROBIOLOGIC TESTING

All microbiologic testing of *tissue* to be released for *transplantation shall* be performed by a qualified laboratory using appropriate test methods. If microbiologic testing is to be performed by the *tissue bank*, the requirements at K2.100 and K2.200 *shall* apply. If the services of an outside laboratory are used, the requirements at K1.300 and K1.310 *shall* apply.

NOTE: For international members that do not export *tissues* to the U.S., applicable requirements of the government/competent authority having jurisdiction apply regarding qualification of laboratories via accreditation, designation, authorization and/or licensure.

K3.100 Microbiologic Subcultures

The testing lab *shall* subculture a positive microbiologic culture to identify the organism(s) by genus, and species where appropriate. See Guidance Document No. 5.

K4.000 INVESTIGATIONS

The *QA program shall* ensure there is an investigation and review for completeness of *accidents, errors, complaints, deviations, and adverse outcomes*. Investigation *shall* include a summary report, precipitating events, recommendations, and resolutions. The *QA program shall* retain for 10 years all reports generated.

K4.100 Errors and Accidents

The *QA program shall* ensure a documented investigation of any *error-or accident* in obtaining *informed consent* or *authorization*, in *donor screening, collection, acquisition, or tissue recovery, processing, quarantining, releasing, labeling, storing, and distribution* or dispensing

may affect the *safety* of *tissue* to be released or that has been released, the Medical Director or licensed physician designee *shall* also review and evaluate the incident. When *tissue* may have been contaminated, the *QA program shall* ensure the documented review and evaluation both of *processing procedures* and of any other *tissue processed* simultaneously or from the same.

K4.200 Complaints

The *QA program shall* ensure that a written and oral *complaints* regarding *tissue quality, safety, packaging, or effectiveness* are expeditiously investigated to determine whether the *complaint* is related to an *error, accident, adverse outcome*, or other factor, unless such investigation has already been performed for a similar complaint. If it is determined that no investigation is necessary, a *responsible person shall* document the reason that no investigation was made and the name of the individual responsible for the decision not to investigate. Each investigation *shall* determine whether associated *tissue may* be affected. If it is determined that they may be affected, *then* those associated *tissues shall* be located and *quarantined* until *resolution* of the incident (which *may* involve initiation of a *recall*). The Medical Director or licensed physician designee *shall* review *complaints* that are medical in nature.

When an investigation is made, a *record* of the investigation *shall* include:

- 1) the date the complaint was received;
- 2) the name of the *tissue*;
- 3) the unique *tissue identification number*;
- 4) the name, address, and phone number of the complainant;
- 5) the nature and details of the *complaint*;
- 6) the dates and results of the investigation;
- 7) any *corrective action* taken; and
- 8) any reply to the complainant.

K4.300 Adverse Outcomes

The *QA program shall* ensure that all reported *adverse outcomes* that are potentially related, directly or indirectly, to an *allograft* are investigated thoroughly and expeditiously. The Medical Director or licensed physician designee shall review all potential *adverse outcome* reports and participate in determination of the impact and *resolution* of any *adverse outcome*. If investigation indicates that the *adverse outcome* is related to an *error* or *accident*, then the *tissue bank shall* follow *procedures* for *errors* and *accidents* (see K4.100).

K4.310 Reporting

The *QA program shall* ensure that all cases of transmissible disease in a *recipient* attributed to the *allograft* are reported in writing as required by public health authorities, and in a timely fashion to organ procurement organizations and *tissue banks* involved in any manner with *tissue recovered* from the same *donor* and to the physician(s) involved in the *transplantation* of *tissue* from that *donor*. Reporting *shall* be

documented in the *donor's record*.

See the Accreditation Policies for Transplant Tissue Banks for other required reporting.

K5.000 INTERNAL AUDITS

All *tissue banks shall* establish policies and *procedures* regarding the scope and frequency of routine and focused *QA audits*. The *QA program staff shall* perform *audits*, at least annually, of the major *tissue banking* operational systems to identify trends or recurring problems in: *donor* evaluation and acceptance; *tissue recovery* or *collection*, *processing*, *preservation* and *packaging*; *donor* and *tissue* testing; *quarantining*; *labeling*; *storage*; *distribution*; *electronic systems*; and *records* management. The *QA program shall* perform focused *audits* of *critical areas* (unless the annual routine *audit* covers all *critical areas*), and of any area with a pattern of *quality* problems. All *audits shall* be performed by persons who do not have direct responsibility for the process being *audited*. The *tissue bank shall* take *corrective action(s)* when necessary, including a re-*audit* of deficiencies. The *QA program staff shall* document and report the dates and results of each *quality audit* (and re-*audit*) to management responsible for the *audited* systems, who *shall* review each report.

K6.000 EXTERNAL AUDITS

External *audits may* be indicated for certain services, suppliers, contractors, and consultants. See K1.300 and B1.520.

K7.000 ELECTRONIC SYSTEMS CONTROLS

K7.100 Authorized Access

Each *tissue bank shall* exercise appropriate controls over *electronic systems* to *limit* general access to authorized personnel and to permit only authorized personnel to alter master production and control *records* or other.

K7.200 Error Reduction

When automated data processing is used for decision-making in *processing*, adequate procedures *shall* be designed and implemented to prevent inaccurate input or output of data and programming *errors*.

K7.300 Backup Files

A backup file *shall* be maintained of all data that are entered into an *electronic system* and subsequently used for decision-making purposes, and of all data that are not otherwise *recorded* and accessible.

K7.400 Security

Electronic systems shall be designed to assure data integrity and maintained in a secure manner to prevent alteration or loss.

K7.500 Audit Trail

Records revised electronically *must* have an *audit trail* that includes the altered information, date of the revision, and the individual that made the revision.

SECTION L TISSUE DISPENSING SERVICES

L1.000 TISSUE DISPENSING SERVICES

Medical, dental, and hospital facilities, and physician offices that are *tissue dispensing services* shall establish policies and *procedures* to ensure the *safety* and *traceability* of *tissue* from receipt through *storage* and final *disposition* such as *transplantation*, further *distribution*, or destruction.

L1.100 Responsibilities

Activities of a *tissue dispensing service* shall be supervised by a physician, dentist, podiatrist, or other qualified medical professional.

L2.000 STORAGE

L2.100 General

Tissue storage shall be in conformance with *labeling materials*.

L2.200 Equipment

Freezers and refrigerators shall be regularly maintained, calibrated, and monitored using *QC* written *procedures*.

L2.300 Labeling

Tissue shall not be *relabeled*. Existing *labels* shall not be altered.

L3.000 DISPENSING, FURTHER DISTRIBUTION AND DISPOSAL

L3.100 Dispensing

Tissue shall not be dispensed for use in *recipients* without an order from a physician or other authorized health professional. Human *tissue* shall not be offered or dispensed for *veterinary use*. *Tissue* shall be transported and prepared for *transplantation* in accordance with *labeling materials*. All associated *labeling material*, including the *package insert*, shall be made available to the *end-user* physician and/or other qualified medical professionals.

L3.200 Further Distribution

When further *distributing tissue*, all accompanying original *labeling materials* or other enclosures shall be forwarded with the *tissue*. A *record* shall be made of the type and quantity of *tissue*, *tissue identification number(s)*, *redistribution* date and destination.

L3.300 Tissue Disposal

Tissue that is unused, partially used, or expired, damaged or otherwise unsuitable for *distribution* shall be disposed of in such a manner as to minimize any hazards to staff or the environment, in conformance with applicable laws and regulations. When applicable, the *tissue*

dispensing service shall notify the tissue bank, or the tissue distribution intermediary from whom the tissue was obtained, of the final disposition of the tissue. Documentation of such notification shall be recorded.

(A) Disposal of *autologous tissue shall consider the following:*

- 1) *there shall be a written policy for the discard of autologous tissue;*
- 2) *the tissue dispensing service, in consultation with the autologous donor's physician, shall approve discard of the tissue, and shall be responsible for documentation of the method and date of discard; and*
- 3) *autologous tissue should not be used for transplantation after the expiration date.*

(R) *There shall be a written policy for discard of reproductive tissue from a client depositor or directed donor. The reproductive tissue bank shall approve discard of reproductive tissue from anonymous donors and shall document the date of discard.*

L4.000 RECORDS

Tissue dispensing services shall concurrently record all steps in the receiving, storage, and dispensing of tissue so that all steps can be clearly traced. Records shall be maintained for a minimum of ten years after expiration of the tissue or, in the case of tissue with no expiration date, ten years after dispensing.

L4.100 Tissue Receipt Records

Each tissue specimen shall have a tissue identification number. Tissue receipt records shall contain, at a minimum, the following information:

- 1) *name and address of tissue supplier;*
- 2) *description of tissue and quantity received;*
- 3) *date of tissue receipt;*
- 4) *condition of tissue upon receipt; and*
- 5) *expiration date, if applicable, of tissue.*

L4.200 Dispensing Records

Disposition of tissue shall be documented. When tissue is dispensed for transplantation, the following information shall be recorded:

- 1) *name, address, and telephone number of the tissue bank (tissue supplier or tissue processor);*
- 2) *type and quantity of tissue and unique tissue identification number(s);*
- 3) *recipient's name and medical record number, or social security number or similar unique identifier;*
- 4) *transplantation site and date and time of release;*

- 5) name of the ordering physician or other authorized health professional;
- 6) name of the person dispensing the *tissue*; and
- 7) name of the person preparing the *tissue(s)* for use, if *tissue* is prepared at the site of dispensing.

This information *shall* be maintained in the *tissue dispensing service records* in a log format. The *tissue recipient's* medical *records shall* contain, at a minimum, the first five items to permit tracing of each *tissue* from the *tissue bank* (*tissue* supplier or *tissue* processor) to each *recipient*.

The *tissue bank's* *tissue tracing* forms *shall* be completed, specifying the *disposition* of the *tissue*, and returned as instructed in *labeling materials*.

L5.000 ADVERSE OUTCOMES

Potential adverse reactions, suspected transmission of disease, or other complications, directly or indirectly related to the *allograft*, *shall* be reported as instructed in *labeling materials* and thoroughly investigated and documented.

L6.000 FIELD CORRECTIONS AND REMOVALS

The *tissue dispensing service shall* have specific written policies and *procedures* for the performance of a *field correction* or *removal*, if applicable. *Procedures shall* include, but are not limited to, the following:

- 1) designation of a *responsible person(s)*;
- 2) location and *quarantine* of affected inventory, in a timely manner;
- 3) communication with the *tissue bank* (*tissue* supplier or *tissue* processor);
- 4) communication with the *end-user*; and
- 5) documentation and *record* requirements.

SECTION M TISSUE DISTRIBUTION INTERMEDIARIES

M1.000 TISSUE DISTRIBUTION INTERMEDIARIES

An agent who acquires *distributed tissue* for *storage* and further *distribution shall* establish policies and *procedures* to ensure the *safety* and *traceability* of *tissue* from receipt through *storage*, clinical use, further *distribution*, or destruction. See relevant parts of Section B and Section J.

NOTE: When any *tissue banking* activities are performed beyond the few functions that identify an entity as a *tissue distribution intermediary* (i.e., an agent that only acquires and *stores tissue* for further *distribution*), relevant *tissue bank* standards apply and compliance is required for accreditation. *Tissue bank* functions that surpass functions solely under the definition of a *tissue distribution intermediary* include:

- 1) designing, creating, maintaining, or controlling the specifications for *finished tissue*, relevant parts of Section E apply (e.g., the *series of standards* at E2.600 and E2.421);
- 2) designing, creating, specifying, or maintaining responsibility for the contents of the *label* for *finished tissue*, relevant parts of Section G apply;
- 3) performing any *labeling* functions to include the physical application of a *label* to *finished tissue*, relevant parts of Section G apply; and/or
- 4) final review for *tissue* release, relevant parts of Section F apply (e.g., F1.300, *series of standards* at F4.000).

M2.000 STORAGE

M2.100 General

Tissue storage shall be in conformance with the *package insert* and monitoring expectations. See E3.330, E3.331, E3.340, and C1.300.

M2.200 Equipment

Freezers and refrigerators *shall* be regularly maintained, calibrated, and monitored according to written *QC procedures*. See the *series of standards* at J5.000.

M3.000 LABELING

Tissue shall not be *relabeled*. Existing *labels shall* not be altered. Additional *labels shall* not be applied unless pre-approved by the *tissue bank* processor that applied the original *label*. Refer to the *series of standards* at G1.000.

M4.000 DISTRIBUTION

There *shall* be written *procedures* for the receipt of *tissue* orders, unit selection, final *container*, and/or *package* inspection, shipping, and transportation of *tissue* for *transplantation*. When a *tissue distribution intermediary* further *distributes tissue*, all accompanying *labeling materials* or other enclosures *shall* be forwarded with the *tissue*.

M4.100 Tissue Distribution Restrictions

Provision of *tissue* for *transplantation* shall be restricted to hospitals, free-standing medical facilities, *tissue banks*, *tissue dispensing services*, another *tissue distribution intermediary*, and *end-users* (e.g., physicians, dentists, podiatrists or other medical professionals) for use in *recipients* with the *veterinary use* exception that follows. *Tissue distribution intermediaries* shall have *procedures* that describe evaluation of requests from new customers for *tissue*. Human *tissue* for *transplantation* shall not be offered or *distributed* for *veterinary use* unless such use is specifically granted in a *document of gift/authorization* or in a *record of informed consent*. Controls *must* exist to ensure *distribution* restrictions are met such as those found on the *document of gift/authorization* or *informed consent*.

M4.200 Distribution to Another Tissue Distribution Intermediary

If *tissue* is distributed to another *tissue distribution intermediary*, that *tissue distribution intermediary* shall meet the requirements of Section M.

M4.300 Requests for Donor Status and Tissue Processing Information

Donor risk assessment, *tissue* condition(s), and *tissue processing* details, with the exception of information that may infringe upon the confidentiality of *donor* information, shall be made available to the *transplanting* physician upon request.

M5.000 CONSIGNMENT INVENTORY MANAGEMENT

If *tissue* is provided on *consignment*, the *tissue distribution intermediary* shall maintain *procedures* to ensure *traceability* and that appropriate *storage* conditions are maintained during *consignment*, further *distribution* or return.

M6.000 PACKAGING AND SHIPPING

M6.100 Pre-Shipping Inspection

Prior to shipping, *packages* shall be inspected to ensure the external *packaging* and *labels* are undamaged, the *tissue* is not expired and the *tissue* being shipped is consistent with the *tissue* requested. The exterior of the transport *package* shall be inspected to *verify* that requirements in G3.310 are met. These inspections shall be documented, including identification of staff conducting inspections.

M6.200 Validation and Packaging Expiration

If *tissue* to be shipped requires specific environmental conditions other than ambient temperature, the capability of the transport *package* to maintain the required environmental conditions shall be demonstrated and documented in a *validation* study. The length of time those conditions can be maintained by the *packaging* (assuming normal handling) shall also be determined. Expiration dates of the *packaging* shall be noted on the outside of the transport *package*.

M6.300 Transportation

The mode of transportation selected shall be determined by any special shipping and handling

requirements of the *tissue* and/or shipping refrigerants, shipping restrictions of commercial carriers, and the urgency of the *tissue* request.

M6.310 Domestic Shipments

The transport *package label* shall include the following information:

- 1) name, address and telephone number of the *tissue distribution intermediary*;
- 2) name and address, and telephone number of the *consignee* or *end-user*;
- 3) prominent identification of contents as “DONATED HUMAN TISSUE.” Note: If the *reproductive tissue* in the shipment was collected from a *client depositor*, prominent identification as “HUMAN TISSUE”;
- 4) recommended *storage* conditions and transport expiration date (if applicable);
- 5) type and quantity of refrigerant or other hazardous materials enclosed in the transport *package*;
- 6) transport (shipping) expiration date (if applicable), and
- 7) any special handling instructions, when applicable (e.g., “DO NOT FREEZE,” “DO NOT X-RAY,” “DO NOT IRRADIATE”).

M6.320 International Shipments

Labels for international shipments shall contain all of the information required for domestic shipments; however, information may be modified to meet requirements of the federal government and those of the receiving country.

M7.000 RETURN OF TISSUE

A *tissue distribution intermediary* shall establish a policy authorizing or prohibiting the return of *tissue* in its original, unopened *container*. If returns are permitted, the integrity of the *container*, transport *package*, and *labeling* shall be examined for evidence of contamination or tampering. If there is any evidence of contamination, tampering, mishandling, or failure to maintain required *storage* temperatures, *tissue* shall not be returned to *distribution* inventory. Information pertaining to the return of *tissue* shall be recorded in the *disposition records* for that *tissue* as follows:

- 1) documentation of *container* examination;
- 2) documentation of *end-user storage* and shipping conditions;
- 3) reason for the return;
- 4) *disposition* of the returned *tissue*; and
- 5) date and name of the staff member who evaluated and determined the *disposition* of the *tissue*.

M8.000 FIELD CORRECTIONS AND REMOVALS

The need to perform a *field correction* or *removal* may be identified as a result of a *complaint*, *adverse outcome*, *accident*, *error*, *deviation*, *audit*, or by any other means. For applicable *quality assurance* requirements, see relevant parts of Section K. An evaluation to determine if *field correction* or *removal* is warranted *should* be made whenever *distributed tissue* may not meet specifications related to *safety*, *quality*, identification, function and/or use. This evaluation *must* consider both risk to health posed by the *tissue* and applicable regulatory requirements, and be documented.

Tissue distribution intermediaries shall have specific, written policies and *procedures* for the performance of a *field correction* or *removal*. Procedures *shall* include, but are not limited to, the following:

- 1) designation of a *responsible person(s)*;
- 2) location and *quarantine* of affected inventory, in a timely manner;
- 3) communication with the *tissue bank* (*tissue* supplier or *tissue* processor);
- 4) communication with the *end-user*; and
- 5) documentation and *record* requirements.

M8.100 Field Correction and Removal Records

All information relating to the *field correction* or *removal* of *tissue* and resulting communications *shall* be documented and retained on file for at least 10 years beyond the date of *distribution*, the date of *transplantation* (if known), *disposition*, or expiration of the *tissue*, whichever is latest. The file *shall* include, but not be limited to:

- 1) reason for the *field correction* or *removal*;
- 2) identification and location of affected *tissue* in a timely manner, including *quarantine* steps;
- 3) steps taken to correct or retrieve *tissue*;
- 4) documentation of all related communications (e.g., phone calls and/or written correspondence, including copies of *field notifications* or letters and a list of those to whom notice was sent);
- 5) final *disposition* of the *tissue*;
- 6) *corrective actions* recommended and implemented; and
- 7) documentation of review.

M9.000 RECORDS

The *tissue distribution intermediary* shall concurrently *record* all steps in the receiving, *storage*, and dispensing of *tissue* so that all steps can be clearly *traced*. Records *shall* be maintained for a minimum of ten years after the expiration date of the *tissue*, or in the case of *tissue* with no expiration date, ten years after *distribution*. See applicable requirements of Section C.

M9.100 Tissue Receipt Records

Each *finished tissue* shall have a *tissue identification number*. *Tissue receipt records* shall contain, but not be limited to, the following information:

- 1) name and address of *tissue* supplier;
- 2) description of *tissue* and quantity received;
- 3) date of *tissue* receipt;
- 4) condition of *tissue* upon receipt; and
- 5) expiration date, if applicable, of *tissue*.

M9.200 Distribution Records

Tissue distribution intermediaries shall maintain *distribution records*. These records shall be designed to permit *tissue* to be traced from the *donor* to a *consignee* or *end-user*, and from a *consignee* or *end-user* back to the *donor*. Records shall indicate the final disposition of all *tissue* handled by a *tissue distribution intermediary*. *Tissue distribution records* shall include, but not be limited to:

- 1) date of order placement;
- 2) name of the site to which the *tissue* is distributed;
- 3) name of the individual placing the order;
- 4) type and quantity of *tissue* ordered; and
- 5) information pertaining to *tissue* selected for shipment, including:
 - a) identification number(s) of *tissue*;
 - b) collection or expiration date of the *tissue*;
 - c) date of shipment;
 - d) type and amount (if applicable) of refrigerant used for shipment;
 - e) mode of transportation; and
 - f) name of the person releasing the *tissue*.

Prior to *distribution*, the *labeled tissue* shall be reviewed to *verify* that *tissue* has been properly identified and *labeled*. Such inspection shall be documented.

Any completed *tissue tracing* forms, specifying the *disposition* of the *tissue*, shall be returned as instructed in *labeling materials*.

M9.300 Tissue Disposal

Unused, partially used, or expired *tissue shall* be disposed of in such a manner as to minimize any hazards to staff or the environment in conformance with applicable laws or regulations.

The *tissue distribution intermediary shall* notify the *tissue bank* of the final *disposition* of the *tissue* and all actions taken *must* be documented.

M10.000 ADVERSE OUTCOMES

Reports of *adverse outcomes*, transmitted disease, or other complications *shall* be documented and reported to the *tissue processor* in a timely fashion and in accordance with applicable laws or regulations.

Appendix I: REQUEST FOR VARIANCE FROM STANDARDS

Introduction

AATB-accredited *tissue banks* may request a *variance* when a policy, process, or *procedure* is in conflict with requirements in current AATB *Standards*. A *variance* request may be submitted for specific AATB standards appearing in this edition or in announced, approved updates to this edition. AATB-accredited *tissue bank* may request a *variance* to *Standards* but may not violate current *Standards* by implementing the change without first receiving notice of written approval from the AATB Executive Office.

A *tissue bank* seeking initial AATB accreditation may submit a *variance* request with a completed application for accreditation. A request for *variance* to *Standards* cannot be submitted when noncompliance is discovered during application for re-accreditation, and such a request cannot be used as a *corrective action* in response to a *nonconformity* cited at an AATB accreditation inspection.

Requests for *variance* cannot be acted upon if they are sent by an entity that is not an AATB-accredited *tissue bank*, or has not applied for AATB accreditation.

The timeline for reviewing a request for *variance* can be affected by additional requests for information by those who review the submission as well as by the time associated with response(s) by the requestor. The burden is on the *tissue bank* to provide supporting documentation that adequately describes how the proposed practice will meet the ultimate intent of *Standards*.

Process

SUBMISSION:

- 1) *Tissue banks* requesting a *variance* from current *Standards* must provide the following information to the AATB Senior Vice President of Policy by using the Request for Variance to AATB Standards Submission Format that follows. The format *must* be completed in entirety and include:
 - a) the request for *variance*, including the particular standard number(s) that apply to the request;
 - b) justification of the alternative *procedure(s)*, policy or process which assure(s) equivalency to the intent of *Standards*; and
 - c) supporting information such as worksheets, records, data, or other information (e.g., *validation* of the process to be used in support of the *variance* or modification, including the scientific data and *quality assurance* steps). All data and proprietary information provided to the AATB by the *tissue bank* in connection with a request for *variance* shall be treated in accordance with AATB's policy governing confidential and proprietary information.
- 2) Within thirty (30) days of a request for *variance*, the Senior Vice President of Policy and the Chairperson of the Standards Committee will review the information submitted for applicability and completeness. These individuals may:
 - a) request more information to complete the submission;
 - b) consult with officers of appropriate committees and/or councils; and/or
 - c) determine the submission does not satisfy requirements for a request for *variance*.

REVIEW:

- 1) The Senior Vice President of Policy will forward the request and supportive information to the Standards Committee. These documents *may* or *may* not be blinded, depending on the nature of the submission and whether withholding the *tissue bank's* identity could adversely affect appropriate review of their submission. This decision will be made in consultation with the person who submitted the *variance* request.
- 2) *Variances* are reviewed without prejudice, and individuals involved in the preparation of the request or who have any conflict relating to the request are to exclude themselves from committee or council discussion. Subject matter experts *may* be sought for consultation at the discretion of the Standards Committee Chairperson and/or Board of Governors.
- 3) At the next scheduled meeting, the Standards Committee will review and evaluate the acceptability of the request.
 - a) If adequate information has been received, the Standards Committee *may* vote to approve or disapprove the request. Within thirty (30) days, this recommendation will be forwarded to the Board of Governors.
 - b) If additional information is required, the Senior Vice President of Policy or Chairperson will request information directly from the contact person who submitted the request.

The Standards Committee *may* determine that the request *must* be reviewed by another committee or council, or *may* seek consultation with other subject matter experts. For example, requests of a scientific nature *may* be forwarded to the Scientific and Technical Affairs Committee for review and recommendation, and those of a medical nature *may* be forwarded to the Physicians' Council for review and recommendation.

If consultation with another committee or council has been requested, the recommendation regarding the request *shall* be sent to the Standards Committee Chairperson and Senior Vice President of Policy within sixty (60) days of receipt. This time period *may* be extended if additional supportive information is desired by reviewers, but *should* be no longer than ninety (90) days from receipt.

Within thirty (30) days of receipt of the recommendation from another committee, a council, or subject matter expert(s), the Standards Committee will forward its recommendation, and rationale that supports the recommendation, to the Board of Governors.

RESPONSE:

- 1) Within thirty (30) days of its receipt of the Standards Committee's recommendation, the Board of Governors *shall* take formal action on the request for *variance* and *shall* issue a written response to the *tissue bank* regarding its request. Requests for *variance* *may* be approved, delayed pending receipt of more information requested by the Board of Governors, rejected, or approved in modified form.
- 2) The Standards Committee *shall* provide notice of action on a request for *variance* to the Accreditation Manager for placement in the *tissue bank's* file.

The Board of Governor's action on a request *shall* be communicated by the Senior Vice President of Policy to the Chairperson of each committee and/or council that reviewed the request.

Notice of the grant or rejection of a *variance* from the *Standards* may be included in AATB published materials or reports.

APPROVED VARIANCES:

- 1) A *variance* from *Standards* may not be implemented by the *tissue bank* until the request for *variance* has been approved by the Board of Governors.
- 2) A *variance* from *Standards* approved by the Board of Governors is applicable only to the *tissue bank* that requested the *variance*. It may also be applicable to a *tissue bank* performing activities directly related to the approved *variance* under written agreement/contract with the requesting *tissue bank*.
- 3) Should the Standards Committee consider the *variance* to have universal application, the Standards Committee may recommend that the Board of Governors make the approved *variance* applicable to all accredited members under such conditions as may be prescribed.
- 4) A record of the approved *variance* must be maintained at the requesting *tissue bank* as well as at any other accredited *tissue bank* directly affected by the approval. Evidence of approval of the request for *variance* must be available during an accreditation inspection.
- 5) Approved *variances* shall remain in effect until:
 - a) the *variance* is rescinded;
 - b) the applicable standard on which the *variance* is based is amended or deleted thereby rendering the *variance* null and void; or
 - c) the *variance* becomes meaningless due to changes in other circumstances.

Request for Variance to AATB Standards (current edition)
— Submission Format —

Standard for which a *variance* is submitted

Standard number and title:

Enter current text of standard:

Reason

Describe justification of *variance* request:

Supporting Information

Attach worksheets, records, data, or other documentation that supports your request. List them here by title.

Accredited Tissue Bank Name & Representative

Accredited *tissue bank* name:

Email address:

Phone number:

Representative (this is the contact person for this request)

Name:

Title:

Statement of Tissue Bank Representative

I request that for purposes of AATB accreditation our *tissue bank should* be granted a *variance* from this standard.

Signature:

Date Submitted:

Appendix II:
CRITERIA FOR PREVENTING TRANSMISSION of RCDADs
(Relevant Communicable Disease Agents and Diseases)¹
THROUGH TRANSPLANTATION OF HUMAN TISSUE

Behavior/History Exclusionary Criteria:

- 1) men who have had sex with another man within the preceding five years;
- 2) persons who have injected drugs for a non-medical reason in the preceding five years, including intravenous, intramuscular, and subcutaneous injections;
- 3) persons with hemophilia or related clotting disorders who have received human-derived clotting factor concentrates in the preceding five years;
- 4) persons who have had sex in exchange for money or drugs in the preceding five years;
- 5) persons who have had sex in the preceding 12 months with any person described in the 4 items above or with any person who has HIV infection, including a positive test for HIV, hepatitis B infection, or clinically active (symptomatic) hepatitis C² infection;
- 6) persons who have been exposed within the preceding 12 months to known or suspected HIV, HBV, and/or HCV infected blood through percutaneous inoculation (e.g., needlestick) or through contact with an open wound, non-intact skin, or mucous membrane;
- 7) children born to mothers known to be infected with, or at risk for, HIV, HBV or HCV infection, who are 18 months of age or less and/or have been breastfed within the preceding 12 months, regardless of the child's (*donor's*) HIV, HBV or HCV status;

NOTE: Children over 18 months of age born to mothers infected with, or at risk for, HIV, HBV or HCV infection, who have not been breastfed within the preceding 12 months and whose infectious disease testing, *physical examination/physical assessment*, and review of medical records do not indicate evidence of HIV, HBV or HCV infection, *may* be accepted as *donors*.

- 8) persons who have been in a juvenile correctional facility, lockup, jail or prison for more than 72 consecutive hours in the preceding 12 months;
- 9) persons with a generic history of hepatitis of an unspecified etiology or a current or past diagnosis of clinical, symptomatic viral hepatitis unless evidence from the time of illness documents that the hepatitis was diagnosed as either hepatitis A or due to cytomegalovirus or Epstein-Barr virus hepatitis. (Note: A verbal history of viral hepatitis occurring before the age of 11 years is acceptable);
- 10) persons who have lived with (resided in the same dwelling) another person who has hepatitis B or clinically active (symptomatic) hepatitis C² infection in the preceding 12 months;
- 11) persons who had or have been treated for syphilis or gonorrhea during the preceding 12 months. *Donors may* be acceptable if evidence is presented that the treatment occurred more than 12 months ago and was successful;
- 12) persons who within 12 months prior to donation have undergone tattooing, acupuncture, ear or body piercing in which shared instruments are known to have been used;

- 13) persons with a diagnosis of any form of Creutzfeldt-Jakob disease (CJD) or known family history (blood relative) of a person with non-iatrogenic CJD;
- 14) persons with a diagnosis of dementia or any degenerative or demyelinating disease of the central nervous system (CNS) or other neurological disease of unknown etiology. Note: Tissues from donors with dementia, confirmed by gross and microscopic examination of the brain to be caused by cerebrovascular accident, brain tumor, head trauma, or toxic/metabolic dementia and who are confirmed not to have evidence of transmissible spongiform encephalopathy (TSE) on microscopic examination of the brain, *may* be acceptable based on an evaluation of this information by the Medical Director;
- 15) persons who have received injections of human pituitary-derived growth hormone (pit-hGH);
- 16) persons who are known to have received transplants of human *dura mater*;
- 17) persons with encephalitis or meningitis of viral or unknown etiology that is active;
- 18) persons who have received transfusions of blood or blood products outside of the United States (U.S.) during specific time periods in the following countries:
 - a) from 1980 to present: France or the United Kingdom (includes England, Northern Ireland, Scotland, Wales, the Isle of Man, the Channel Islands, Gibraltar, and the Falkland Islands); and/or
 - b) after 1977 to present: Central or west Africa (includes Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, or Nigeria)³.
- 19) persons determined to be at risk for variant CJD (vCJD) because they are known to meet any of the following criteria:
 - a) spent three months or more cumulatively in the United Kingdom (U.K.) from the beginning of 1980 through the end of 1996;
 - b) lived cumulatively for 5 years or more in Europe⁴ from 1980 until the present (note this criterion includes time spent in the U.K. from 1980 through 1996); and/or
 - c) is a current or former U.S. military member, civilian military employee, or dependent of a military member or civilian employee who resided at U.S. military bases in Northern Europe (Germany, Belgium, and the Netherlands) for 6 months or more from 1980 through 1990, or elsewhere in Europe (Greece, Turkey, Spain, Portugal, and Italy) for 6 months or more from 1980 through 1996;
- 20) persons who, within the previous 120 days, have been told by a healthcare professional that they were suspected or known to have had a West Nile virus (WNV) infection based on symptoms, and/or those who are known to have tested positive for WNV by a NAT assay within this time frame;
- 21) persons who are known to have risks associated with xenotransplantation⁵ (i.e., receipt of a xenotransplantation product⁶ or who has had intimate contact⁷ with a recipient of a xenotransplantation product);
- 22) persons who have been permanently deferred as a blood donor for unknown reasons or who have a history of positive infectious disease test results for HIV, HBV, or HCV;
- 23) persons who, within the past six months, were bitten by an animal suspected to be infected with

rabies. Individuals with suspected rabies *shall* not be accepted as *donors* under any circumstances (see Title 10 of New York Codes, Rules and Regulations, Section 52-3.4);

- 24) persons who had known or suspected sepsis at the time of death, or at the time of donation in the case of a *living donor*;
- 25) persons who, since 1977, were born in or have lived in any area of central or west Africa (includes Cameroon, Central African Republic, Chad, Congo, Equatorial Guinea, Gabon, Niger, and Nigeria) and persons known to have had sexual contact with any such person³;
- 26) persons who have had a recent smallpox vaccination (vaccinia virus) and persons who acquired a clinically recognizable vaccinia virus infection by close contact⁸ with someone who received the smallpox vaccine;
- 27) persons whose cause of death (COD) cannot be determined and there is likelihood of other exclusionary criteria;
- 28) persons who are known to have malaria or be at risk for malaria;
- 29) *reproductive donors* who have had or have been treated for *Chlamydia trachomatis* or *Neisseria gonorrhoea* infection in the preceding 12 months. If infection and treatment occurred more than 12 months ago, evidence of successful treatment such as a negative test result *must* be documented.
- 30) *living donors* who received a blood transfusion within the preceding 12 months unless approved by the Medical Director in conformance with generally accepted standards of practice (see Title 10 of New York Codes, Rules and Regulations, Section 52-3.4);
- 31) *birth tissue* donated at vaginal delivery when there is significant local viral, parasitic, mycotic, or bacterial infection of the birth canal and, for any delivery, a current intrauterine infection;
- 32) persons with a history of being diagnosed with Ebola virus disease or who are at risk based on current CDC risk information; and
- 33) based on current recommendation published in FDA guidance, persons who have been determined to be at risk for infection with Zika virus.

¹RELEVANT COMMUNICABLE DISEASE AGENT OR DISEASE (RCDAD) - A potentially infectious *microorganism*, virus, or other disease agent that may pose a risk of transmission to *recipients* of, or those who come in contact with, *tissues*. These disease agents/diseases: have sufficient incidence and/or prevalence to affect the potential *donor* population; could be fatal, life-threatening, result in permanent impairment, or necessitate medical or surgical intervention to preclude permanent impairment; and, for which appropriate screening measures have been developed or an appropriate screening test for *donor* specimens has been cleared, approved, or FDA-licensed, and is available. There can also be those disease agents or diseases that could place potential *donors* and/or *recipients* at risk for infection due to accidental or intentional release. RCDADs applicable to all *tissue donors* are (but are not limited to): HIV 1/2, HBV, HCV, human TSE, syphilis, communicable disease risks associated with xenotransplantation, WNV, vaccinia, and sepsis. Donors of viable, leukocyte-rich *tissues* must additionally consider HTLV I/II, and *donors of reproductive tissues* must generally consider *Chlamydia trachomatis* and *Neisseria gonorrhoea*.

²CLINICALLY ACTIVE HEPATITIS C - Infection with hepatitis C virus when it is symptomatic. This means that: the person demonstrates related symptoms such as jaundice, icterus, fatigue, abdominal pain, loss of appetite, nausea, vomiting, diarrhea, low grade fever, headache, joint pain, and/or “flu-like symptoms” **AND**, HCV infection is suspected or has been diagnosed or anti-HCV (EIA) testing is

positive. Also, knowledge of a recent/current positive test for HCV NAT would qualify as a clinically active HCV infection.

³*Tissue banks* using an HIV test that has been approved by FDA to include a *donor* screening claim for detection of HIV Group O antibodies are not required to screen for this risk history.

⁴European countries to be used for deferral of donors based on geographic risk of Bovine Spongiform Encephalopathy (BSE): Albania, Austria, Belgium, Bosnia-Herzegovina, Bulgaria, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Liechtenstein, Luxembourg, Macedonia, Netherlands, Norway, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, United Kingdom, and Yugoslavia.

⁵XENOTRANSPLANTATION - Any procedure that involves the transplantation, implantation, or infusion into a human recipient of either: (1) live cells, tissues, or organs from a nonhuman animal source; or (2) human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs.

⁶XENOTRANSPLANTATION PRODUCT - Live cells, tissues, or organs used in xenotransplantation. Biological products, drugs, or medical devices sourced from nonliving cells, tissues, or organs from nonhuman animals, including but not limited to porcine insulin and porcine heart valves, are not considered xenotransplantation products.

⁷XENOTRANSPLANTATION INTIMATE CONTACT - An “intimate contact of a xenotransplantation product recipient” is a person who has engaged in activities that could result in the intimate exchange of body fluids with a xenotransplantation product recipient. Examples of intimate contacts include, but are not limited to, sexual partners, household members who share razors or toothbrushes, and health care workers or laboratory personnel with repeated percutaneous, mucosal, or other direct exposures. Mere sharing of domicile or casual contact, such as hugging or kissing without the exchange of saliva, would not be interpreted as intimate contact.

⁸CLOSE CONTACT: SMALLPOX - Physical contact with the vaccination site, touching the bandages or covering of the vaccination site, or handling bedding or clothing that had been in contact with an unbandaged vaccination site.

Sources:

U.S. Department of Health and Human Services, Food and Drug Administration, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule (69 FR 29785, May 25, 2004).

U.S. Department of Health and Human Services, Food and Drug Administration, Final Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/PS) dated August 8, 2007.

U.S. Department of Health and Human Services, Food and Drug Administration, Final Guidance for Industry: Recommendations for Donor Questioning, Deferral, Reentry and Product Management to Reduce the Risk of Transfusion-Transmitted Malaria dated August 2013. Updated August 2014.

Title 10 (Health) New York Codes, Rules and Regulations, Part 52. February 24, 2007

Appendix III: TISSUE DONOR PHYSICAL ASSESSMENT FORM REQUIREMENTS

Introduction

This new appendix was derived from a document formerly titled “AATB Guidance Document No 1, v2 Tissue Donor Physical Assessment Form, 6-27-05.” As an appendix, compliance is mandatory. The form and instructions that follow *must* be used to document the *tissue donor physical assessment*.

There are specific requirements related to *tissue donor* identification and *physical assessment*. Standard D4.120 requires that, “Prior to the *recovery* of *tissue* from a deceased *donor*, a *physical assessment* shall be performed by a *responsible person*.” This standard also lists physical findings that may be an indication of infection with, or high risk behavior for, HIV or viral hepatitis, observations that may alert *recovery* personnel to signs related to an active infection (communicable disease) or to contamination due to trauma or medical intervention, all of which can affect *donor* eligibility. Other standards related to significant steps of this process are found in Section C and parts of Section D and Section F such as: *authorization*, *relevant medical records* review, autopsy report, *donor* identification *verification procedures*, and disease screening for infections and conditions that include risk factors and malignancies. These standards cover and exceed expectations in relevant FDA guidance [1].

In 2004, to completely and properly document the *physical assessment* of a *donor*, the AATB membership developed a “Tissue Donor Physical Assessment Form” and a corresponding “Standard Operating Procedure (SOP)”. The original version was a guidance document and it was updated once. Version 2 was issued in 2005 after a work group, comprised mostly of the members who created the original version, suggested improvements to the form after it was in use for about a year.

Six years later, new volunteers headed by the officers of the Recovery and Donor Suitability (RADS) Council, began to meet by conference call and online meetings to modernize the form and the instructions. Their expertise provided many improvements and added a page to the form. Review opportunities were provided to the Quality Council, the Processing and Distribution Council, all members of the RADS Council, as well as to the Physicians’ Council, and their comments were deliberated before sending final recommendations to the Standards Committee. The Standards Committee reviewed the updates and sent the recommendations to the Board of Governors who approved it as a new appendix to the *Standards*.

Tissue banks can adapt and personalize forms and *SOPs* for use in either paper or electronic format, however, all of the contents of this form *must* be included in any format used. *Tissue donor physical assessment* is a significant step in the *donor* eligibility process therefore staff training and periodic evaluation of *competency* is expected. Electronic documentation systems *shall* meet the same requirements for compliance as paper documentation *records*. Uploads (e.g., photos, documents, etc.) can occur during certain steps of the documentation expectations for *physical assessment*. The size of the body schematic is important to optimize documentation; the size of the schematic *must* not be reduced to the point that a reviewer is unable to distinguish the many notations that can be made.

Instructions

The purpose of these instructions is to describe how to properly complete the three-page AATB Tissue Donor Physical Assessment Form. The information contained on these pages and in *relevant medical records* will be used as an aid to determine *donor* eligibility in order to proceed with *tissue recovery*.

This form *shall* be completed in its entirety, prior to *recovery* of *tissues*. Internal findings *should* also be documented in *tissue recovery records* but, except for documenting whether lymph nodes appear

abnormal, this aspect is not addresses here. An “internal findings form” *may* be developed separately.

This *record* identifies the staff involved in each significant step of the *physical assessment procedure*, and documents: *donor* identification and *authorization verification procedures*; the *donor’s* appearance and evidence of donation of organs and/or ocular tissues; the status of an autopsy (if any); a description of each finding; whether photos were taken and if consultations occurred; if there were personal effects and their disposition; and, a summary that attests to acceptability to proceed with *recovery*.

Abbreviations

The following abbreviations are used:

- e.g. - *exempli gratia*; for example, such as; the list is not finite
- i.e. - *id est*; that is; indicates a finite list
- ft - feet
- cm - centimeters
- in - inches
- kgs - kilograms
- lbs - pounds
- ET - endotracheal
- ID - identification
- IV - intravenous
- N/A - not applicable
- NG - nasogastric
- Ortho – orthopedic
- UNOS - United Network for Organ Sharing

Materials

- Indelible ink (blue or black);
- AATB Tissue Donor Physical Assessment Form or fully compliant version (paper or electronic substitute); and
- *Relevant medical records*, including but not limited to: the *document of gift* or *document of authorization*, the *donor risk assessment interview* form, and available, *relevant medical records*.

Safety

Follow established blood borne pathogen precautions.

Instructions for Completing Page 1

Completion of this page: 1) describes how the *donor* was identified; 2) describes the *donor’s* appearance and documents evidence of previous donation of ocular tissues and/or organs; 3) describes the status of an autopsy; 4) documents the *recovery* team’s *physical assessment* findings using a required list of potential risk factors; and, 5) identifies personnel who *verify donor* identification. Information may be derived from available *relevant medical records*, source documents, and/or personnel involved with the care of the patient/*donor*.

Step	Action
Identification	
1	Document the complete name of the <i>donor</i> as written on the <i>document of gift/authorization</i> .
2	Document the recovery agency’s unique <i>donor</i> ID.
3	The manner in which the <i>donor</i> was identified is documented by checking the box next to the

	applicable word(s): “ID Band,” “Body/Toe Tag,” or “Other.” If “Other” is selected, it <i>must</i> be described. Multiple identifiers <i>may</i> be checked.
4	Recreate the ID Band/Tag containing the most information. All identifying tags/bands <i>should</i> match. Or check N/A ID not present if there is no ID band/tag present, or check N/A Photo taken/saved if a photo of the ID Band/Tag was taken/saved instead.
5	Check the “Yes” or “No” box to indicate if there is agreement among <i>recovery</i> team personnel that the body’s physical characteristics (e.g., age, gender, race, height, weight, signs associated with the cause of death, or information on the <i>DRAI</i> form) are consistent with available <i>relevant medical records</i> and the identification is consistent with other documents. If “No,” appropriate management <i>shall</i> be contacted for guidance before proceeding with <i>recovery</i> . The <i>SOPM</i> <i>shall</i> include directions when the <i>donor’s</i> identification is discrepant or questionable.
6	On the line provided, print the names or initials of the <i>tissue recovery</i> personnel present that <i>verified</i> the <i>donor’s</i> identification. Document the date and time noting when this step was completed. Identify the appropriate time zone per <i>SOPM</i> .
Appearance/Evidence of Donation	
7	Enter a number for the height of the <i>donor</i> followed by checking a box indicating the appropriate selection designating whether this is inches (in.) or centimeters (cm.).
8	Check the box that indicates the method the team used to obtain the height: use “estimated/team” if estimation by the team's <i>responsible person(s)</i> ; use “actual” if direct measurement was performed; use “reported” if <i>relevant medical records</i> (for “source”, enter the specific source). The <i>responsible person(s)</i> of the team <i>must</i> agree upon and document one value for height. Check multiple boxes if the team used multiple methods.
9	Enter a number for the weight of the <i>donor</i> . Check the box for units used [pounds (lbs) or kilograms (kgs)].
10	Check the box that indicates the method the team used to obtain the <i>donor’s</i> weight: use “estimated/team” if estimation by the team’s <i>responsible person(s)</i> ; use “actual” if direct weighing; use “reported” if relevant medical records (for “source”, enter the specific source). The <i>responsible person(s)</i> of the team <i>must</i> agree upon and document one value for weight. Check multiple boxes if the team used multiple methods.
11	Upon initial body assessment, check the box to describe the state in which the body was found such as: evidence of decomposition (e.g., skin sloughing, putrefaction); or, “cleanliness” (e.g., presence on the body of broken glass, dirt, leaves, grime, road abrasions). If “Poor”, describe condition.
12	Check “No” or “Yes” to document evidence of ocular donation. If “Yes”, then check either “corneas only” or “whole eyes” as appropriate.
13	Check “No” or “Yes” to document evidence of organ donation. If “Yes”, then enter the UNOS #.
Autopsy Status	
14	Check appropriate box to indicate if <i>tissue recovery</i> is “pre” or “post” autopsy, if no autopsy is planned, or, if the autopsy plan is unknown.
15	If an autopsy has been done or is planned, indicate the appropriate type describing it as “full”, “limited (e.g., head only),” “view only,” “toxicology screen only,” or if the plan for autopsy is “unknown.” Check only one. Intent can be met if knowledge of the autopsy plan is documented on a form other than the Tissue Donor Physical Assessment Form, however, the information included on the Tissue Donor Physical Assessment Form <i>must</i> be covered in entirety (i.e., all the options listed <i>must</i> be covered). In cases where some <i>tissue</i> is <i>recovered</i> pre-autopsy (e.g., ocular) and more tissue (e.g., bone) is recovered post-autopsy, the events <i>should</i> be documented in the <i>donor record</i> and reflected on the schematic.”

Assessment	
16	For each step #17 through # 28 inclusive, check “No” or “Yes”. If “Yes”, then describe the finding thoroughly. If visualization or palpation is not possible, then check the box and explain why.
17	Are abnormal ocular findings (e.g., icterus, scarring) present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”). If ocular tissue was <i>recovered</i> prior to this assessment, then check “Unable to visualize” and follow-up with personnel at the local Eye Bank to obtain document.
18	Are white or yellow spots in the mouth present? Check “No” or “Yes”. If “Yes”, then describe. Check “Unable to visualize” if oral cavity is not accessible to visualize and explain why. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
19	Is jaundice present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
20	Are signs of trauma or infection present on the body where <i>recovery</i> of <i>tissue</i> is planned (<i>tissue recovery</i> areas)? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
21	Is a rash, scab, or non-genital <i>skin</i> lesion present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
22	Are blue/purple (gray/black) spots/lesions present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
23	Are signs of non-medical injections present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
24	Document if no enlarged lymph/abnormal node(s) is (are) observed (“No”), or if any are observed (“Yes”). Explain any “Yes” findings here or, if space is limited, document where the description can be found (e.g., see schematic, see Notes, etc.). Lymph nodes can be palpated bilaterally just under the <i>skin</i> of the neck, axilla, and groin. When lymph nodes can be visualized and are found to be enlarged/abnormal, such findings <i>must</i> be documented in the <i>recovery records</i> however there is not an expectation to identify them on the body schematic. An enlarged lymph node can appear swollen [a node that is an inch (2.5 centimeters) or more in diameter in an adult], and abnormal findings can be if it is draining pus or feels hard [2].
25	Is evidence of an enlarged liver (hepatomegaly) present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”). If the liver cannot be assessed, then check “Unable to assess” and explain. If liver is not present, there is an expectation to follow-up to obtain documentation of the description of the liver (e.g., with OPO personnel, a pathologist, a researcher).
26	Are genital lesions present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
27	Are perianal lesions or anal trauma present upon rectal examination? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).
28	Are tattoos/piercing present? Check “No” or “Yes”. If “Yes”, then describe. If additional space is needed, then write where to find details (e.g., “see schematic”, “see Notes”).

Instructions for Completing Page 2 (Schematic)

Completion of this page documents all of the *physical assessment* findings by team members by recording them on anterior and posterior body diagrams (schematics) using a standardized Key. This will include

those findings documented during assessment on page 1 plus any other observations. Documentation also occurs if no findings are seen on either schematic view. Personnel who perform the *physical assessment* are identified as well as when it was performed.

1	Document the recovery agency's unique <i>donor</i> ID.
2	All gross findings are appropriately drawn or otherwise identified (i.e., such as when using electronic <i>records</i>) on the anterior and posterior body schematics using the lettered Key provided. Blank schematic Key spaces are available to document gross findings not listed and/or to provide areas to further describe any listing [e.g., (H), (N)]. Piercing location, body jewelry, and each tattoo's location and content are important to describe on this form or in additional notes.
3	If no findings are evident on either schematic view, check the appropriate box below it to indicate "no observations noted."
4	Document the name or initials of each team member who performed the <i>physical assessment</i> . Document the date and time noting when this step was performed. Identify the appropriate time zone per <i>SOPM</i> .

Instructions for Completing Page 3 (Summary)

Completion of this page documents: 1) if any photos of the body were taken; 2) if consultation occurred regarding *physical assessment* findings; 3) if personal effects were with the body and if so a description of which ones and their disposition; and, 4) a summary and whether this *donor* is acceptable or not to proceed with *tissue recovery*.

1	Document the recovery agency's unique <i>donor</i> ID.
2	Were photos of the body taken? Check "No" or "Yes". If "Yes", then provide relevant information about the photos in the "Notes" section. A process <i>should</i> be established to share photos upon request from the <i>tissue bank</i> determining donor eligibility. This question regarding taking of photos <i>must</i> be addressed but intent is met if this information is captured on a form other than the Tissue Donor Physical Assessment Form.
3	Did consultation of <i>physical assessment</i> findings occur? Check "No" or "Yes". If "Yes", then provide relevant information about any consultation in the "Notes" section. This area can also be used for documenting details regarding whether a biopsy was requested and taken.
4	Document if there are no personal effects with the <i>donor</i> body ("No") or check "Yes" if personal effects are present. Personal effects can be, for example, clothing, a wallet/purse, cash, credit cards, drug paraphernalia, mobile phone, and/or jewelry but, if present, require a description and their disposition. Intent is met if personal effect information is documented on a form other than the Tissue Donor Physical Assessment Form.
5	After a review of available <i>relevant medical records</i> and the <i>physical assessment</i> findings have been completed, a <i>responsible person</i> from the <i>recovery</i> team must indicate "acceptable" or "not acceptable," then document their name or initials and date of completion of this process. Identify the appropriate time zone per <i>SOPM</i> .
6	After all documentation has been reviewed for legibility, completeness and accuracy, the form is appropriately forwarded.

Notes Regarding Documentation

Standard C1.100 requires that "Documentation must be made concurrent with each significant step." All findings *must* be documented concurrently with the performance of the physical assessment. Any changes made to the document after the examination *must* include the date the change was made, initials of the person making the change, and the reason/rationale for the change. Changes to actual findings *should* be

based on photos that support the change.

The spaces provided on this form for documenting observations *may* be expanded to meet local policy, such as adding a listing for “lividity” or “rigidity/contractures” in the Key, adding space reserved for documenting more notes, or increasing the space for documenting names, numbers, or identifiers. Other additions *may* be made but the content of this form *must* be included in entirety. For example, the letter selected to identify any listing in the Key can be different but all of the listings in the Key to this guidance document *must* be used. The size of the body schematic is important to optimize documentation; the size of the schematic *must* not be reduced to the point that a reviewer is unable to distinguish the many notations that can be made.

Proper methods of documentation *must* be utilized, including revisions to *records*. Revisions *shall* be made with a single line drawn through the altered text with the revision initialed and dated by the person making the revision. Additions to a completed *record shall* be initialed and dated by the individual making the additions (see C1.500). All entries *must* be legible.

It’s preferred that documentation concerning “time” be based on a 24-hour clock (military time). Use of the notations “pm” and “am” is not preferred. *Tissue recovery* documentation *shall* use the time zone appropriate to the time and place of *recovery*.

Deviations from written *procedures shall* be documented and shared with all entities that determine *donor* eligibility and approve release of *tissue*.

References

1. U.S. Department of Health and Human Services, Food and Drug Administration, Final Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 8, 2007.
2. The Merck Manual, Home Health Handbook for Patients and Caregivers, http://www.merckmanuals.com/home/heart_and_blood_vessel_disorders/lymphatic_disorders/swollen_lymph_nodes.html (accessed April 30, 2016)

Historical Changes

Previous Page #	Summary of Changes
New on 2/23/04 (SAB/AM/AG)	
Version 2 effective date 6/27/05 (PA Workgroup/SAB)	
1	Added reference to this being “Version 2”, new date, and address updated
3	Table of Contents pages and titles updated
4	Provided listing of standards that are related; verbiage changes and additions made for clarification; reference to staff training and competency added.
5	Updates made to abbreviations in B.; addition of “available, relevant” to medical records; and punctuation changed in part E.
6	Verbiage additions and changes made for clarification.
7	Verbiage additions and changes made for clarification. “Globes” replaced with “whole eyes” to match EBAA terminology.
8	Removed “icterus” in step 17 and placed it in later step (28); adjusted wording accordingly.
8	Step 19 amended to document the new observation listing for “tattoos/piercings” to

	accommodate new federal guidance (Donor Eligibility).
8	Removed instruction in step (old 22) that is no longer considered part of <i>physical assessment</i> : “Document by checking the appropriate box, if infectious precautions are known for this patient (“Yes”), or not (“No”).”
8	Changed “perianal warts” to “perianal lesions” to encompass more possibilities that may be seen.
8	Added provision for documenting evidence of rash, scab, or skin lesion (non-genital) to accommodate new federal guidance (Donor Eligibility).
9	Change to step 28 is to address documentation of abnormal ocular findings that was added to accommodate new federal guidance (Donor Eligibility).
9	Documenting limitations of visualization when it’s restricted is offered as needed.
9	Body Appearance section amended to report “Cleanliness” instead of “Basic Hygiene” to accurately reflect intent; and, “Body Profile” deleted since height and weight is previously reported.
9	Step numbers updated and order of last two steps changed.
10	In step 2, use of blank schematic Key spaces is now described.
10	Ampersand (&) included in deletion example.
10	Part G. amended to include general instruction to document/share any deviations from written procedures that occur.
13	Identification area updated by: 1) adding “/gender” to “sex”; 2) adding checkbox for height measurement in centimeters; 3) addition of “source:” and lines for documenting it for both “reported” height and weight assessments. “Actual” assessment box for height and weight moved to last selection in the row since it likely occurs less often than others. Changed case for capitalizations of measurements.
13	Evidence of Donation/ Autopsy area changed to list “whole eyes” instead of “globes”.
13	Recovery Team Assessment area updated by: 1) removal of icterus from first checklist item, then added later in listing for ocular findings; 2) addition of individual checklist item for “tattoo/piercing”; 3) addition of individual checklist item for “rash, scab, skin lesion (non-genital)”; 4) additional individual checklist item for “abnormal ocular finding (i.e. icterus, scarring)” with further checkbox provision for “unable to visualize”, if applicable; 5) limitation for visualization of “oral cavity” removed since there are two scenarios that can occur now. Added “Notes/” to “Explain if unable to visualize...” to clarify intent to document anything relevant in space provided.
13	In the General Appearance area, deleted “Basic Hygiene” and changed to “Cleanliness”; entirely deleted Body Profile and selections.
13	Switched order of last two line items.
14	Added a selection for labeling a ‘scab’ by using the letter W. Changed “for” to “prior to” in Summary.
15, 16	Added example pages of the sample form completed in entirety for a fictitious donor.
13–16	Removed all checkboxes and spaced selections appropriately.
6–8	Changed all references to “checking” or “box” and replaced them with directions to circle appropriate selection or word.
Appendix III (RADS Council Workgroup/SAB)	
1	The title was changed from a guidance document to an appendix. This was done to clarify original intent that using this form and following the instructions are mandatory.
3	The list of latest contributors was added.
4	Section listings have been expanded with new subsections; pages and titles updated.
5	The Introduction was expanded to include: a broader description of other standards related to significant steps of the <i>donor</i> eligibility determination process; a description that this method, or an equivalent method, <i>shall</i> be implemented, and that periodic evaluation of

	competency is expected for staff performing <i>physical assessment</i> ; clarification that electronic documentation systems <i>shall</i> meet the same requirements for compliance as paper documentation records; and, a description of this version’s development and the approval process.
6, 7	The Purpose is described in more detail, more Definitions and Abbreviations were added, and the Materials section updated to clarify that full compliance is expected. It is additionally described that, except for documenting whether lymph nodes appear enlarged/abnormal, this guidance document does not address internal findings and that an “internal findings form” can be developed separately.
8 to 11	On each page, the procedural steps were updated to align with changes to the form in regard to: the new order of the listing of signs in the Assessment box; the switched order of documenting “No” and “Yes” which are now further separated on the form to provide better documentation practice; and, descriptions changed to documenting “No” or “Yes” instead of using directions to “circle appropriate selection or word.”
8	In the Identification box, procedural steps have been revised to meet changes to the form such as: documentation of agreement among <i>recovery</i> team personnel that the body’s physical characteristics and identification are consistent with available <i>relevant medical records</i> ; direction provided to contact appropriate management for guidance prior to <i>recovery</i> if there is a discrepancy regarding identification of the body; the procedure describes an expectation that the SOPM shall include directions when the donor’s identification is discrepant or questionable; and, there was an addition made to document not only the date and time when these critical steps were performed but also the appropriate time zone.
9	Procedural steps were updated to describe more detail how the donor’s weight was derived and that the weight documented was agreeable to all recovery personnel, and a new selection was added to the type of autopsy (i.e., toxicology screen only).
10	Procedural steps were updated to describe more detail, especially: when there is an expectation to contact the local Eye Bank and obtain documentation of their ocular assessment; the possible color of spots in the mouth was expanded to include not only white but also yellow; the locations on the body where lymph nodes can be palpated were added; findings of abnormal lymph nodes <i>must</i> be documented but there is not an expectation to identify them on the body schematic; a description was added to provide background on the size of an enlarged lymph node and that abnormal findings can relate to draining pus and/or if it feels hard; and, a reference to the Merck Manual was added. For a few listings that have multiple terms in a listing, a new description states there is no longer an expectation to also circle the word(s) in the listing to indicate which finding(s) were identified, but it (they) <i>must</i> be clearly explained and identified on the schematic.
11	Procedural steps were updated to describe more detail, especially: to allow documentation when the liver cannot be palpated and space to explain why; that there is an expectation to document if a tattoo is suspected to be recent/new and descriptive examples are now provided (i.e., scabbing is present on tattoo, tattoo area is shaved, tattoo has vibrant colors, or if there is inflammation/swelling/redness within the tattoo), and that providing a description (location and content/subject) of any tattoos and the location of piercings and type of body jewelry are also expectations; and, the observation for “perianal lesions or insertion trauma” was changed to “perianal lesions or anal trauma” because referencing “insertion trauma” could be subjective. At “Instructions for Completing Page 2 (Schematic)” it now states that a standardized Key is used, and that documentation also occurs if there are no findings on either schematic view. A summary was added that completion of a new page expects the following additional documentation: 1) if any photos of the body were taken; 2) if consultation occurred regarding <i>physical assessment</i> findings; and 3) if personal effects were with the body. Direction includes that any consultation be explained in the “Notes” section, and that this area can also be used for documenting details

	regarding whether a biopsy was requested and taken. If personal effects are present a description and their disposition is now required documentation.
12	A new section (Notes Regarding Documentation) gives a description that spaces provided on this form for documenting observations can be expanded to meet local policy and that additions can be made to the form but the content of this form <i>must</i> be included in entirety. It's now clarified that documentation concerning "time" is preferable when based on a 24-hour clock (military time). Use of the notations "pm" and "am" are now described as not preferred. Documenting the appropriate time zone for the respective region has been added. Documenting and sharing deviations is now required when the deviation can affect the eligibility determination of the donor or release of tissue. The list of references was updated and a few added. The section on Historical Changes was reformatted.
13	A comment period produced a number of recommendations that were accepted in full, accepted in part, or rejected. Refer to "Compiled Comments & Responses to Tissue Donor Physical Assessment Form".

The AATB recognizes the efforts of the following individuals who generously donated their time and expertise to creating these requirements.

Versions 1 & 2

Murray Anderson
D. Shawn Archer
Ken Blair
Dorothy Daniel
Daniel De'Lap
Joe Ferlise
Edmundo Ferreol, MD
Pat Fiedler
Tim Fischer
Mary Beth Fisk
Tammy Franz
Amy Gamble
Gail Gantt
Sara Gonce
Glenn Greenleaf
Rusty Kelly (EBAA)
Dave Korroch (EBAA)
John Lee
Allyson May
Catherine A. Mazzei, MD
Orlando Merced-O'Neill
Carolyn Pinckley
Ricky Roth
Larry Sussman
Carol Vaught
Randy White
Diane Wilson
Tina Wilusz
Erin Wray
Jerry Wright
Bruce Zalneraitis

Appendix III

Patrick AbdelMessih
Krissy Andrzejewski
Luba Ashurov
Ryan Cady
Kelly Cendrowski
Debbie Columbia
Edmundo Ferreol, MD
Catherine Hankins
Laura Kline
Paul Kostiak
Stephanie McGaffin
Arnitha Lim
Ryan Nelson
Brian Roe
Erica Stone
Juli Tripple
Marja van Wijk, MD
Jie Zhao

RADS Council Officers:

Ronda Horstman
Rick Kolovich
Walter Recker

AATB Accreditation Program

Liaison:
Jason LoVerdi

Scott A. Brubaker (editor)

AATB Tissue Donor Physical Assessment Form

Identification:

Name on Document of Gift/Authorization: _____ Recovery Agency ID: _____

Manner identified by: ID Band Body/Toe Tag Other (describe): _____

Identification Band/Tag:

ID re-created:

Or:

- N/A Photo taken/saved
 N/A ID not present

The body's physical characteristics (e.g., age, gender, race, height, weight, signs associated with the cause of death, or information on the DRAI form) are consistent with available relevant medical records, and the identification is consistent with other documents.

Yes No

If answered "NO," contact appropriate management for guidance before proceeding with recovery.

Personnel verifying donor ID: _____ **Date/Time/Zone:** _____ / _____ / _____

General Appearance/Evidence of Donation:

Height: _____ in cm **Height is:** estimated/team actual reported (source : _____)

Weight: _____ lbs kgs **Weight is:** estimated/team actual reported (source : _____)

Cleanliness: Good Poor (Describe if poor): _____

Ocular Donation: No Yes If "Yes," corneas only whole eyes

Organ Donation: No Yes If "Yes," UNOS # _____

Autopsy Status: Pre-Autopsy Recovery Post-Autopsy Recovery No Autopsy Planned Unknown

Type: Full Limited View only Toxicology screen only Unknown

Assessment:

Are there signs of any of the following? Explain "Yes" answers, or any if "unable to visualize/palpate."

No....Abnormal ocular findings (e.g. icterus, scarring) ... Yes Unable to visualize: _____

No....White/Yellow spots in the mouth Yes Unable to visualize: _____

No....Jaundice Yes: _____

No....Trauma/Infection to tissue recovery areas Yes: _____

No....Rash/Scab/Skin lesion (non-genital) Yes: _____

No....Blue/Purple (gray/black) spots/lesions Yes: _____

No....Non-medical injection site Yes: _____

No....Enlarged/Abnormal lymph node(s) Yes: _____

No....Enlarged liver Yes Unable to assess: _____

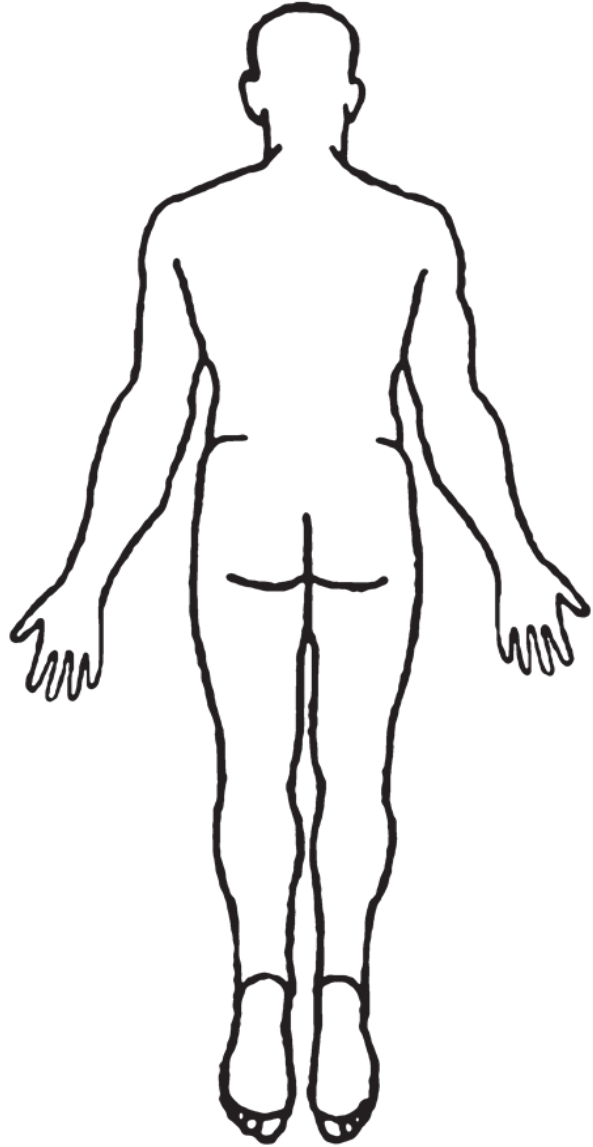
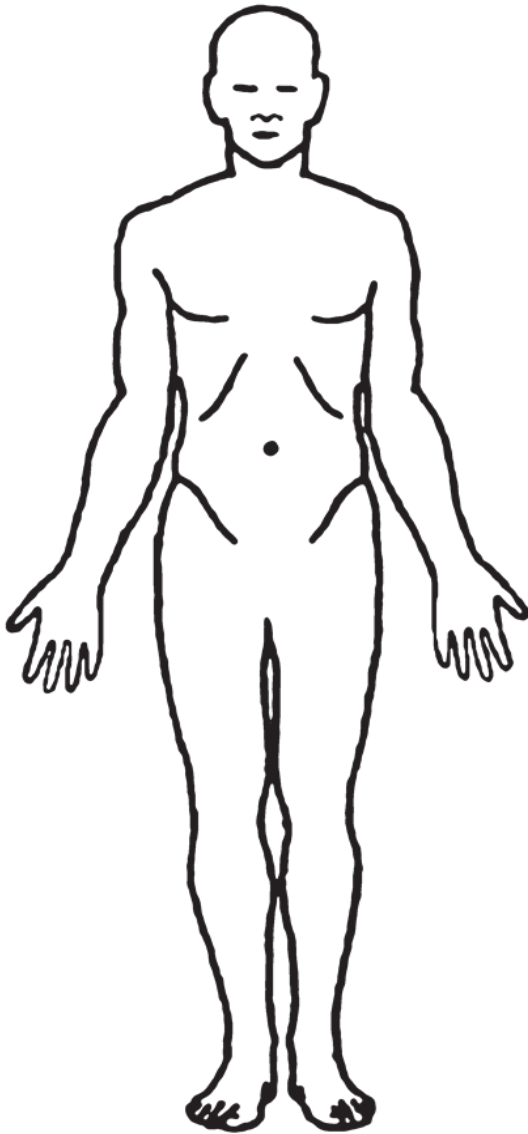
No....Genital lesions Yes: _____

No....Perianal lesions or Anal trauma Yes: _____

No....Tattoos/piercing Yes: _____

Tissue Donor Physical Assessment Schematic

Recovery Agency ID: _____



Check if no observations noted

Check if no observations noted

Key to Schematic:

<ul style="list-style-type: none"> (A) Abrasion (B) Bruise/Contusion/Hematoma (C) Cast/Ortho device (D) Dressing/Bandage (E) ET tube/NG tube (F) Fracture/Dislocation (G) IV/IO/Arterial Line (H) Skin Tag(s) (I) ID Band/ Tag (J) Laceration/Wound (K) Autopsy Incision (L) Needle entry site (M) Organ Recovery Incision 	<ul style="list-style-type: none"> (N) Body piercing – requires description (O) Urethral catheter (P) Skin lesion – requires description (Q) Scar (surgical/trauma) (R) Rash (S) Ocular Donation (T) Tattoo – requires description (also note if suspected to be new) (U) Stretch mark(s) (V) Mole (W) Team Blood Draw Site (X) _____ (Y) _____ (Z) _____ (AA) _____
---	--

Physical Assessment performed by: _____ **Date/Time/Zone:** _____ / _____ / _____

Tissue Donor Physical Assessment Summary

Recovery Agency ID #: _____

- No..... Were photos of the body taken?..... Yes
 No..... Did consultation of physical assessment findings occur? ... Yes

Notes:

- No..... Personal effects with body..... Yes

If yes, check only those that apply and describe:

- Clothing Describe: _____
 Wallet/purse..... Describe: _____
 Jewelry Describe: _____
 Other Describe: _____
 Other Describe: _____
 Other Describe: _____
 Other Describe: _____

Disposition:

Summary:

A review of available relevant medical records and physical assessment findings were completed prior to recovery and found to be: **acceptable.** **not acceptable.**

Responsible Person

_____/_____/_____
Date/Time/Zone

Appendix IV:
PREVENTION OF CONTAMINATION AND CROSS-CONTAMINATION AT RECOVERY:
PRACTICES AND CULTURE RESULTS REQUIREMENTS

Introduction

In the spring of 2002, the Board of Governors assembled a Task Force to review reports of recipient infections that were allegedly associated with *tissue allografts*. In 2003, the Task Force made several recommendations that were considered by the Standards Committee. It was determined that additional steps could be taken to control the possibility of contamination and/or *cross-contamination* during *recovery* of *tissue* from deceased *donors*, and that the presence of certain *microorganisms* would necessitate discard of the *tissue*. The Committee also agreed that the interpretation of associated *recovery* (pre-processing) cultures from the same *donor* warrant scrutiny, and that sharing culture results is important.

The Board of Governors decided to include some of these recommendations in the AATB's *Standards for Tissue Banking*. Other recommendations were more representative of good practice, and these recommendations were published in the original version of this work when it was titled "Prevention of Contamination and Cross-contamination at Recovery: Practices & Culture Results, Guidance Document (No. 2), October 20, 2004."

In early 2006, a technical work group was formed to expand the content of the guidance to include another factor that could prevent contamination and *cross-contamination at recovery*. Suitability of the site where *tissue recovery* takes place *must* be evaluated and determined to be acceptable prior to *recovery*, and revisions were made to D5.500. The goal is to set specific guidelines/suitability parameters that define required controls. There is not an expectation that actual detailed monitoring be performed at each *recovery site*. Parameters have been developed that, when applied, can ensure that the environment in which *recovery* occurs meets minimum specifications and *should* not introduce, transmit, or spread contamination. These additional controls are appropriate and reasonable and have been formulated by this work group from practices tested and used by AATB-accredited *tissue banks*.

In January of 2007, another work group of subject matter experts was organized to collect information regarding how *tissue banks* were applying the *zone recovery* concept and *sequencing* to their *recovery* operations. These practices were reviewed for consistency and common practices were added to this work. There is consensus that documentation methods that describe zones and *sequencing* facilitate *tissue* suitability determinations. Version 2 of the guidance document was published on May 29, 2007 and included updates for *zone recovery* and *sequencing*, and added *recovery site* suitability parameters along with a sample form.

In 2016, the guidance document became an appendix to the *Standards* when the 14th edition was published.

Definitions

As used in this appendix, the following definitions apply:

SEQUENCING - A procedure utilized at *tissue recovery* that documents the order (sequence) that *tissues* were *recovered* from one *donor*.

ZONE RECOVERY - A *tissue recovery* method by which specific, well-defined areas of the body are identified as zones and from which individual *tissues* are *recovered* using the same sterile instrumentation/equipment and sterile gloves. It is recommended that *skin recovery* be performed as a separate zone so that *pre-sterilization/pre-disinfection culture* results of other *tissues* can be independently reviewed.

ISOLATION DRAPING - A method used whereby areas adversely affected by trauma are first segregated (isolated) by entirely covering them to contain potential contamination and prevent *cross-contamination* to other *tissues recovered* from the same *donor*. If *tissues* from these areas are retrieved, they *should* be sequenced as the last to be recovered.

Recovery Practices

RECOVERY TECHNIQUES:

Certain *tissue recovery* practices may be helpful in controlling contamination and *cross-contamination* of individual *tissues*. These include *recovery* techniques such as *sequencing* of the *tissue recovery*, use of well-defined *zone recovery* techniques, and *isolation draping* in the presence of trauma (see D5.530). *Recovery* activities *should* be reviewed to help determine the likelihood of *cross-contamination* of individual *tissues*.

RECOVERY SITE QUALIFICATION:

Parts of applicable federal regulations can be referenced (at §1271.190 Facilities, and at §1271.195 Environmental Controls and Monitoring) and used as guides for practical application when determining that a *recovery site* is satisfactory. The evaluation of the suitability of the site of *recovery* *must* be documented and this *record* shared with entities that receive *tissues* from the *donor* [at §1271.160 Quality Program, (b) Functions (2)]. Due to many circumstances related to events that could occur after death, the donor body may be moved to various sites (e.g., dedicated tissue recovery site, healthcare facility operating room, autopsy suite). The room in the building where *tissue recovery* takes place *must* offer a level of control that will not increase the potential to introduce contamination or cause *cross-contamination*. Minimum qualification parameters have been established that *should* ensure control of this environment and be *qualified* for *tissue recovery*.

Prior to *recovery*, the following evaluations are performed and there *must* be:

- 1) adequate floor and tabletop space to allow separation of sterile instrumentation and performance of *aseptic recovery procedures* (i.e., *zone recovery*, *sequencing*, *draping*, *tissue wrapping*);
- 2) adequate lighting to perform *physical assessment* and *tissue recovery*;
- 3) adequate plumbing and drainage for the intended purpose to include access to an adjacent or suitably located hand-washing area that can be used to perform a hand/forearm surgical scrub or wash;
- 4) a controlled, closed airflow system in the *recovery* area. This means there is no direct access to the outside of the building from the room at any time during, before, or after *tissue recovery* (e.g., doors, windows that can open, fans, air conditioners); In addition, all vents appear clean and there is no vented airflow noted to be directed and flowing onto sterile fields;
- 5) walls, floor, and work surfaces that are easily cleanable (i.e., non-carpeted, not porous) and in a good state of repair;
- 6) no visible signs of insects, rodents, or other pests;

- 7) an evaluation for any standing fluids or contaminated waste in the room that could be a source of airborne bacteria, mycobacteria, yeasts or fungi, and if present, it *must* be rectified prior to *recovery*; and
- 8) proper preparation of the *recovery site* by cleaning and *decontaminating* all working surfaces prior to *recovery of tissue*;

Concurrent with *tissue recovery*, the following site parameters *must* be controlled:

- 1) human traffic is restricted and all personnel entering the *recovery* area must be properly outfitted and their movement controlled; and
- 2) no other activities (i.e. embalming, autopsy, another *tissue donor recovery*) can occur simultaneously in the same room as this *tissue recovery*;

After *tissue recovery*, the following activities *must* be performed:

- 1) all contaminated/biohazardous re-usable supplies were *decontaminated*, and adequately contained for transport, and that contaminated/biohazardous waste was properly disposed, or contained and transported to a disposal site; and
- 2) all working surfaces and the floor were *decontaminated* using approved solutions and equipment.

Note: If there is an ability to rectify certain parameters that may not be initially met (e.g., there is a need to cover room furniture, drains, sinks, or walls), this *must* be described in *procedures*, and such a scenario warrants review by a designated, *responsible person* prior to proceeding with *recovery*. There *must* be assurance that there is no evidence that the scenario would compromise the suitability of the *recovery site* by being a source of contamination or *cross-contamination*.

Recovery personnel *must* document whether the above parameters have been met, and if the *recovery site* has been determined to be suitable. See “Sample Tissue Donor Recovery Site Assessment Form” in this appendix.

ZONE RECOVERY AND SEQUENCING:

The primary objective of *zone recovery* is to reduce the potential spread of *microorganisms* (*cross-contamination*) from one region of the body to another by employing isolation techniques. Isolation is accomplished through evaluation of trauma, specific draping if necessary, placement of drapes after the *skin prep* has occurred, and by using dedicated instruments for each zone. The recovery technician *must* also make glove changes between zones and *may* change their gown when indicated (e.g., when it becomes soiled or contaminated, or when *sequencing recovery* from a zone that is at increased risk for contamination to a zone of lesser risk). By performing these functions and documenting actions this will facilitate suitability determinations made from *pre-sterilization/pre-disinfection culture* results. These guidelines are reproducible in multiple settings and scenarios and, when followed, can reduce the risk of contamination and *cross-contamination* at *recovery*.

A zone is identified as a region of the body. Zones are recovered in a sequence that is recorded, but the sequence order cannot be prescribed due to many possible variables. If preferred, gloves can be changed following each *tissue recovered* within a zone. In the presence of trauma when *isolation draping* methods are used, these areas become zones that are prepped and *tissue* excised only after *recovery* of all other *tissue* has occurred.

Some zones (i.e., *skin*, vertebrae/spine, the pelvis, thoracic cavity, traumatized areas) *should* be treated as inherently possessing an increased risk for contamination and warrant special consideration when *recovering tissue* in that zone (e.g., deciding the sequence of *zone recovery* and whether extra gown changes *should* occur). *Recovery records should* include space to document unanticipated zones due to trauma or other factors.

Common zones:

- *skin* - back, abdomen, left anterior leg, right anterior leg, left posterior leg, right posterior leg;
- ocular - corneas, sclera, whole globes;
- intracranial *tissue* - *dura mater*, brain;
- mandible;
- thoracic - heart, thoracic aorta, pericardium, ribs, nerves;
- abdomen - abdominal aorta, iliac artery and vein, nerves;
- upper extremity left - rotator cuff, humerus, radius, ulna, metacarpals, nerves;
- upper extremity right - rotator cuff, humerus, radius, ulna metacarpals, nerves;
- lower extremity right - vessels, assorted tendons, fascia lata, femur, tibia (with patellar ligament), tibia, fibula, Achilles tendon with calcaneus, talus, nerves;
- lower extremity left - vessels, assorted tendons, fascia lata, femur, tibia (with patellar ligament), tibia, fibula, Achilles tendon with calcaneus, talus, nerves;
- left hemi-pelvis/ilium - due to proximity of the hemi-pelvis to the viscera, these *tissues should* be *recovered* after all other *musculoskeletal tissues* from the respective extremity have been *recovered* and *packaged*;
- right hemi-pelvis/ilium - due to proximity of the hemi-pelvis to the viscera these *tissues should* be *recovered* after all other *musculoskeletal tissues* from the respective extremity have been *recovered* and *packaged*; and
- vertebrae/spine - cervical, thoracic, lumbar; due to the proximity of the vertebrae/spine to central nervous system fluids and *tissues*, these *tissues must* be considered a separate zone.

DOCUMENTATION:

Practices to control contamination and *cross-contamination* at *recovery must* be utilized as described and *recovery agencies must* document these significant steps. *Recovery records* (forms) *must* reflect the sequential *recovery* of all *tissues* and there *should* be a written statement to acknowledge “*zone recovery* techniques were utilized.” The individual zones for each *donor must* be identified on the paperwork so all processors can utilize this information along with the results of the *pre-sterilization/pre-disinfection cultures*. The order of *recovery* of each zone cannot be prescribed but the sequence of zones *must* be recorded in the *recovery records*. It is recommended that order of *recovery* within a zone be recorded. Any *deviation* from established protocols for *isolation draping*, *zone recovery*, or *sequencing*, *must* be approved by a *responsible person* and details documented.

Records must be maintained and shared demonstrating that pre-established suitability parameters for the recovery site were determined to be acceptable prior to tissue recovery. See “Sample Tissue Donor Recovery Site Assessment Form” in this appendix.

Pre-sterilization/pre-disinfection Cultures Results

RESULTS REPORTING AND SHARING:

To facilitate *tissue* suitability determinations, *pre-sterilization/pre-disinfection cultures* results *must* be provided to recovery agencies by testing laboratories or *tissue* processors within a reasonable amount of time after *recovery*.

Knowledge of a *donor’s pre-sterilization/pre-disinfection cultures* results could affect the eligibility determination made by different processors. Therefore, recovery agencies *must* share relevant *tissue recovery* culture information (*pre-sterilization/pre-disinfection cultures*) with all tissue establishments who are known to have also *recovered tissues*, or to have received *recovered tissues*, from the same *donor* (see D4.300). Procedures *must* be used that describe how this information is received and disseminated in a timely fashion so that proper *tissue* disposition decisions can be made. The “Current Good Tissue Practices for Human Cells, Tissues, and Cellular and Tissue-Based Product Establishments, Final Rule¹” (CGTPs) describes the need for *procedures* for sharing of results from the same *donor* that relate to the possible contamination of the product or potential transmission of disease [at §1271.160 Quality Program, (b) Functions (2)]. For details regarding expectations for sharing of *records*, refer to B1.500, D4.300, F3.100, J1.200, and K1.100.

PATHOGENIC, HIGHLY VIRULENT MICROORGANISMS:

Two *microorganisms* (and others that have been identified for specific *tissue* types, see E2.800), are considered pathogenic, highly virulent organisms. Individual *tissues* with culture results yielding *Clostridium* or *Streptococcus pyogenes* (group. A strep.) *should* be discarded (see K2.310). Other individual *tissues* from the same *donor* that were *recovered* under conditions that could result in *cross-contamination* *should* also be discarded unless they can be treated with a *validated sterilization* process (see K2.320). Tissue establishments (i.e., processors) that determine final *donor* eligibility *may* consider that more *microorganisms* fit this classification.

Considerations

CULTURING METHODS:

There are different *pre-sterilization/pre-disinfection culturing* methodologies in use. The filter-culturing technique that is used for *tissue* types such as *cardiac tissue* (C) and *vascular tissue* (V) has a sensitivity that is likely higher than that experienced by the swabbing techniques that are most popular for use with *musculoskeletal tissue* (MS) types. Establishing quantifiable bioburden, actual colony forming units per mL (CFU/mL), can be accomplished via filter-culturing and fluid-extraction techniques² but not by limitations of swabbing techniques and protocols used. The low accuracy, sensitivity, and reliability of swab culturing³⁻¹¹ plays heavily upon the decision to discard *tissues* with positive cultures of pathogenic, highly virulent *microorganisms*, since the level of bioburden cannot be established. Also, a negative swab culture may be a false negative result and any result can under-represent all organisms present³⁻¹¹. This is especially suspect if one *tissue* grows *Clostridium* or *Streptococcus pyogenes* yet another *tissue* sequentially *recovered* in the same *recovery* zone does not. *Validated sterilization* processes *must* be in place to allow *processing tissues* meeting this scenario.

PROCESSING METHODS:

Generally, there are two *processing* methods: *disinfection* and *sterilization*. If a *tissue* type is *processed* in a fashion where it is not *sterilized*, only *disinfected* [e.g., *cryopreserved* (MS) like tendons, (OA), (C) and (V)], then considerations *must* be made if there is an associated culture result from that *donor* that is considered pathogenic, highly virulent. If *tissue recovery* controls are in place and documented that offer assurance that *cross-contamination* did not occur, then that *tissue may* be suitable if its own culture result is acceptable. If such controls are not in use and documented (i.e., *sequencing*, *zone recovery*, trauma *recovery* protocols such as *isolation draping*), the intent of this appendix is to discard all *tissues* that were only *disinfected* (not *sterilized*).

References

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10. Mills AR, Roberts MR: "Evaluation of Culturing Methods at Predicting Allograft Sterility for Aseptically Processed Tissue"; AATB Posters and Abstracts, 25th Annual Meeting (2001).
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Sample Tissue Donor Recovery Site Assessment Form

Tissue Donor ID #: _____ **Recovery Site Name:** _____

Recovery Site Location (circle one):

Dedicated Tissue Recovery Site Healthcare Facility Operating Room Autopsy Suite
 Other Area (describe): _____

Check the appropriate box. Any "No" answer *must* be described in detail, rectified if possible, and requires review by a *responsible person*.

Pre-Recovery Evaluation:	Yes	No
1. Adequate floor and tabletop space to allow separation of sterile instrumentation and performance of aseptic recovery procedures (i.e., zone recovery, sequencing, draping, tissue wrapping) is present.		
2. Adequate lighting to perform physical assessment and tissue recovery is present.		
3. Adequate plumbing and drainage for the intended purpose to include access to an adjacent or suitably located hand-washing area that can be used to perform a hand/forearm surgical scrub or wash is present.		
4. The recovery area has a controlled, closed airflow system. This means there is no direct access to the outside of the building from the room at any time during, before, or after tissue recovery (i.e., doors, windows that can open, fans, air conditioners, etc.); In addition, all vents appear clean and there is no vented airflow noted to be directed and flowing onto sterile fields.		
5. The walls, floor, and work surfaces are easily cleanable (i.e., non-carpeted, not porous) and in a good state of repair.		
6. Signs of insects, rodents, or other pests are not visible.		
7. Standing fluids or contaminated waste in the room, that could be a source of airborne bacteria, mycobacteria, yeasts or fungi, are not present.		
8. The recovery room was properly prepared by cleaning and disinfecting all working surfaces prior to recovery of tissue.		

Concurrent with Recovery:	Yes	No
1. Human traffic is restricted and all personnel entering the recovery area are properly outfitted and their movement controlled.		
2. Other activities (e.g., embalming, autopsy, another tissue donor recovery) did not occur simultaneously in the same room as this tissue recovery.		

Post-Recovery Activities:	Yes	No
1. All contaminated/biohazardous re-usable supplies were decontaminated, and adequately contained for transport, and that contaminated/biohazardous waste was properly disposed, or contained and transported to a disposal site.		
2. All working surfaces and the floor were cleaned using approved solutions and equipment.		

Comments: _____

The above parameters have been met and the *recovery site* has been determined to be suitable (check one): Yes _____ No _____

Completed By: _____ Date/Time: _____
 Document Control No./Date

In conjunction with input provided by members of AATB's Standards Committee who served during the time when this work was developed, the following members contributed to the original document and a subsequent revision:

Co-editor - Bruce Zalneraitis
Co-editor - Scott A. Brubaker, AATB Liaison

Allison Bagley (Rickman)

Kelley Bennett

Ken Blair

Christy Bramlett

Harry Celestine

Tyler Cochran

Matthew Crump

Marcy Dimond

Donna Drury

Edmundo Ferreol

Mary Beth Fisk

Nancy Gallo

Emily Goldbloom

Glenn Greenleaf

Jean Herman

Robert Hinely

Corinne Kereszturi

Perry Lange

Heather Luders

Lance Murdock

Marilyn Murray

Heather Overman

Kathy Pearson

Jan Pierce

Nick Sodermann

Carolyn Spivey

Dan Towers

Randy White

Rodney Williams

Tina Wilusz

Jerry Wright

Yuriy Yushkov

Appendix V
RECOVERY PARTNER AUDIT TOOL REQUIREMENTS

This text is still being developed and will be placed as soon as it is complete.



American Association of Tissue Banks®

Accreditation Policies
for
Transplant Tissue Banks

March 30, 2016

ACCREDITATION POLICIES FOR TRANSPLANT TISSUE BANKS

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American Association of Tissue Banks Accreditation Policies for Transplant Tissue Banks

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The American Association of Tissue Banks' ("AATB", or "Association") Accreditation Policies for Transplant Tissue Banks ("Accreditation Policies") are specifically for tissue banks that provide human tissue for *transplantation* or *transfer*.

A tissue bank, reproductive tissue bank, tissue distribution intermediary, tissue dispensing service, or satellite facility as defined in the current edition of the AATB's Standards for Tissue Banking ("AATB Standards"), that voluntarily agrees to abide by these Accreditation Policies is eligible to apply for AATB accreditation as a transplant tissue bank. For use in the Accreditation Policies, these entities are collectively referred to as a "tissue establishment."

I. ACCREDITATION PROGRAM—GENERAL PROVISIONS

A. Definitions

Words that appear in *italics* (e.g., *satellite facility*, *nonconformity*, *etc.*) are defined at standard A2.000 Definitions of Terms in the AATB Standards.

As used throughout these Accreditation Policies, the word "including" means including but not limited to.

The following terms and definitions are not found in AATB Standards but apply to these Accreditation Policies and appear in *italics* and are capitalized:

1. *Accreditation Application* – required documentation, in a format directed by AATB, used to assess eligibility of a tissue establishment for institutional accreditation.
2. *Owner* - means any person who, directly or indirectly, (i) owns, controls or has the power to vote or sell, or direct the vote or sale of, 25 percent or more of any class of shares or ownership units of, or interests in, a tissue establishment, or (ii) otherwise has the power to control the actions, decisions, policies and/or management of a tissue establishment whether or not through ownership of securities.
3. *Reportable Event* - a major change in operations or the report to an authority of any contrary event, as described in Section V.

4. *Written Notification* – communication to the AATB on matters related to institutional accreditation submitted using the firm’s corporate letterhead, dated and signed by a *responsible person*, and sent electronically (i.e., by email) or by using a reputable nationwide courier service.

B. Eligibility

An eligible tissue establishment may submit an application for accreditation at any time. To be eligible, a tissue establishment must demonstrate that it has been in continuous compliance with AATB Standards for a minimum of six (6) months prior to the date of application for all tissue banking functions it performs. Additionally, the amount of activity for these functions may be considered by the Accreditation Committee in making a determination whether an adequate level of activity has been reached to support an inspection to evaluate compliance. Mock records may not be used to approximate actual activities.

All *satellite facilities* and their tissue banking functions:

- must be identified to AATB when a tissue establishment applies for accreditation or when reportable as a major change (refer to Section V. A. 2.);
- must be in compliance with the AATB Standards and these Accreditation Policies; and
- are subject to inspection.

When a tissue establishment has been determined by the AATB to be eligible, its application will be considered pursuant to the procedures described in Section VIII.

C. Limitation of Assurances of Accreditation

Awarding accreditation is intended to indicate that the general operation and procedures of the tissue establishment were found to be in compliance with the Association’s requirements for accreditation at the time of its review. Accreditation is not to be construed as reflecting or warranting that the accredited tissue establishment, in any or all instances, either before or after accreditation, has properly followed the AATB’s requirements at all times.

D. Logo Use Privileges and Trademark Restrictions

AATB accreditation confers the privilege to use the AATB Accredited Institution logo. It may be used only by an AATB-accredited tissue establishment in accordance with the Association’s current “Policy for the Use of Trademarks, Servicemarks and Certification Marks” and current “Policy on the Use of Internet Links to the Association’s Website.” Accreditation does not confer the right to use any other trademark of the Association, including its Corporate Logo.

The AATB does not authorize, and expressly prohibits, entities not accredited by the AATB from stating or implying, directly or indirectly, that they are AATB-accredited even if a tissue banking services (multi-facility tissue banking) agreement is in place. It is the responsibility of the accredited tissue establishment to include a clause to this effect in written agreements/contracts that such entities are prohibited from using AATB trademarks. For example, when a distributor receives tissue supplied by an AATB-accredited tissue bank, the distributor may not use any AATB trademark if the distributor is not accredited by AATB. For specific information, refer to AATB's current "Policy for the Use of Trademarks, Servicemarks and Certification Marks."

An accredited tissue establishment that desires a *satellite facility* to be shown in the results of an "Accredited Bank" search available to the public on the AATB website must submit a separate and complete application for accreditation for such a site, and the site will be inspected and considered separately for accreditation. Any and each claim of AATB accreditation by a *satellite facility* that has not separately applied for and been granted AATB accreditation must be linked prominently to the parent institution's AATB accreditation.

E. Certificate of Accreditation

Upon a final decision to accredit, one certificate of accreditation will be issued to the tissue establishment. The certificate will indicate the following:

- accreditation approval date;
- accreditation expiration date;
- the tissue types and tissue banking activities for which accreditation is awarded (refer to Section II. E.); and
- the tissue establishment's name and its primary address such as city and state (or similar identifier if outside of the United States).

An accredited tissue establishment's *satellite facility(ies)* will be identified by name and address in a formal letter that accompanies the certificate.

F. Agreement with Requirements

By accepting AATB accreditation, the tissue establishment agrees to comply with all accreditation requirements, including current AATB Standards.

II. REQUIRED ELEMENTS

A. Compliance Requirements

AATB accreditation requires compliance with these Accreditation Policies and current AATB Standards, including periodic, published changes and their

effective dates. On-site inspections may be performed to verify compliance and can occur at any time, with or without advance notification.

B. Additional Compliance

An accredited tissue establishment must also comply with the following additional requirements. Failure to meet any of these additional requirements will result in steps to suspend or withdraw accreditation. To maintain accredited status, the tissue establishment must:

- fully cooperate with and complete AATB-sanctioned surveys;
- tender payment to AATB of its annual maintenance fee before May 15 of each year;
- tender payment to AATB within forty-five (45) calendar days of an invoice related to a special inspection, a level B inspection, or an international inspection; and
- continue to perform tissue banking functions for which it is accredited.

To maintain continuous accreditation, a tissue establishment must submit a properly completed *Accreditation Application* at least nine (9) months before the current AATB accreditation expiration date.

C. Good Faith Provisions and Ethical Considerations

Each tissue establishment that seeks accreditation must engage in the accreditation process in good faith. Failure to participate in good faith, including, but not limited to, falsification of documents, intentional or negligent provision of incorrect or incomplete information, withholding of requested information, or failure to cooperate in any inspection conducted in accordance with these policies, constitutes grounds for denial, suspension or withdrawal of accreditation. In addition, if any of these conditions is noted during an inspection, the inspection may be suspended or terminated immediately.

Accredited tissue establishments and/or applicants for accreditation may not present any false or misleading information, or omit material information, regarding their accreditation status.

Accredited tissue establishments agree to operate in accordance with AATB's bylaws, objectives, rules, policies, standards and codes, including without limitation the ethical standards and codes, of the Association.

D. Declaration

Each applicant for accreditation will provide with its application, declarations, executed by the *Owner(s)*, the Medical Director(s), and the person designated as the most senior position for tissue banking operations on a form prescribed

by the Association, in which the declarant will attest to the absence of criminal history and/or other designated factors that could render the applicant ineligible for accreditation. The Association reserves the right to also perform a criminal records history check regarding such persons. The Executive Committee of the Board of Governors will be informed of any declaration or records check that reflects any past or present criminal or otherwise potentially disqualifying conduct.

E. Inspections and Activities

AATB accreditation requires that a tissue establishment be inspected for compliance with requirements applicable to all tissue banking activities it performs. A tissue establishment may not elect to be inspected for certain tissue banking activities and not for other tissue banking activities it performs. Tissue banking activities include but are not limited to any of the following:

1. Donor

- a. eligibility assessment (screening and/or testing);
- b. *authorization*; and/or
- c. *informed consent*.

2. Tissue

- d. *recovery* and/or *collection*;
- e. *processing*;
- f. release or transfer;
- g. *storage*;
- h. *distribution*; and/or
- i. *dispensing*.

F. Joint Activities and/or Services

A tissue establishment will be inspected and accredited for the specific activity(ies) or service(s) that it performs. However, if the tissue establishment participates jointly with other entities that provide tissue banking activities or services on their behalf, the accredited tissue establishment is responsible for providing evidence of compliance with AATB Standards for all tissue banking activities or services performed by other entities on its behalf.

When two or more tissue establishments participate jointly in tissue banking activities and/or services (multi-facility tissue banking), accreditation awarded to one entity is independent of the other(s).

G. Attendance at AATB Meetings/Workshops

As described immediately below, documentation of attendance must be provided with the *Accreditation Application* and may be requested by the inspector during an accreditation inspection. Such documentation must be in the form of the Certificate(s) of Attendance from the AATB. Continuing Medical Education units (CMEs) or Continuing Education Units (CEUs) from other sources or meetings do not qualify and may not be substituted. The AATB Executive Office is not responsible for producing previously issued CME or CEU Certificates of Attendance.

1. Medical Director

By the time of the inspection of an applicant for accreditation, a designated Medical Director for the applicant must have attended (in person) at least one AATB meeting/workshop within the three-year period prior to the expiration of accreditation if accredited, or within the previous three years for an initial applicant. At these AATB meetings, she/he must acquire a minimum of **10** CMEs or CEUs from the AATB.

2. Management with Executive Responsibility for Compliance Requirements

By the time of the inspection of an applicant for accreditation, a person designated as *management with executive responsibility* for the applicant who is responsible for compliance with AATB Standards and Accreditation Policies must attend (in person) at least one AATB meeting/workshop within the three-year period prior to the expiration of accreditation if accredited, or within the previous three years for an initial applicant. At these AATB meetings, she/he must acquire a minimum of **15** CMEs or CEUs from the AATB.

H. Assignment of Representative to the Accredited Tissue Banks Council

An accredited tissue establishment must assign a representative to the Accredited Tissue Banks Council who is authorized and empowered to vote at meetings of the Council.

III. RESPONSIBILITIES

A. Board of Governors

The Board of Governors is responsible for the Association's accreditation program, including these Accreditation Policies.

B. Accreditation Committee

The Accreditation Committee:

- develops accreditation requirements and submits recommendations for changes to these requirements to the Board of Governors for approval;

- reviews blinded inspection reports and responses, can make requests for more information, can order special inspections, and, by majority vote, makes decisions regarding accreditation; and
- acts on a request to review an application for accreditation to approve or reject it, as provided for in these Accreditation Policies (refer to Section I. B.).

A member may not vote or actively participate in accreditation discussions when a conflict of interest is identified.

C. Accreditation Committee Composition and Member Requirements

The appointments of the members and the Accreditation Committee Chair (“Chair”) are subject to the following requirements:

- the Chair must previously have served a full 2-year term as a member of the Accreditation Committee (“Committee”) and must be an Individual Member in good standing of the Association;
- each Committee member must have at least five years of experience in tissue banking (transplant) or anatomical donation and use (non-transplant) prior to appointment to the Committee;
- no Committee member may serve more than two consecutive 2-year terms;
- no more than two individuals from a tissue establishment and its *satellites*, if any, or from multiple tissue establishments operating under the same *Owner* may serve concurrently on the Committee;
- the Committee may have one, but not more than two, individual members from each council as provided in the Association’s Bylaws;
- the Chair appoints the Accreditation Committee Vice Chair (“Vice Chair”) from the Committee’s current membership and, as provided in the Association’s Bylaws, may appoint additional members to the Committee who must be Individual Members of the Association in good standing;
- each member is required annually to review, sign and date acknowledgement to the Association’s current AATB Policy Regarding Confidentiality Obligations and the current Policy Regarding Conflicts of Interest;
- the members shall meet in person or by conference call as needed to conduct the business of the Committee; and
- the Chair does not vote as a member of the Committee, except in the case

of a tie.

- D. Non-voting Participants in Meetings of the Accreditation Committee
The Senior Vice President of Policy, the Accreditation Manager, the CAPA Analyst, the Accreditation Coordinator, and contracted inspectors, are non-voting participants in meetings of the Committee.

IV. IMPARTIALITY, CONFIDENTIALITY AND DISCLOSURE

- A. Impartiality and Confidentiality
To maintain impartiality and confidentiality, all materials submitted to the Committee will have identifying information redacted or otherwise blinded. AATB will treat all information and documents regarding applicants seeking accreditation and accredited tissue establishments, according to the AATB Policy Regarding Confidentiality Obligations.

Committee members, including the Chair, will receive information only in blinded form. Un-blinded information is available only to the AATB Executive Office staff, contracted inspectors, and the Hearing Panel, who shall treat all information as confidential, according to the AATB Policy Regarding Confidentiality Obligations.

- B. Disclosure
Information obtained as a result of the accreditation process will be maintained as confidential and will not be released by the AATB unless:
- the applicant has specifically authorized release of such information;
 - the information is included in aggregate form or with other information so as to ensure that an individual tissue establishment cannot be identified;
 - the information is already a matter of public record;
 - release of the information is required by federal, state or local statute, regulation or other law, or court or administrative order; or
 - release of the information pursuant to Section IV. B. 2. is deemed necessary.

In the event staff of the AATB Executive Office becomes aware of information relating to an accredited tissue establishment or an applicant for accreditation that presents a serious hazard to human health, the AATB will provide such information to responsible international, federal, state and/or local government agencies or authorities having jurisdiction over the tissue establishment.

AATB will identify accredited tissue establishments on its website (refer to Section VII. A.), and will respond to telephone inquiries regarding a tissue establishment's current accreditation status by indicating only:

- whether the tissue establishment is accredited;
- for which activities the tissue establishment is accredited;
- the name and location of any *satellite facility* of the tissue establishment;
- the tissue establishment's accreditation number; and
- the period(s) during which the tissue establishment has been accredited.

Except as noted above, AATB will not publicly disclose any information relating to an applicant or accredited tissue establishment without written consent from the person designated as *management with executive responsibility* most responsible for compliance with AATB Standards and Accreditation Policies.

C. Conflict of Interest

When the Chair is identified, by self-reporting or by the Accreditation Manager, as having a conflict of interest regarding review of documentation pertaining to a particular applicant, the Vice Chair will assume the Chair's role and responsibilities for that applicant. If both the Chair and Vice Chair have a conflict of interest, the remaining members of the Accreditation Committee will select a member to serve as temporary Chair.

D. Inquiries Related to the Accreditation Process

All inquiries related to the accreditation process should be addressed to the Accreditation Coordinator, the CAPA Analyst, the Accreditation Manager, or the Senior Vice President of Policy. Contracted AATB inspectors and members of the Accreditation Committee may not answer inquiries related to accreditation applications, Accreditation Committee activities, or any topics related to an inspection.

V. REPORTABLE EVENTS

A. Required Reporting

Accredited tissue establishments and applicants must send *Written Notification* to the Accreditation Manager within fifteen (15) calendar days following a major change in operations or the report to an authority of any contrary event (collectively, "*Reportable Events*"). Failure to notify AATB of a *Reportable Event* may result in proceedings to suspend, withdraw or deny accreditation. All documents submitted related to *Reportable Events* must be submitted in their entirety and not redacted. *Reportable Events* become part of the accredited tissue establishment's file at the AATB Executive Office and may be cause to hold a special inspection.

1. Contrary Events

Contrary events include, but are not limited to:

- a. any international, federal, state or local action, including but not limited to:
 - i. any order to *recall* tissue or to cease manufacturing;
 - ii. receipt of an FDA Form 483 or state, local or international equivalent, and all responses until the citation(s) is(are) closed;
 - iii. receipt of an FDA Warning Letter, Untitled Letter, or an equivalent warning by another federal, state, local or international authority, and all responses by the tissue establishment;
 - iv. a change in licensure, permit, registration or similar listing with or authorization by a federal, state, local or international government authority related to tissue banking functions; and
 - v. all submissions of FDA MedWatch reports or adverse reaction reports originating from another country involving *finished tissue* processed by or distributed by the accredited tissue establishment (or equivalent report if an accredited tissue establishment is located outside of the United States).
 - b. any voluntary *recall*, notification, or *market withdrawal* of *finished tissue*;
 - c. when provided, the FDA Establishment Inspection Report (EIR) or equivalent report from a state, local or international inspection authority;
 - d. any disease transmission confirmed to be caused by *finished tissue* processed and/or distributed by the accredited tissue establishment; and
 - e. any Biological Product Deviation Report (BPDR) submitted to the FDA or equivalent report submitted to an international government authority.
2. Major Changes
 Major changes involving personnel or operations, including but not limited to:
- a. changes to key personnel, including:
 - i. the *Owner(s)* and the person designated as the most senior position of authority for tissue banking

operations.

- ii. the person designated as *management with executive responsibility* for compliance with AATB requirements including AATB Standards and Accreditation Policies;
- iii. the Medical Director(s);
- iv. the designated representative to the Accredited Tissue Banks Council; or
- v. the person(s) designated to receive AATB Bulletins.

Note: A current curriculum vitae for *management with executive responsibility* most responsible for compliance with AATB Standards and Accreditation Policies and for the Medical Director must be submitted with the *Written Notification of change*.

- b. change in the information contained in the declarations completed by the designated individuals identified in in Section II. D.;
- c. change in scope of operations of the tissue establishment, including changes to the following services and/or activities:
 - i. cessation or suspension for a period of six (6) months or longer of any tissue banking activities or services or of any tissue types handled, for which the tissue establishment is accredited;
 - ii. addition of new, or resumption of previously provided, tissue banking activities or services, or tissue types handled, for which the tissue establishment is not accredited;
 - iii. addition of tissue donation activities or services involving living donors when tissue only from deceased donors was previously handled; or
 - iv. addition of tissue donation activities or services involving deceased donors when tissue only from living donors was previously handled.
- d. change in facilities that affect tissue banking operations such as:
 - i. expansion;

- ii. relocation;
 - iii. renovation; or
 - iv. addition or removal of a *satellite facility*.
- e. change in the *Owner* of or merger with, acquisition by or of, or transfer of control to or of, another tissue establishment;
 - f. subcontracting or assignment to a third party, whether or not accredited by AATB, of any tissue banking activities or services for which AATB accreditation applies;
 - g. legal name change or d/b/a (doing business as) designation; or
 - h. dissolution, bankruptcy, or insolvency of the tissue establishment.

B. Required Information

Written Notification sent pursuant to this section must be sufficiently detailed to explain the nature and extent of the contrary event and/or major change to enable AATB to determine the implications for the accredited tissue establishment's current and future compliance with AATB accreditation requirements. All documents related to Reportable Events must be submitted in their entirety and not redacted.

The tissue establishment must provide the Accreditation Manager with copies of all pertinent documents relating to the major change. At the direction of the Accreditation Manager, an AATB Facilities Change Form must be completed.

The following information must be submitted regarding any *recall*, voluntary *notification*, or *market withdrawal* of *finished tissue*, whether a domestic or an international distribution:

- name of tissue establishment;
- type(s) of tissue;
- number of tissue donors involved;
- number of tissue grafts involved;
- identification of the *consignees* where each tissue graft was distributed;
- reason for taking action;
- nature (voluntary, mandatory); and

- description of corrective action(s) taken and planned to be taken.
- C. Review of Reportable Events
The Senior Vice President of Policy, the Accreditation Manager, and the CAPA Analyst will review each notification of a contrary event or major change and consider whether a special inspection should be performed prior to expiration of the tissue establishment's current accreditation (refer to Section IX.). If a special inspection is necessary, the Accreditation Manager may notify the tissue establishment in advance, or may schedule the inspection to take place without advance notification.

VI. EXPIRATION OF ACCREDITATION

- A. Term of Accreditation
The term of accreditation, which is generally for a period of three years, begins and expires on the specific dates stated on the tissue establishment's certificate of accreditation. Privileges of accreditation cease on the expiration date, unless AATB withdraws, suspends or extends accreditation prior to that date.
- B. Re-accreditation Timelines
An accredited tissue establishment that wishes to apply for re-accreditation shall request an *Accreditation Application* from the Accreditation Manager or the Accreditation Coordinator. The properly completed application must be received by the Accreditation Coordinator no more than twelve (12) months and no fewer than nine (9) months before the tissue establishment's accreditation expiration date.
1. Automatic Extension
An accredited tissue establishment that applies in a timely fashion for re-accreditation will not lose its current accredited status during the re-accreditation process as long as the tissue establishment meets published timelines, completes each stage of the process in good faith, and the delay does not adversely affect the safety of tissue recipients or tissue establishment employees.
 2. Request for Extension
An accredited tissue establishment that applies for re-accreditation will not have its accreditation automatically extended beyond its current accreditation expiration date if it has not met published timelines. To extend accreditation in this circumstance, the tissue establishment must apply for an extension to the Accreditation Manager prior to the expiration date of the applicant's current accreditation. *Written Notification* must include sufficient information including justification for an extension. A request for extension must be submitted prior to the expiration of accreditation. A request for extension may be granted by the Accreditation Manager, or may be evaluated on a case-by-case basis, in blinded fashion, by the Accreditation Committee. The

Committee may decide to award an extension or to proceed to suspend or withdraw accreditation. Refer to Section XI. An extension will be granted for the time period until a meeting of the Committee is convened.

3. Extension(s) and the Accreditation Expiration Date
Should an extension or extensions be granted as described above, and a decision to re-accredit results, the period of re-accreditation will run from the expiration date, not from the date of any extension(s).
4. Limit
An extension will not be granted for longer than sixty (60) calendar days at a time. In the case where a tissue establishment requires more than three extensions, information in blinded format will be sent to the Accreditation Committee for review. An additional extension will only be granted for the time period until a meeting of the Committee is convened.

- C. Lapse of Accreditation
If a tissue establishment's accreditation expires and it is not extended pursuant to these policies, the tissue establishment must immediately remove all indications of AATB accreditation from its forms, letters, signs, labeling and advertisements, and it may not state or imply, directly or indirectly, that it continues to be accredited by AATB.

VII. PUBLIC RECOGNITION

- A. Publication
Approximately monthly, the database linked to the accredited bank search function on the AATB website will be updated to reflect changes in the status of accredited tissue establishments.

A *satellite facility* of an accredited tissue establishment may identify itself as being accredited by AATB as a *satellite facility* of its parent tissue establishment. However, a *satellite facility* is not searchable using the AATB-accredited tissue establishment search function, unless it is separately accredited.

- B. Removal
The following circumstances will result in removal of the name of a tissue establishment from the accredited bank search function on the AATB website:
 - accreditation has been suspended;
 - accreditation has expired or has been withdrawn;
 - accreditation has been denied; or

- all tissue banking operations have ceased.
- C. Unauthorized Use of AATB Accreditation Status
A tissue establishment not currently accredited by AATB is forbidden from stating or implying, directly or indirectly, in its literature or elsewhere that it is accredited by AATB, that it has applied for AATB accreditation, or that it meets, complies with, follows or exceeds AATB accreditation requirements. Refer to the Association’s current “Policy for the Use of Trademarks, Servicemarks and Certification Marks.”

VIII. ACCREDITATION PROCESS

A. Application

Prior to submitting an application for accreditation, the tissue establishment must be determined to be eligible. Refer to Section I. B.

1. Internal Audit/Pre-Inspection Checklist

The applicant must properly complete the AATB Pre-Inspection Checklist (“Checklist”). The applicant must ensure that each response is complete and fully responsive in all respects. The applicant must cite the policy number and section and/or page number of the tissue establishment’s *standard operating procedures manual (SOPM)* or other official reference of the institution that corresponds to each AATB standard or policy referenced in the Checklist. This indicates that all AATB Standards and the Accreditation Policies have been addressed by the applicant and assists in performing the pre-inspection review. If an AATB standard does not apply, the tissue establishment should indicate “N/A” in the applicable entry on the Checklist. The Checklist is part of the *Accreditation Application* and is available from the Accreditation Coordinator or the Accreditation Manager.

2. Documentation Requirements

When steps required under Section VIII. A.1. have been completed, the applicant must submit the Checklist and a properly completed *Accreditation Application*. Information required by the *Accreditation Application* must be sent to the Accreditation Coordinator via compact disk or flash drive, and must be accompanied by payment of the non-refundable application fee. To ensure the integrity of these documents, it’s required that the package containing this confidential information be sent via carrier with return receipt or other package tracking capabilities.

3. Confirmation of Receipt of Application and Deadline

Within fourteen (14) calendar days of receipt of the *Accreditation Application*, the Accreditation Coordinator or the Accreditation Manager will send written acknowledgement of receipt. If additional

documentation or information is required, or if the application is incomplete or otherwise improperly completed, the Accreditation Coordinator or Accreditation Manager will request missing documents, information and/or corrections. The applicant's corrected or properly completed information and/or documentation must be submitted to AATB bearing a postmark, or deposited with a nationally recognized courier for overnight delivery, within forty-five (45) calendar days of the date of the initial information request. Failure to do so may result in the applicant being required to submit a new application and application fee. If the applicant is required to submit a new application and fee, this requirement will be communicated in writing to the applicant.

4. Recent Action Against the Applicant

If an international, federal, state or local agency or other authority has initiated any formal or informal inquiry, investigation, proceeding or other action ("action") against the applicant seeking AATB accreditation, or given notice of any of the foregoing, the applicant must immediately inform the Accreditation Manager by *Written Notification*. AATB will review the circumstances of the action in order to determine the impact of such matters on the tissue establishment's *Accreditation Application*. Failure to disclose any such issue promptly as it occurs at any time during the accreditation process may be considered failure to participate in good faith and may result in denial of the *Accreditation Application* and the suspension, denial or withdrawal of accreditation.

B. Scheduling the On-site Inspection

Upon determination that the *Accreditation Application* is complete and acceptable, the Accreditation Coordinator or the Accreditation Manager will contact the applicant to schedule the on-site inspection. The Accreditation Manager will determine the length of time necessary for each on-site inspection based upon the size of the tissue establishment, inclusion of inspection of one or more *satellite facilities*, and the scope of the tissue establishment's operations. Once the on-site inspection has begun, the actual duration may be adjusted after consultation between the inspector(s) and the Accreditation Manager. Costs, fees, and expenses relating to the on-site inspection will be charged to the applicant as follows:

- if the applicant is located within North America, the applicant will not be required to reimburse AATB for costs, fees, or expenses related to the inspection;
- if the applicant is located outside of North America, the applicant will be required to reimburse AATB for one-half of the inspector's(s') travel expenses (air travel, lodging, meals, ground transportation, etc.). An invoice for these expenses will be submitted to the applicant after the inspection; and

- if the applicant, whether located within or outside North America, voluntarily withdraws from, does not comply with, or does not complete the accreditation process after the commencement of any on-site inspection, the applicant will reimburse AATB for all costs, fees and expenses, including the inspector's(s') fees and travel expenses related to the inspection(s).

C. Scope of the On-site Inspection

The scope of the on-site accreditation inspection includes a quality systems audit approach to gain insight into control of the processes performed by the tissue establishment and how accreditation requirements are applied and satisfied. The inspection encompasses record reviews, interviews with staff, observation of activities, and tours of facilities. An Inspection Protocol Document that outlines general items to be made available during the inspection is sent to the applicant well ahead of the agreed date(s) of inspection. The inspector(s) must be granted access to all spaces, records and personnel pertinent to all tissue banking functions. The inspector(s) will conduct an opening conference and a closing conference. Appropriate *management with executive responsibility* as well as the Medical Director shall be available for the duration of the inspection.

D. Inspection report

The inspector's report will identify and describe *nonconformities*.

Within fourteen (14) calendar days following the completion of the inspection, the inspector(s) will complete the inspection report and deliver it to the Accreditation Manager.

Within twenty-four (24) calendar days of receipt of the inspector's(s') inspection report, the Accreditation Manager or responsible designee will prepare the inspection report and deliver it in blinded format to the Accreditation Committee Chair. As applicable, refer to Section IV. A.

Following the Chair's review, the inspection report will be sent in blinded format to the Accreditation Committee members for discussion at their next scheduled meeting.

E. Accreditation Committee Review and Decision

The Accreditation Committee will review and finalize the blinded inspection report and will take action by making a decision to recommend either immediate approval to accredit, designation as Level A, designation as Level B, or suspension, withdrawal or denial of accreditation. Whenever possible, inspectors will be present during the Accreditation Committee meetings and/or conference calls to answer questions about *nonconformities* or other issues pertinent to the Committee's evaluation of a tissue establishment accreditation

inspection report.

Recognizing that there may be varying degrees of *nonconformities* noted during the inspection, as well as varying implications that may be drawn from the *nonconformities*, the Accreditation Committee will determine by majority vote which one of the following Committee actions is appropriate, and the process related to each decision is described as follows:

1. Immediate Approval for Accreditation

Following a report of an on-site inspection that indicates that there are no *nonconformities* that require correction, and that the applicant is operating in compliance with AATB accreditation requirements, the Committee may decide that the accreditation application should be approved. The Accreditation Manager will transmit the decision and the final inspection report to the applicant.

2. Level A - Requires Corrective Action(s)

Following a report of an on-site inspection that indicates that there are *nonconformities*, and that the applicant's compliance with AATB accreditation requirements must be improved, the Committee may determine that the *nonconformities* can be corrected and documented without need for a re-inspection to verify compliance because the *nonconformities* do not appear to present a potential hazard to human health and the tissue establishment's corrective action can be evaluated by reviewing paper documentation. The Accreditation Manager will provide to the applicant the final inspection report, which will be accompanied by a letter informing the applicant of the Committee's decision for a Level A designation and describing all findings of non-compliance. If desired, the applicant may contact the Accreditation Manager or CAPA Analyst for clarification of any *nonconformity(ies)*.

When a Level A designation has been issued:

- a. within seven (7) calendar days of the date of the Committee's decision, the Accreditation Manager will transmit the final inspection report to the applicant. The report will describe all *nonconformities* that require corrective action;
- b. within thirty (30) calendar days of applicant's receipt of the final inspection report, the AATB must receive from the applicant sufficient documentation that demonstrates that corrections have been made to comply with AATB accreditation requirements. Failure to meet the deadline or to sufficiently demonstrate compliance will result in a decision to suspend, deny or withdraw accreditation, unless exceptional *corrective action* or *preventive action* circumstances exist to justify a one-time extension of this deadline;

- c. upon receipt by the CAPA Analyst or Accreditation Manager, the applicant's response will be examined for completeness and compliance with AATB accreditation requirements. If indicated, the CAPA Analyst or the Accreditation Manager will request more information. The requested information and/or documentation must be received by the CAPA Analyst from the applicant within fifteen (15) calendar days of the applicant's receipt of the request. When it is determined that the application is complete, the CAPA Analyst will forward the blinded response to the Committee Chair or designee for review;
- d. if indicated, the CAPA Analyst, the Accreditation Manager, and the Committee Chair or designee may request more information. The requested information and/or documentation must be received by the CAPA Analyst from the applicant within fifteen (15) calendar days of the applicant's receipt of the request. When it is determined that the application is complete, the blinded response will be sent to the Committee for review at their next meeting;
- e. if the Committee decides that the applicant has corrected the *nonconformities*, the Committee members will vote on whether to approve the tissue establishment's accreditation; or
- f. if the Committee decides that the applicant has not corrected the *nonconformities*, the Committee may, in its discretion:
 - i. request that clarification and/or additional information be submitted by the applicant. The requested information and/or documentation must be received by the CAPA Analyst from the applicant within fifteen (15) calendar days of the applicant's receipt of the request. If additional information is requested and it is not forthcoming before the deadline or it is not satisfactory, the Committee may determine that a Level B re-inspection be performed or may determine that accreditation should be suspended, denied or withdrawn. If accreditation is denied or withdrawn, the Committee may, in its discretion, impose a waiting period of up to one year (from the notice of denial) before re-application for accreditation is allowed; at that time, the tissue establishment must submit a new application. The applicant will reimburse AATB for all costs, fees and expenses, including the inspector's(s') fees and travel expenses related to a Level B inspection if a Level B inspection has been conducted;

- ii. determine that a Level B re-inspection be performed. The applicant will reimburse AATB for all costs, fees and expenses, including the inspector's(s') fees and travel expenses related to a Level B inspection. After the Level B inspection is performed, the Level B process described below will be followed; or
 - iii. determine that accreditation be suspended, denied or withdrawn.
3. Level B - Requires Corrective Action(s) and On-Site Re-Inspection
Following an on-site inspection and an inspector's report that indicates compliance with AATB accreditation requirements must be improved, the Committee may require corrective action(s) and an additional on-site inspection to determine compliance. The Accreditation Manager will notify the tissue establishment of the Committee's decision for a Level B designation and that it requires a re-inspection. When a Level B designation has been issued:
- a. the Accreditation Manager will transmit the final inspection report to the applicant. The report will describe all *nonconformities* that require corrective action;
 - b. within sixty (60) calendar days of receiving the inspection report, the AATB must receive from the applicant documentation that demonstrates correction of the noted *nonconformities* and compliance with AATB accreditation requirements. Failure to do so will result in a recommendation for suspension, denial or withdrawal of accreditation, unless exceptional circumstances exist to justify a one-time extension of the response period;
 - c. upon receipt by the CAPA Analyst or Accreditation Manager, the applicant's response will be examined for completeness and compliance with AATB accreditation requirements. If additional information is required, the CAPA Analyst or the Accreditation Manager will send a request to the applicant. The requested information and/or documentation must be received by the CAPA Analyst from the applicant within fifteen (15) calendar days of the applicant's receipt of the request. If the response appears to be complete, the Accreditation Manager will forward the blinded response to the Accreditation Committee Chair or designee for review;
 - d. if indicated, the Committee Chair or designee may request more information. If the Chair or designee determines that the applicant has not corrected the *nonconformities*, the following

- may occur:
- i. the Accreditation Committee Chair may request clarification and/or additional information, and the applicant's response must be received by AATB within fifteen (15) calendar days of the applicant's receipt of the request; and
 - ii. the tissue establishment's response may be sent to the Accreditation Committee to determine if accreditation should be suspended, denied or withdrawn. If accreditation is denied or withdrawn, the Committee may, in its discretion, impose a waiting period of up to one year (from the notice of denial) before re-application for accreditation is allowed. At that time, the tissue establishment must submit a new application;
- e. if the Chair or designee determines from the applicant's submission that the applicant has corrected the *nonconformities*, the Level B on-site re-inspection will be scheduled. The applicant will reimburse AATB for all costs, fees and expenses, including the inspector's(s') fees and travel expenses related to a Level B inspection; and
- i. following the Level B on-site re-inspection, the Committee will review the inspector's findings. If the applicant has failed to demonstrate that *nonconformities* have been addressed, the Committee may:
 - a) request additional information; or
 - b) decide that accreditation be suspended, denied or withdrawn; and
 - ii. an applicant assigned a Level B status may receive only one additional on-site inspection. However, if the inspector notes new or additional findings as a result of the on-site Level B inspection, the Committee may assign a Level A or a Level B based on these new or additional findings. The Committee will then finalize this inspection report and it will be delivered to the applicant. The Committee may order another on-site inspection.
- f. the Accreditation Committee may decide to either:
- i. accredit;
 - ii. request further information;

- iii. suspend;
- iv. deny; or
- v. withdraw accreditation.

4. Denial or Withdrawal of Accreditation

In the event that the on-site inspection and the inspector's report reflect significant violations of AATB accreditation requirements, the Accreditation Committee may determine that accreditation be denied or withdrawn without an opportunity for corrective action.

If a decision is made to deny or withdraw accreditation, the Committee may, in its discretion, impose a waiting period of up to one-year (from the notice of denial) before re-application for accreditation is allowed. At that time, the tissue establishment must submit a new application.

5. Suspension of Accreditation

There may be instances where the inspector's report of the on-site inspection indicates noncompliance with the accreditation requirements, but the Accreditation Committee believes that these *nonconformities* do not warrant withdrawal of accreditation, and that the tissue establishment could comply with the accreditation requirements in a short period of time. There also may be instances where regulatory agencies issue inspection-related violations, sanctions, or other actions against an accredited tissue establishment that raise questions about the tissue establishment's compliance with the accreditation requirements. In such cases, the Committee may suspend the tissue establishment's accreditation for a period of time not to exceed ninety (90) calendar days to allow it to correct its *nonconformities*.

- a. If the tissue establishment does not come into compliance with the accreditation requirements within the ninety (90) calendar day suspension period, the Committee may, in its discretion, extend the suspension for additional periods of ninety (90) calendar days or more, not to exceed one year. The Committee also may determine that a Level B inspection should be performed or may proceed to withdraw accreditation and deny the application for accreditation.
- b. During the period of suspension, the tissue establishment is not considered an accredited tissue establishment or otherwise in good standing with the Association. In addition, beginning on the effective date of the suspension and continuing until the suspension is lifted, the tissue establishment is prohibited from using the AATB accreditation logo on or in connection with any

finished tissue produced during the period of suspension. The tissue establishment is also prohibited from indicating AATB accreditation, directly or indirectly, including on its letterhead, brochures, advertising materials, and website.

F. Notification

The Accreditation Committee's decision on an application for accreditation is final. After notice to the President and Chief Executive Officer, the tissue establishment and the AATB Board of Governors Chairman will be notified of the decision. The tissue establishment will be notified in writing using a carrier with return receipt or other package-tracking capabilities.

IX. INSPECTIONS WITH OR WITHOUT NOTICE

A. Right to Inspect

AATB reserves the right to perform on-site inspections at any time, with or without notice. Conducting an inspection without notice does not necessarily indicate a suspected violation of AATB accreditation requirements.

B. Ordering an Inspection

With the concurrence of the President and Chief Executive Officer, the Accreditation Committee, the Accreditation Committee Chair, the Senior Vice President of Policy, or the Board of Governors may order an inspection for cause and/or as a stipulation of accreditation.

It may also be determined that an inspection is warranted of an accredited tissue establishment's recovery partner that is not accredited by the AATB. If possible, the tissue establishment will be notified when the inspection(s) is (are) being scheduled that one or more of their recovery partners will be inspected by AATB; however, AATB reserves the right to make this determination. If the non-accredited entity(ies) does(do) not allow the inspection or is(are) found to not comply with AATB Standards, the following actions may become necessary:

- the accredited tissue establishment will be required to immediately terminate the business relationship with the non-conforming recovery partner if the non-conforming recovery partner will not comply with AATB Standards; and
- if the accredited tissue establishment does not immediately terminate the business relationship, AATB may suspend or withdraw the accreditation of the accredited tissue establishment.

C. Types of Inspections

Inspections may be general or focused, and the scope will be defined by the entity that ordered the inspection (refer to Section IX. B.). Inspections take place as described in Section VIII. C. An inspection may occur if the tissue

establishment's location, facilities, and/or activities change, or other major changes have been reported. The Accreditation Manager in conjunction with the Accreditation Committee Chair will review major changes to determine if an on-site inspection is required. Additionally, the need to investigate a report of a contrary event or a report of a violation of accreditation requirements may be cause to hold a special inspection. The Accreditation Manager in conjunction with the Senior Vice President of Policy will review the report of a contrary event or a report of a violation of accreditation requirements to determine if an on-site inspection is indicated.

D. Notice of Inspection

Without limiting AATB's right to inspect without notice, where circumstances permit, AATB may give prior notice to the tissue establishment of its intent to inspect.

E. Reviews and Decisions

Review of, and decision on, the final inspection report will take place as described in Section VIII. E.

F. Inspection Costs and Fees

The tissue establishment will reimburse the AATB for all costs, fees and expenses, including the inspector's(s') fees and travel expenses, that are related to an on-site inspection performed due to a major change. The tissue establishment is not responsible for costs incurred by AATB if a special inspection occurs due to a report of a contrary event or to investigate a report of a violation of accreditation requirements.

X. REPORTING VIOLATIONS OF ACCREDITATION REQUIREMENTS

A. Reporting

Reports of suspected violations of the accreditation requirements by accredited tissue establishments should be made in writing to the President and Chief Executive Officer and signed with the name(s), address(es) and telephone number(s) of the individual(s) alleging the violations. The Association will treat the identity of the person(s) alleging a violation as confidential.

B. Investigation

Upon receipt of a report of an alleged violation of the accreditation requirements by an accredited tissue establishment, the President and Chief Executive Officer, the Senior Vice President of Policy, and the Accreditation Manager will review and investigate the report. If they conclude there is sufficient reason to believe that a violation has occurred, the Accreditation Committee, by majority vote, with the concurrence of the President and Chief Executive Officer, may order an investigation and an on-site inspection with or without notice as provided for in Section IX. If an inspection is ordered, the Association will assume the costs of the inspection.

C. Further Review and Action

Following an investigation and any on-site inspection, the Accreditation Manager will submit a written report to the Accreditation Committee. Upon receipt of the report and if a violation of the accreditation requirements is noted, the Accreditation Manager and Accreditation Committee Chair may convene an emergency meeting of the Accreditation Committee. The Accreditation Committee will determine what, if any, action to take. The procedures described in Section VIII. E. will be followed.

XI. SUSPENSION, DENIAL OR WITHDRAWAL OF ACCREDITATION

A. General

Accreditation of a tissue establishment may be suspended, denied or withdrawn pursuant to the following steps.

B. Notification

Following review and decision by the Accreditation Committee, the President and Chief Executive Officer will notify the AATB Board of Governors Chairman and the tissue establishment of the decision. The tissue establishment will be notified in writing using a carrier with return receipt or other package-tracking capabilities. The decision must indicate that the tissue establishment has violated the terms of its accreditation and is operating contrary to the AATB accreditation requirements. The notice will also state the reasons for the decision and the organization's right to appeal.

C. Appeals

If a tissue establishment is notified that its accreditation has been denied, suspended or withdrawn, or that transfer of accreditation has been denied (refer to Section XII. below), it shall have fifteen (15) calendar days from the date of receipt of the notification to appeal. The appeal must be submitted in writing to the President and Chief Executive Officer, using a carrier with return receipt or other package-tracking capabilities. If an accredited tissue establishment appeals the decision to withdraw its accreditation in a timely manner, the proposed withdrawal will be stayed pending the outcome of the appeal, provided there is no potential hazard to human health. In the event that the tissue establishment does not appeal the decision to deny, withdraw, suspend, or deny transfer of accreditation within the fifteen (15) calendar day period, the proposed suspension, denial or withdrawal of accreditation will become final.

Should the tissue establishment file an appeal within the fifteen (15) calendar day period after notification, a Hearing Panel will be established and shall consist of the following members: the President and Chief Executive Officer, who shall act as the non-voting Chair of the Hearing Panel, the Senior Vice President of Policy, the Accreditation Manager, the CAPA Analyst, and a legal

counsel representative of the AATB who shall be non-voting.

D. Hearing

The hearing will be held within thirty (30) calendar days of, but not fewer than twenty (20) days following, AATB's receipt of the request for such a hearing. The hearing may be held in person or by teleconference.

At the hearing, the tissue establishment's designated *management with executive responsibility* most responsible for compliance with AATB Standards and Accreditation Policies, and/or the Medical Director may appear and may be accompanied by up to three other members of the tissue establishment. At least seven (7) calendar days prior to the date of the hearing, the tissue establishment must submit to the AATB a written statement of specific reasons indicating why suspension, withdrawal or denial of accreditation is believed to be not warranted, as well as all written and documentary evidence in support of the organization's position. Testimony, if any, must be presented by sworn affidavit. The tissue establishment will be allotted one hour to present its position and such additional time as needed to respond to the Hearing Panel's questions.

E. Decision

The Hearing Panel will reach its decision by simple majority vote. The tissue establishment and the AATB Chairman will be notified of the decision within seven (7) calendar days of the conclusion of the hearing. The tissue establishment will be notified in writing using a carrier with return receipt or other package-tracking capabilities.

A tissue establishment that has its accreditation denied or withdrawn is not eligible to reapply for accreditation for one year from the date of notification of denial or withdrawal.

XII. TRANSFER OF ACCREDITATION

A. General

An accredited tissue establishment may request that its accreditation, or any portion thereof, be transferred when the establishment is reorganized or dissolved and a successor entity is incorporated, or when the establishment is to be merge with or acquired by, or control is to be acquired by, another establishment whether or not the transferee is already accredited by the AATB. AATB accreditation, however, does not automatically transfer to the successor entity.

B. Request for Transfer

To transfer AATB accreditation, an accredited tissue establishment that is reorganizing, merging with, being acquired by, or control of which is being transferred to another organization must first request permission from the

AATB to transfer its accreditation to the transferee. The request must be made in writing, signed by the designated *management with executive responsibility* most responsible for compliance with AATB Standards and Accreditation Policies, and sent to the Accreditation Manager at least seven (7) calendar days prior to the transfer. The request must specify the reasons for the requested transfer, identify the entity to which the Accreditation is to be transferred, and provide necessary documentation as described below. At the time the request is made, the accredited tissue establishment must be in good standing and its accreditation must be current. Failure to file a timely and complete request may result in the denial of such a request, or suspension or withdrawal of accreditation.

C. Documentation

The documentation to be provided in addition to the written request for transfer of accreditation (refer to Section XII. B.), must be sufficient to show:

- the nature and extent of the ownership and operational changes that will result from the transaction giving rise to the request for transfer of accreditation;
- any changes in the scope of the tissue establishment's operations or management responsibilities following consummation of the transaction giving rise to the request for transfer of accreditation;
- any post-consummation changes that would alter the tissue establishment's continuing compliance with the accreditation requirements;
- any audits, findings, enforcement actions by or proceedings involving any governmental agency or authority, within the past three (3) years or outstanding as of the time of the request for transfer of accreditation), involving either the petitioning tissue establishment or the merging or acquiring entity; and
- continued compliance with accreditation requirements by the transferor prior to the transfer, and that the transferee will remain in compliance subsequent to the transfer.

D. Review

In the case of a request for transfer of accreditation to an entity that is not AATB-accredited, the procedures described in Section II. D. will be followed.

The Accreditation Manager and the Accreditation Committee Chair will review the request and documentation. The request to transfer accreditation may be cause to hold a special inspection. Based upon review of documentation, the Accreditation Manager and the Accreditation Committee Chair will decide whether to approve the transfer of accreditation.

E. Consummation; Notification

The tissue establishment and the AATB Board of Governors Chairman will be notified of the decision. The tissue establishment will be notified in writing using a carrier with return receipt or other package-tracking capabilities. In the event that the AATB grants the request, the reorganization, merger, acquisition or transfer of control that was the subject of the request to transfer accreditation must be completed within sixty (60) days of receipt of the AATB's approval, and within seven (7) calendar days following consummation of the transaction the tissue establishment receiving the transfer of accreditation must provide *Written Notification* to the Accreditation Manager of the date on which the transaction was completed.



Guidance Document

Current Good Tissue Practice

[No. 3, June 27, 2006]

American Association of Tissue Banks' (AATB) guidance documents, including this one, do not establish legally enforceable responsibilities. Instead, these guidelines describe the AATB's current thinking on this topic. They are intended solely for the use of AATB accredited tissue banks in conjunction with the AATB's Standards for Tissue Banking. They should be viewed only as recommendations, unless specific AATB Standards or regulatory or statutory requirements are cited. The use of the word "should" in these guidance documents means that something is suggested or recommended, but not required. As with other AATB guidance documents, the recommendations included in this document do not represent the sole approach. Alternative approaches can be used.

***American Association of Tissue Banks
1320 Old Chain Bridge Road
Suite 450
McLean, Virginia 22101
(703) 827-9582 (703) 356-2198 Facsimile***

Additional copies of this *Guidance Document* are available from the AATB office. In addition, comments on this document may be submitted at any time to the AATB. The Association will review any comments received and revise the *Guidance Document* as appropriate. All requests and comments should be addressed to:

American Association of Tissue Banks
1320 Old Chain Bridge Road
Suite 450
McLean, Virginia 22101
www.aatb.org

For questions on the content of the document, please contact the AATB at:

(703) 827-9582 or (703) 356-2198 (Fax)

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Efforts are made to have publications of the AATB consistent in regard to acceptable practices. However, for several reasons, they may not be. As new developments in the practice of tissue banking occur, changes may be recommended to the *Standards for Tissue Banking*. It is not possible, however, to revise each publication at the time such a change is adopted. Thus, it is essential that the most recent edition of the *Standards* be consulted as a reference in regard to current acceptable practices. The publication of this guidance document does not constitute an endorsement by the AATB of these recommendations as the only acceptable practice. The AATB expressly disclaims any liability arising from any inaccuracy or misstatement herein.

The AATB recognizes the efforts of the following individuals who generously donated their time and expertise to creating this document.

Scott A. Brubaker (Task Force Coordinator)

Recovery

Mitch Cohen
Sean Conley
Reg Dawson
Amy Erickson- Hagen
Glenn Greenleaf
Jason Mahood
Darilyn Million
Heather Myers
Scott Nanbara
Kevin Noyes
Marvin Smoot
Alex Veve
Gary Walters

Donor Screening

Karen Baker
Barb Bianchi
Scott A. Brubaker
Mitch Cohen
Jeff Cox
Amy Gamble
Bob Hinely
Jackie Hodgdon
Denise Horvath
Linda Martin
Orlando Merced-O'Neill
Sue Monte
Kathy Pearson
Anthony Schiavoni
Mary Szaro
Judi Torgerson

Donor Testing

Rusty Adams
Matthew Bankowski
Michael Bauer, MD

Nancy Dock
Kelley Fitzgerald
Ellen Heck
Connie Jones
Sue Monte
P.J. Pardo
Linda Weiss
Penny White

Processing

Murray Anderson
Michael Barile
Beverly Bliss
Bud Brame
Robert Carpenter
Jerry Chang
Tamera Duncan
Amy Erickson-Hagen
Liz Horn-Brinson
Pete Jenkins
C. Randy Mills
Karen Mosley
Diane Munro
Marilyn Murray
Jan Pierce
Kim Raineri
Pat Thompson
Martell Winters

Storage

Steve Broder
Jim Colyn
Richard Jordan
Areta O. Kowel-Vern
Marilyn Murray
Diana Schillinger
Mark Smith

Labeling

John Chappell
Jim Colyn
Robert Carpenter
Allyson May
Charlie Nettles
Donna Ridder
Michael Roberts
Mark VanAllman

Packaging

Trabue Bryans
Jim Colyn
Robert Mayes
Bill Pintarelli
Donna Ridder
Carole Vaught

Distribution

Sue Dennis
Linda Humphries
Dawn Johnson
Vicki Mansavage
Robert Mayes
Rebecca Roberts
Diana Schillinger
Chris Talbot
Fred Walker

At-Large Members

Joel Osborne
Diane Wilson

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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 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.



Guidance Document

Providing Service to Tissue Donor Families

[No. 4, version 2, March 9, 2015]

*Certain American Association of Tissue Banks (AATB) guidance documents describe mandatory requirements with which accredited tissue banks must comply fully, whereas other AATB guidance documents present only recommendations regarding possible approaches, but not necessarily the only approach, for compliance by accredited tissue banks with AATB Standards. **This guidance document is advisory in nature only, and does not establish legally enforceable responsibilities with which AATB accredited tissue banks must comply.** Absent imposition of a specific requirement by AATB that a tissue bank must comply with one or more of the provisions of this guidance document, its provisions (1) should be viewed only as recommendations reflecting AATB's current thinking on the subject, unless specific AATB Standards or regulatory or statutory requirements are cited, (2) the use of the word "should" means that something is suggested or recommended, but not required, and (3) the recommendations do not represent the sole approach, and alternative approaches may be satisfactory to establish compliance with Standards. This guidance document is intended solely for the use of AATB accredited tissue banks in conjunction with the AATB's Standards for Tissue Banking.*

*American Association of Tissue Banks
8200 Greensboro Drive
Suite 320
McLean, Virginia 22102
(703) 827-9582 (703) 356-2198 Facsimile*

Additional copies of this *Guidance Document* are available from the AATB office. In addition, comments on this document may be submitted at any time to the AATB. The Association will review any comments received and revise the *Guidance Document* as appropriate. All requests and comments should be addressed to:

American Association of Tissue Banks
8200 Greensboro Drive
Suite 320
McLean, Virginia 22102
www.aatb.org

For questions on the content of the document, please contact the AATB at:

(703) 827-9582 or (703) 356-2198 (Fax)

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Efforts are made to have publications of the AATB consistent in regard to acceptable practices. However, for several reasons, they may not be. As new developments in the practice of tissue banking occur, changes may be recommended to the *Standards*. It is not possible, however, to revise each publication at the time such a change is adopted. Thus, it is essential that the most recent edition of the *Standards* be consulted as a reference in regard to current acceptable practices. The AATB expressly disclaims any liability arising from any inaccuracy or misstatement herein.

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Maggie Coolican (co-editor)
Robin Cowherd (co-editor)

Pam Albert
Mary Beth Aubry
Christine Belitz
Scott A. Brubaker (AATB liaison)
Jeff Cox
Sara Craig
Julie Crumbacker
Mary Beth Fisk
Catherine Hackett
Mary Ellen McGlynn
Victoria McNeel
Amy Moeder
Cynthia Reed
Rita Reik
Paula Symons
Candy Wells

Version 2 update:

Maggie Coolican (co-editor) – (retired)
Robin Cowherd (co-editor) – LifeNet Health

Pam Albert – New England Organ Bank
Michelle Andrews – Tissue Center of Central Texas
Mary Beth Aubry – Community Tissue Services
Maureen Balderston – Washington Regional Transplant Community & AOPO rep
Scott A. Brubaker – AATB liaison & document coordinator
Bethany Conkel – Purposeful Gift
Veronica Fernandez – New York Organ Donor Network
Myrna Garcia – Donor Alliance
Sarah Gray – AATB liaison
Catherine Hackett – Regional Tissue Bank (Halifax, NS, Canada)
Eleanor Haley – Living Legacy Foundation of Maryland
Mary Ellen McGlynn - New Jersey Sharing Network
Cynthia Reed – Iowa Lions Eye Bank
Candy Wells – LifeCenter Northwest

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AATB GUIDANCE DOCUMENT
PROVIDING SERVICE TO TISSUE DONOR FAMILIES

I. INTRODUCTION

A. History and Purpose

Each year approximately 30,000 individuals become tissue donors in the United States. Their family members follow previously known wishes of the donor or are asked to make a decision or authorization about tissue donation on behalf of the donor. Through these generous donation decisions, about two million tissue grafts are distributed annually and more than one million tissue transplants may occur every year.

There are many more tissue donors than organ donors. However, the standard of practice of providing services for *Tissue Donor Families* may be inconsistent, and for this reason, some families may not receive support services³. In recommendations provided by a subcommittee of the Association of Organ Procurement Organizations (AOPO), tissue donor families are entitled to the same level of follow-up care as are organ donor families².

The AATB's *Standards for Tissue Banking* at Standard D2.600 Services To Donor Families, and AATB's *Standards for Non-Transplant Anatomical Donation* at Standard NT-D2.600 describe *Services to Donor Families* or a referral to a support system must be offered to the *Authorizing Person*. The requirements additionally expect subsequent communications and periodic evaluation of services to be documented, maintained, and readily available, and a reference to AATB Guidance Document No. 4 is made. To meet the intent of these standards *Tissue Banks* and *Non-transplant Anatomical Donation Organizations* must consider this guidance document when providing *Services to Donor Families*.

The Bill of Rights for Donor Families³ also provides guidance for services that are, or should be, offered to Donor Families. By listing primary considerations in regard to specific aspects of bereavement, this document provides additional and more specific recommendations as guidance in providing a best practices standard of care for all families who authorize tissue donation.

This guidance document was originally issued in March 2007 and underwent extensive editing over a year-long period to create version 2. New sections include "evaluation of services," "gifted tissue for research," and "terms to avoid." Updates were made to expand sections such as "definitions," "family needs," and "components of a support services program."

¹AOPO Donor Family Services Council, Donor Family Follow-Up Survey, September 2003

²AOPO Donor Family Services Council, Tissue Subcommittee Position Statement on Level of Care for Tissue Donor Families, December 2005 (found at the Donor Family Council library, see Shared Files, of the AOPO portal)

³*Bill of Rights for Donor Families*, National Donor Family Council, National Kidney Foundation, 1994, 2004

B. Definitions

As used in this Guidance Document and/or in AATB *Standards*, the following definitions apply where indicated for deceased donation [Words that are defined in Standard A2.000 Definitions of Terms appear in italics and are capitalized (e.g., *Signed*)].

Authorizing Person: Upon the death of the *Donor*, the person, other than the *Donor*, authorized by law to make an anatomical gift.

Bill of Rights for Donor Families:

A document developed by the National Donor Family Council of the National Kidney Foundation, that provides guidance for the rights and legitimate expectations of families whose loved ones die and are considered or become potential organ and/or tissue donors.

Document of Authorization:

Legal record of the gift of tissue, permitting and defining the scope of the postmortem recovery and use of tissues for transplantation, therapy, research and/or education *Signed* or otherwise recorded by the Authorizing Person, pursuant to law.

Document of Gift: The *Donor's* legal record of the gift of tissue permitting and defining the scope of the postmortem recovery and use of tissues for transplantation, therapy, research and/or education. It must be *Signed* or otherwise recorded by the *Donor* or person authorized under law to make a gift during the *Donor's* lifetime.

Document of Gift/Authorization:

Term used when the standard refers to both a *Document of Gift* and a *Document of Authorization* as defined above.

Donation Coordinator:

A *Responsible Person* who seeks *Authorization* from an *Authorizing Person*, or who makes *Notification* concerning donation, recovery and use of the gift, or in the case of a *Living Donor* or *Client Depositor*, the *Responsible Person* who seeks *Informed Consent*. For *Authorization* purposes, this person may also be referred to as a “designated requestor.”

Donor Risk Assessment Interview (DRAI)⁴:

A documented dialogue in person or by telephone with an individual or individuals who would be knowledgeable of the donor's relevant medical history and social behavior. For example this may be: the donor, if living;

⁴ For use when communicating with a *Tissue Donor Family*, it's advised that other terms are used, such as Medical History Interview, Medical/Social History, Donor Family Questionnaire, etc., in place of “Donor Risk Assessment Interview.”

the next of kin; the nearest available relative; a member of the donor's household; other individual with an affinity relationship (e.g., caretaker, friend, significant life partner); and/or the primary treating physician. Alternatively, a living donor may complete a written questionnaire. The relevant social history is elicited by questions regarding certain activities or behaviors that are considered to place such an individual at increased risk for a relevant communicable disease agent or disease (RCDAD).

Experience of Care Survey:

A series of questions formulated to gather *Donor Families'* thoughts about services provided. Questions should confirm whether services have met their needs. Surveys may be conducted face to face, over the phone, via email or Internet, or on handwritten forms. Answers provided can be assessed to determine if modifications to services are needed. This survey can be titled to meet local needs.

Limited English Proficiency (LEP):

When used in respect to an individual, a person who does not speak English as their primary language and who has limited ability to read, speak, write, or understand English.

Recipient: A person into whom tissue is transplanted.

Services to Donor Families:

A defined policy or support program describing tissue donation follow-up offered to the *Authorizing Person* (or party). This may include written communications regarding: potential uses of tissue; recovery outcome information; bereavement information and support; provision of a copy of the *Document of Gift/Authorization*; and/or guidance describing how to contact the tissue bank if any questions arise regarding the donation. Frequency of follow-up and program maintenance is at the discretion of the tissue bank, however, periodic evaluation of services is required.

Tissue Bank: An entity that provides or engages in one or more services involving tissue from living or deceased individuals for transplantation purposes. These services include assessing donor suitability, recovery, (processing)⁵, storage, labeling, and distribution of tissue.

Tissue Donor Family (aka Donor Family, Donor Families):

Family members/persons who follow the tissue donation wishes of, or who provide the authorization decision for, a decedent.

⁵ For use when communicating with a *Tissue Donor Family*, it's advised that "preparation" or "making tissue ready for transplant" be substituted in place of "processing."

II. BEREAVEMENT SUPPORT SERVICES

A. Philosophy

Support *Services to Donor Families* may be characterized by:

- An appreciation that potential *Donor Family* members are the experts about their own bereavement.
- An understanding that bereavement services begin with the first contact the family has with a health care professional.
- A consideration that *Tissue Donor Families* should be expert resources in the planning, development, and review of a program developed to support them.
- Interaction between tissue bank staff members with specific skills and training and the *Donor Family* to effectively meet bereavement and donation needs.
- An understanding that organizations that recover and prepare tissue have a responsibility to address *Donor Family* questions and/or concerns regarding tissue donation in a timely, effective, and compassionate manner.

B. Family Needs

A comprehensive *Tissue Donor Family* support program provides the following:

- During the authorization/notification conversation, the *Donation Coordinator* will:
 - offer sympathy for the death of the donor and allow family members the time to express grief and tell their story before any donation discussion;
 - refrain from using medical, regulatory, or tissue banking jargon (See Appendix I Terms to Avoid, Terms to Use);
 - be present for the family through active listening in an ongoing and systematic way with continual empathetic assessment;
 - identify and respect family's, cultural, religious, and/or ethnic differences and/or requests;
 - provide an estimated time line for the discussion; and
 - offer non-judgmental respect for decision-making.
- Information should:

- be presented with a modulated tone of voice;
- be offered in smaller amounts (dosing) dependent on family needs;
- be complete to ensure family understanding of tissue donation and transplantation, research, and compliance with regulations;
- outline how family members may carry out the decedent's donor designation;
- provide an opportunity to make a donation decision;
- include the tissues that might be available for donation, transplantation, and/or research, and how they could benefit others;
- describe that tissues are recovered by specially trained technicians in a way that is similar to a surgical procedure;
- include the time elements involved in tissue preparation (recovery, preparation, distribution and transplantation/research);
- be about grief and mourning;
- be presented with sensitivity and compassion in language and terms that are easily understood by the family; and
- every reasonable effort should be made to ensure that the opportunity for donation is provided as needed when a Limited English Proficiency (LEP) scenario is encountered, such as:
 - utilizing interpreters when communicating with *Donor Families* identified with LEP;
 - employing bilingual support services personnel; and
 - translating the *Document of Gift/Authorization* into the *Donor Family's* or *Authorizing Person's* language of proficiency.
- Conversation will allow for:
 - family empowerment and control over whatever is within the ability of the family to influence or make decisions about;
 - time to answer or explain family questions;
 - probing to ensure complete answers to questions;

- echoing: repeating key words from what the person has just said;
- reflecting content: summarizing what the person has said;
- reflecting feelings: helping the person label the feeling;
- paraphrasing: a restatement giving the meaning in another form;
- exchange of contact information between tissue bank staff and the *Donor Family* after the discussion; and
- appreciation to the family regardless of the outcome of the discussion.

Throughout services provided after donation, the donation professional should:

- enhance their skills with an understanding of current issues and models in loss, grief and mourning;
- have a responsibility to understand what the family is experiencing and where they may be in their grief;
- respect the privacy of the family and adhere to confidentiality;
- be highly skilled in oral and written communication and able to define medical terminology in layman's terms;
- demonstrate compassion and empathy regarding information about their loved one's death;
- provide details on how the family may obtain an autopsy report, or learn the cause of death or reason the donation cannot be placed for transplantation and/or research; and
- refer the *Donor Family* to an appropriate agency (Medical Examiner, Coroner, Hospital) for information concerning the death.

C. **Components of a Support Services Program**

Services to Donor Families may include:

- Information concerning the donation outcome or support services shall be presented with sensitivity and in language and terms that are easily understood by the family. Every reasonable effort should be made to ensure that support services are provided to potential *Donor Families* with Limited English Proficiency (LEP).

- An initial letter expressing sympathy for the family's loss and gratitude for the donation with information on the outcome of the tissue donation recovery for transplant or research.
- Provision of a copy of the *Document of Gift/Authorization* if requested by the *Donor Family* or required by law or internal policy. These may be mailed, faxed or emailed.
- Information about the family support follow-up program.
- Grief materials, bereavement support information, and other resources.
- General information about tissue donation, transplantation and research.
- Affirmation of the value of their loved one's donation.
- An opportunity to have their questions and concerns addressed regarding their donation experience.
- Periodic contact through telephone calls, cards, or letters for at least one year, unless family chooses to opt out.
- Upon request, provision of updated information about how the tissue was used for transplant or research.
- A process that supports communication initiated by *Recipients* for *Donor Families* if agreeable, and, when possible, from *Donor Families* to *Recipients* (i.e., cornea donation, donation of the heart for valves).
 - As necessary, a process for communication from researchers with *Donor Families*, if agreeable, or for information about how tissues were used in research.
- An opportunity to honor and/or memorialize the donor.
- An opportunity to participate in community events promoting tissue donation.
- An opportunity to evaluate the donation and bereavement experience.
- A *Donor Family* group that assists with planning and review of the *Donor Family Services* program.
- Follow-up services may also be offered to those *Donor Families* who have authorized donation but:
 - the donor was determined to be ineligible and recovery did not occur; or
 - donated tissue was recovered but not able to be used for transplant/use.

D. Gifted Tissue for Research

When a family donates for research and/or medical education the entity that obtained authorization should:

- Provide the family with information regarding how patients will benefit from this research as well as the way(s) in which the gift will be used to facilitate advances in medical/surgical research and/or procedures;
- Develop a process that supports communication initiated by research organizations if agreeable, and, if possible, from *Donor Families* to research organizations; and
- Upon request, provide updated information about the gift.

E. Evaluation of Services

Services to Donor Families must be periodically evaluated for effectiveness. The evaluation should include contacting *Donor Families* about their experience regarding the support provided by the program. The evaluation schedule may vary but information collected should help guide changes/additions/deletions to the current program to meet ongoing bereavement/support needs of *Donor Families*. Use of an *Experience of Care Survey* has become common practice for evaluating services. See Appendix II Experience Of Care Survey.

F. Resources for Donor Families

Individual websites of OPOs and tissue banks provide useful information for *Donor Families*. The following website can be accessed for a comprehensive list of grief resources for *Donor Families*:

<http://www.aatb.org/Grief-Resources>

III. APPENDIX I

Importance of Language when Supporting Families

Terms to Avoid	Terms to Use Instead
<i>Approach</i>	Donation discussion, Discuss donation, Provide donation information to the family, Conversation about donation
<i>The Ask</i>	Offer donation information/opportunity to a family
<i>Body</i>	Name of patient
<i>Body Parts</i>	Donated organ and/or tissues, the gifts

Terms to Avoid	Terms to Use Instead
<i>Declare Brain Death</i>	Determine brain death
<i>Discarded tissue</i>	Tissue that cannot be used for transplantation or research; cannot be placed
<i>Cadaver</i>	Deceased donor
<i>Case or referral</i>	Donor, patient, working with a family using the patient's name
<i>Committed suicide</i>	Completed suicide, died by suicide
<i>Distributed tissue</i>	Tissue used for transplantation or research
<i>Donor Pool</i>	Patients who may be able to donate, maximize donation, expand the potential for donation, patients who provide the opportunity for donation
<i>DRAI</i>	Life review; Medical/social history or questionnaire, similar like when you give blood; medical and lifestyle questionnaire
<i>Eligible</i>	Able to donate
<i>Expired Goods</i>	Tissue that can no longer be transplanted
<i>Expired</i>	Died
<i>Fetal demise</i>	Cause of death <i>in utero</i> (in the womb) or shortly after birth
<i>Fetus</i>	Baby, or baby's name
<i>FPA</i>	First person authorization, patient made a personal donation decision
<i>Goods</i>	Tissue, specific name of tissue, tissue grafts, tissue forms
<i>Harvest</i>	Recover, surgical recovery, donate (i.e., we can recover bone, he can donate bone)
<i>Incinerate</i>	Cremate
<i>Incompatible with Life</i>	Life limiting diagnosis, terminal condition, non-survivable diagnosis
<i>Ineligible</i>	After further evaluation, we will not be able to move forward with donation
<i>Legal Death</i>	Death
<i>Life Support</i>	Artificial support, respirator support, ventilator support, mechanical support

Terms to Avoid	Terms to Use Instead
<i>Non-heart beating donation</i>	Donation after cardiac death
<i>Non-viable</i>	Life limiting diagnosis, terminal condition
<i>OA (osteoarticular), or OC (osteochondral)</i>	Tissue grafts used to repair a person's damaged joint
<i>Option</i>	Opportunity
<i>Processing tissue</i>	Preparing tissue
<i>Processor</i>	Company that prepares tissue for transplantation or research, Partner
<i>Product</i>	Tissue, organ, gift
<i>Recovered or heal from the death</i>	Learning to live with the death, finding a new normal, making sense of the death
<i>Rejected donor</i>	After further evaluation; not able to donate; Tissue cannot be used for transplantation
<i>Shelf Life</i>	Transplantable, viable, the amount of time that tissue can be used for transplantation after recovery
<i>Stillborn</i>	Delivery after your baby died
<i>Suitable</i>	Able to donate
<i>Unsuitable</i>	After further evaluation; not able to donate
<i>Used or Utilized</i>	Shared, helped, gifted, transplanted
<i>Vegetable</i>	Someone who is no longer able to communicate with others
<i>Will save lives</i>	Possibility of saving lives
<i>Yield</i>	Number of gifts that are able to be transplanted

IV. APPENDIX II

Experience Of Care Survey

If an *Experience of Care Survey* is used to evaluate effectiveness, it could:

- include all or a representative sample of willing participants;
- be sent approximately one year after the donation occurred, or at the conclusion of the *Donor Family Services*;

- include a list of all or specific materials provided as part of the program with a request for the *Donor Family* to evaluate the materials and/or services provided;
- solicit demographic information about the *Donor Family*;
- request additional comments regarding the program, the organization (tissue bank), or the *Donor Families'* overall donation experience. (Note: This survey is not intended to evaluate the *Donor Family's* experience with hospital personnel);
- provide results that influence budgetary decisions involving bereavement services, and
- include some or all of the following questions:
 - How has the opportunity for tissue donation affected your grieving?
 - Given your experience, would you be willing to donate again? If no, please explain.
 - On a scale of 1-5 with 1 being not satisfied and 5 being extremely satisfied, how would you rate *Donor Family Services* overall?
 - What services did our staff provide that was most helpful to you? Why were they helpful?
 - What services did our staff provide that was least helpful to you? Why do you believe they were not helpful?
 - Would you like to receive additional resources at this time? If so, what types of resources would be helpful?
 - Would you be willing to submit a story/poem/photo to our family support newsletter?
 - Would you like instructions on how to submit a quilt square to our quilt project/donor quilt program?
 - Are you interested in information about our volunteer program?
 - Sample surveys and sample letters are available on the AATB website:

<http://www.aatb.org/Donor-Family-Service>

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Guidance Document

Microbiological Process Validation & Surveillance Program

[No. 5, version 2, July 18, 2016]

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*American Association of Tissue Banks
8200 Greensboro Drive
Suite 320
McLean, Virginia 22102
(703) 827-9582 (703) 356-2198 Facsimile*

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American Association of Tissue Banks
8200 Greensboro Drive
Suite 320
McLean, Virginia 22102
www.aatb.org

For questions on the content of the document, please contact the AATB at:

(703) 827-9582 or (703) 356-2198 (Fax)

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Martell K. Winters (Task Force Lead, Primary Author)

Primary Contributors:

Lori Bachtel
Grace Bolton
Scott A. Brubaker
Martin Byrne
Nita Chettier
Ellen Dumont
Dean Elliott
Miriam Estrano
Stephan Gambon
Bhagyashree Govindaraju
Carrie Hartill
Alyce Linthurst Jones
Patty Malone
Sally McFarland
Joel Osborne
Geri Roberts
Tracy Ross
Christopher Talbot
Linda Weiss
Yee Yang
Jan Zajdowicz

Contributors:

Béatrice Allard
Fouad Atouf
Karen D'Amico
Jorge Duran
Dave Fronk
Tonya Gray
Catherine Hackett
Joyce M. Hansen
Debbie Meade
Paul Morris
Tyrone L. Pitt
Adrienne Pryor
Debby Sartain
Archana Sharma
Mark Spilker
Jacynthe Tremblay

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AATB GUIDANCE DOCUMENT
MICROBIOLOGICAL PROCESS VALIDATION AND SURVEILLANCE
PROGRAM

I. INTRODUCTION

A. History and Purpose

AATB's *Standards for Tissue Banking (Standards)* and various global regulatory authorities with oversight of cell and tissue establishments require validation of procedures related to tissue processing. Lack of stepwise instructions for validating such procedures is a recognized gap that exists worldwide. This Guidance Document provides detailed information to assist tissue banks in development of a comprehensive microbiological surveillance program and describes steps to consider when validating processing of 'conventional' allograft tissue (e.g., skin, bone, cartilage, ligaments, tendons, dura mater, amnion, vessels, heart valves, and cellular tissue), similar autograft tissue, and allografts regulated as biologics, medical devices or combination products. Scenarios (see examples and annexes) are included to further illustrate expectations.

Due to evolving information regarding the critical role of microbiological test methods used for human tissue recovered for transplantation, as well as a need to establish microbiological sampling plans that can sufficiently establish a validated process's capabilities, updates were issued to *Standards* during early 2011 accompanied by an AATB Interim Guidance Document (i.e., No. 5, Standard K2.210 Pre-Sterilization/Pre-Disinfection Cultures). The guidance was referenced within *Standards* and became required (see AATB Bulletin #11-01, January 4, 2011). It described a more detailed document would be issued in the future; this guidance document replaces that interim guidance.

AATB-accredited tissue banks are expected to use the following guidelines when validating microbial surveillance methods and when validating processing methods and steps. Documentation, including relevant data, is expected to support decisions and must be made available to AATB when requested. **The advisory nature of this guidance will eventually become mandatory.**

B. Definitions

Terms used throughout this Guidance Document are defined here and are generally accepted definitions. Where applicable, the source of the definition is referenced.

Allograft: Tissue intended for transplantation into another individual of the same species. (1)

Aseptic Processing: The processing of tissue using aseptic techniques when tissue, containers and/or devices are handled in a controlled environment in which the air supply, materials, equipment and personnel are regulated to prevent microbial contamination of tissue.

Note: This term is used in different ways in various industries, including the tissue banking profession.

The primary differences between uses of the term aseptic process for tissue versus applicability to other products are:

- Generally, for aseptically manufactured healthcare products that do not contain human tissue, all components and products are sterilized in some manner prior to assembly and packaging in an aseptic process; sterility of the components and products are maintained during assembly and packaging. (2)
- For aseptically manufactured products that contain human tissue, the non-tissue components are sterile prior to entry into the aseptic process, but the tissue may not be sterile entering the aseptic process. Thus, the aseptic process may include bioburden reduction steps for the tissue, and the aseptic process environment prevents any subsequent contamination of the tissue and maintains the sterility of the other components.

Bioburden: Population of viable microorganisms on or in tissue and/or the sterile barrier system (packaging). (3)

Note: Testing for bioburden can be performed before, during or after tissue processing.

Bioburden reduction: The act of reducing the number of viable microorganism on surfaces and/or tissue.

Cleaning (tissue): The initial step of the tissue disinfection process that can include the removal of extraneous tissue, blood, lipids, certain proteins and many microorganisms. (4)

Companion tissue: Tissue used for microbiological destructive testing that is co-processed from the same donor and is of the same type (e.g., tendon for tendon; bone for bone, and skin for skin) as finished tissue from the same lot. It is not intended for transplant.

Decontamination: Cleaning the environment, facilities, and/or surfaces (sanitation), or instruments, supplies, and equipment (sanitization), with intent to remove or reduce pathogenic microbes. (4, 8, 39)

Destructive testing: When tissue used for microbiological testing is destroyed and can no longer be used as a result of performing the testing.

Disinfectant: An agent (e.g., heat, a chemical) capable of reducing the number of viable microorganisms. A disinfectant might not kill spores. Use of antimicrobials in tissue processing is included here.

Disinfection: A process that reduces the number of viable microorganisms on tissue, but may not destroy all microbial forms, such as spores and viruses. Use of antimicrobials in tissue processing is included here.

Note: In this document the term disinfection has been specified for use on tissue and decontamination has been specified for use on surfaces, however, disinfectants are used with either application. For example one can use a disinfectant to decontaminate surfaces or a disinfectant to disinfect tissue.

e.g.: abbreviation for *exempli gratia*; for example, such as; the list is not finite.

Finished tissue: Tissue that has been fully processed, enclosed in its final container, labeled,

and released to distribution inventory. (1)

Fluid extraction: A solution that has been exposed to tissue and subsequently used for microbiological testing. It is highly preferred that the solution be the last fluid the tissue contacts during packaging for finished allograft end point culture testing.

HCT/P: FDA term for “human cells, tissues, or cellular or tissue-based products”; see 21 CFR Part 1271.3(d) for more information. (5)

i.e.: abbreviation for *id est*; that is; indicates a finite list.

Log reduction: The reduction in number of viable microorganisms, expressed in logarithmic units. (6)

Note: The log reduction value is not equal to a sterility assurance level (SAL) of the same value. For example, if a tissue product has a bioburden of 10^4 CFU, a 3 log reduction will result in a bioburden of 10^1 , **not** an SAL of 10^{-3} .

Method suitability test [also called the bacteriostasis/fungistasis (B/F) test]: A test performed with selected microorganisms to demonstrate the presence or absence of substances that inhibit the multiplication of microorganisms. Note: This is often performed using the approach described in USP <71> (7) under Method Suitability Test.

Microorganism: A microscopic organism, including bacteria and fungi; viruses, while sometimes included in this classification, are not included here. (10)

Process validation: Establishing by objective evidence that a process consistently produces a result or product meeting predetermined specifications. (8, 9)

Processing (FDA 21 CFR Part 1271.3 (ff)): 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. (9)

Quality system: The organizational structure, responsibilities, procedures, processes, and resources for implementing quality management. (1)

Sterile: For tissue, the absence of detectable, viable, microorganisms (10). For reagents, supplies, materials and equipment, free from viable microorganisms.

Sterility assurance level (SAL): The probability of a single viable microorganism occurring on an item after sterilization.

Note: The term SAL is a quantitative value, generally 10^{-6} or 10^{-3} . When applying this quantitative value to assurance of sterility, an SAL of 10^{-6} has a lower value but provides greater assurance of sterility than an SAL of 10^{-3} . (3, 8)

Sterilization: A validated process used to render tissue free from viable microorganisms including spores. (10, 11)

Terminal sterilization: A validated process whereby tissue within its final sterile barrier system (e.g., package, container) is sterilized. (10, 11)

Note: Use of this term is restricted to sterilization that occurs when the tissue is in its sealed sterile barrier system (i.e., primary package).

Validation: Confirmation through the provision of documented objective evidence that predefined specifications have been fulfilled and can be consistently reproduced. (9)

Verification: The confirmation by examination and provision of documented objective evidence that specified requirements have been fulfilled. (8)

II. MICROBIOLOGICAL ASPECTS OF PROCESS CHARACTERIZATION

A. Introduction

This section provides detail regarding validation of processes aimed at reducing or eliminating microorganisms from allografts. Additional aspects of process validation (e.g., physical effects on tissue, chemical residues) are not addressed in this document although some of the concepts may apply.

Successful process validation is heavily dependent on knowledge of the tissue type and the process. A process must be capable of delivering a set of defined conditions to which the tissue is exposed. Additionally, attributes of the tissue must be well understood such that the response of the tissue to the conditions is both consistent and acceptable. Thus, the investigator must verify the critical attributes of both the tissue and the process.

Historical process and knowledge of the tissue type, literature reviews, feasibility studies, and process and allograft characterization are all means by which one can verify critical attributes and process parameters. Verification of critical attributes and process parameters will allow one to define appropriate tissue and process specifications for process validation.

B. Process Characterization; Preparing for Process Validation

Prior to process validation it is important to understand each individual step of the process. This effort is called process characterization. Process characterization is often iterative in nature, intent on defining and optimizing the steps in the process. Steps may include defining the process range by gathering available, relevant data in literature, gathering historical information from subject matter experts, and/or performing feasibility studies.

Each step of the process must be evaluated so that critical steps can be differentiated from non-critical steps (e.g. a step with specific log reduction activities versus a rinse step with no specific outcome). When evaluating a step in the process, it is necessary to identify variables that affect the process step and determine if they can produce an unacceptable outcome for the finished tissue. Critical steps for a process must be well defined, controlled, and documented. Non-critical steps may not require a high level of control, and may not be as well defined.

Annex A provides an example of steps taken in process characterization. Annex B describes how information from process characterization can be used in process validation.

Oftentimes, verification of the tissue quality and performance of equipment are outputs of process characterization. This information may become part of equipment installation qualification (IQ), which is discussed later in this document.

If a step is determined to be non-critical (e.g., tissue transfer, storage step), a rationale should be written describing how that decision was made. Failure to control a seemingly inconsequential step in the process may result in an undesirable or unacceptable outcome.

Example: The physical act of transporting tissue from one location to another may have little impact on the tissue. The transport conditions however, (time, temperature range, exposure to environment) may have a significant impact on the tissue from microbiological and functional perspectives. A seemingly inconsequential step is critical to preserving the attributes of the tissue.

Characterization of a process may include evaluation of parameters such as sensitivity, specificity, linearity, precision, accuracy, and ruggedness. Some parameters are more applicable to an analytical test than to a microbiological test. When designing protocols, it is important to assess which parameters are relevant to the process.

Example: If a process step may be performed by a number of personnel and actions of the personnel involved can have significant impact on the finished tissue, then determination of ruggedness by including multiple personnel may be prudent.

When performing process characterization, it is important to understand the effect of using multiple variables for critical aspects of a step (e.g., temperature, time, concentration). If the number of variables to be evaluated can be minimized, it is easier to determine if optimization of individual steps is necessary. These data may be used to establish proper ranges for individual processing steps.

Example: Process step #2 has four variables (temperature, time, concentration, and life expectancy of a chemical). The tissue processor has determined, through literature and experience, that the optimal working temperature is between 18-25°C, and the life expectancy of the chemical is 8 hours at that temperature. They decide to not perform extensive testing of those two variables, but to focus on optimization of the time and concentration variables. Therefore, during process characterization, the temperature range is set at 18-25°C and time is tested at the maximum life expectancy of 8 hours. However, concentrations of 0.08, 0.1, 0.12 and 0.14 are used, as well as times of 20, 40, 60 and 90 minutes.

When evaluating process steps, it is important to characterize or evaluate microbial reduction as well as the impact of the process steps on the physical and functional aspects of the tissue. A process step may be implemented which is primarily intended to have a physical effect on the tissue, but which also has a microbial reduction aspect as a secondary benefit, or vice versa.

Once a process is well understood/characterized, writing validation requirements becomes a straightforward process because the critical process parameters and the acceptable variability around those parameters have been defined during process characterization.

III. MICROBIOLOGICAL PROCESS VALIDATION

This section addresses process validation for assessment of microbiological aspects of processing. Process validation is performed to demonstrate with a high level of confidence that a consistent finished tissue outcome will occur when the process is properly applied. Process validation is required in instances where a critical process cannot be 100% verified. Documentation of Process Validation (e.g., the protocol and final report) is expected. See AATB Standard K1.100 Basic Elements (at K1.000 Quality Assurance Program) and the relevant definition in A2.000 (1). A validation protocol must be written that includes procedures, rationale, acceptance criteria, etc.

A. Distinguishing Validation of Methods from Validation of Processes

Discussion of validation work in this section is in context of validating a process step rather than validating a test method.

To validate a process step, the proposed process step is applied to representative samples and the samples are tested to demonstrate the ability of the step to consistently provide the desired effect. The process is typically performed multiple times to show reproducibility of the process. Inconsistent data may indicate that changes should be made to the process to provide better or more consistent outcomes.

To validate a test method, representative samples are selected and tested to demonstrate performance of the proposed test method. Data may indicate that changes to the test method should be made so that test parameters (e.g., accuracy, precision, sensitivity, specificity) are improved. See Section XII. Validation and Qualification of Test Methods.

B. Three Stages of Process Validation

An FDA guidance document (9) describes process validation activities are expected to occur in three stages:

- Process Design
- Process Qualification
- Continued Process Verification

This approach entails evaluation of the process during the entire life cycle of the tissue, not just at a single time point.

The process should be designed based on an understanding of the desired outcomes of the process. If specific outcomes of the proposed process are established and documented it will be easier to tailor the process with those outcomes in mind. Previous experience in tissue processing can also be used to assist in designing the process.

In the process qualification stage, testing is performed to evaluate the quality and reproducibility of the established process. This could include testing of individual steps in the process (also known as process characterization) as well as testing of the entire process. During the course of process qualification it might be determined that aspects of the process should be adjusted to result in a more optimized or improved process. In fact, going into process qualification it

should be understood that the proposed process is still somewhat fluid and might change depending on results obtained.

The stage of continued process verification is a reminder that qualification or validation of a process does not guarantee proper implementation or function of that process for its entire life. Process design and qualification stages can assist in determining particular aspects of the process; these are good indicators of continued quality and reproducibility. Those indicators are often called process monitors and should be performed regularly enough to demonstrate maintained control.

C. Step-wise Approach

An individual performing process validation may choose to validate the entire process or may first choose to validate individual steps within the process.

Some aspects of a process step may be validated as a group (if a particular process step has multiple aspects which must be validated), and others may have to be validated individually. If aspects of a step or steps of a process are to be validated together, an important consideration is the number of variables involved. If issues arise from the validation data, the number and complexity of variables involved may hinder determination of the root cause of a validation problem.

Annex B provides an example of the stepwise approach to process validation.

Validating every aspect of each process step can be unmanageable due to time, cost and personnel constraints. It is acceptable to specify some of the aspect details rather than perform validations to optimize all of them. If this approach is used, a rationale detailing how the decision was made and supporting information must be documented.

The scope of a process validation should be well defined prior to initiating the validation. It is often helpful to identify validation limitations and validation related issues that are addressed in other protocols or portions of the Quality System. In validation there are some aspects that are not further tested by the tissue bank.

Example: If your Quality System dictates that sterile water is purchased from an approved vendor whose quality system has been audited and has been deemed acceptable, a requirement to test the specifications of the sterile water may not be necessary if verification can be performed effectively (e.g., a compliance certificate, certificate of analysis).

In evaluating various aspects of a process step, the term ‘address’ may be used rather than ‘validate.’ It may not be necessary or possible to ‘validate’ every potential impact (e.g., microbiological and physical) that every process step may have on tissue. Process engineers should determine, based on the intended purposes and criticality of each step, which aspects should be tested.

D. Validation of the Overall Process

After assessing individual process steps, process validation should be completed by microbiologically challenging the entire process (e.g., with inoculated tissue) and evaluating the

tissue post processing. The results of step-based validations will assist in determining how evaluation of the entire process should be done.

A decision to be made is whether to perform a qualitative or a quantitative analysis after the inoculated tissue goes through the process (see Section IV. General Considerations For Microbiological Testing at B. Qualitative vs. Quantitative Testing).

In a very robust process (e.g., where six or more log reductions are expected during the process) a qualitative analysis of the inoculated tissue post-processing is likely best due to its greater sensitivity. In a less robust process (e.g., fewer than six log reductions are expected during the process) a quantitative analysis of the inoculated tissue post-processing is likely the best approach due to its ability to provide microorganism counts.

Example: If it is known from process characterization that Step A provides a 3 log reduction and Step B provides a 4 log reduction, it is possible that the two processes together would provide enough log reduction to reduce a 10^6 inoculum to almost zero. This means that if tissue is inoculated with the selected microorganism(s) at a level of 10^6 CFU and then processed, the remaining microorganism count would likely be very low. In this situation, a sterility test of the inoculated tissue post-processing might be best.

Example: If it is known from process characterization that one process applied to the tissue, Step A, only provides a 2.5 log reduction there will likely be a high number of microorganisms remaining post-processing if the initial inoculum is 10^6 CFU. In this situation a bioburden test of the inoculated tissue post-processing might be best due to its ability to provide the remaining number of CFUs.

One reason to microbiologically evaluate the overall process is to verify assumptions regarding the potentially additive microbial reduction nature of the individual steps. Generally, log reductions cannot be automatically added together to determine the overall log reduction capability of a process because the modes of action of the various steps in the process might overlap (12). For example:

- if the mode of action of Step A and Step B **are the same** (e.g., both are alcohol-based steps) then log reductions from Step B might not be additive;
- if the mode of action of Step A and Step B **are different** (e.g., alcohol-based and peroxide) then log reductions from Step B could be additive.

Also, evaluation of the overall process can be used to verify the absence of unforeseen interactions between steps of the process that may be detrimental to the finished tissue, either microbiologically or physically.

In validation of the overall process it is best to limit the quantity of variables to be addressed in order to limit the quantity of experiments that must be performed. Process characterization and previous validation of the individual steps play a large role in establishing the conditions of these variables. In characterization of the individual steps, one can determine which variables to use as ‘worst case’ or ‘typical case’ scenario (e.g., high or low temperature, minimum and maximum soak times, high or low concentration). The conditions used in the validation and the rationale for their use should be documented in the validation protocol.

Annex C provides an example of the potential challenges when performing validation on the entire process rather than first on individual steps.

E. Acceptance Criteria

It is important to establish acceptance criteria for process validation *prior to* initiation of the validation. Acceptance criteria must be written in support of the validation protocol. Acceptance criteria are determined by the individual tissue bank and will vary, minimally based on the following:

1. Label claims (e.g., the label claim of ‘sterile’ carries a higher regulatory requirement than other claims);
2. What process characterization data suggests the overall process is capable of; and
3. Statements the individual tissue bank intends to make regarding final tissue attributes (e.g., marketing literature statements must be supported).

Oftentimes components of a tissue process are licensed or purchased pre-validated. If a tissue bank chooses to purchase and use this validated process for its own tissue, the process must be verified for use in their establishment.

Consideration should be given when adopting a previously validated process to a new material or load configuration. Changes to a validated process must be reviewed and evaluated and revalidation performed where appropriate.

Annex D provides an example of a limited validation.

IV. GENERAL CONSIDERATIONS FOR MICROBIOLOGICAL TESTING

A. Introduction

The outcome of a disinfection or sterilization process is related to the capability of that process to reduce or eliminate an expected level and mix of microorganisms on the particular tissue type being exposed to the process. If pre-sterilization/pre-disinfection microbiological load exceeds what the process has been validated to remove or inactivate, there is a lack of assurance the process will result in an expected reduction of microorganisms. Thus, it is imperative that test methods used to identify microorganism contamination at critical, predetermined steps produce accurate results. Pre-sterilization/pre-disinfection microbiological cultures play a critical role in indicating the capability of the validated process will not be exceeded. It is equally important that in-process and final culture methods are not inhibited or influenced by residual processing agents, test material, or other factors.

B. Qualitative vs. Quantitative Testing

Often microbiological evaluation of a process or process step is performed by inoculating tissue with known numbers and types of microorganisms, performing process step(s) on the tissue, and determining if viable microorganisms remain on the tissue after treatment.

A qualitative test might be performed by enumerating the starting microbial population, processing the tissue, immersing the processed tissue in culture media, then looking for turbidity as an indication of growth. The results obtained are limited to either positive or negative for growth. In this approach, statements that can be made are limited regarding the presence or

absence of microorganisms. Turbidity visualized in positive tests may be due to the growth of 1 surviving microorganism or 1,000,000 surviving microorganisms. Exact enumeration of residual microbes is not possible.

A quantitative test might be performed by extracting microorganisms from the tissue and performing plate counts to enumerate starting and ending bioburden. The results obtained provide the quantity of CFU on the tissue. Thus, plate counts allow a description to be made regarding reduction of the microbial population due to the treatment. However, a notable limitation of the quantitative approach is that it requires extraction of organisms from tissue. Extraction methods are not 100% efficient (e.g., counts obtained may be the result of incomplete extraction rather than reduction of the organisms in the process).

Quantitative analysis usually provides better microbiological reduction data for an individual step and is better suited to evaluating different variables of that step and understanding lethality kinetics of treatment.

Example: An evaluation of two or three time points of a process step, using quantitative analysis provides data which can be used to optimize the microbial reduction potential of that step. Microbial counts obtained in the testing make it easier to determine which time point is providing the best microbial reduction. Negative or positive results obtained using a qualitative test would not provide useful data for optimizing the process step.

Additionally, quantitative analysis can assist in determining if the microbial reduction mechanism is linear with respect to time (e.g., the longer the process step is applied the more microbiological reduction occurs) and whether the microbial reduction is consistent with respect to time.

C. Selection of Microorganisms for Process Validation

When performing process validation, relevant microorganisms and microorganism loads must be selected. This determination is based upon knowledge of:

- What the protocol is attempting to achieve (i.e., disinfection or sterilization);
- The type and quantity of bioburden present on the tissues being processed; and
- The capability or limitations of the microbial reduction process being validated.

For low-level disinfection, it is generally acceptable to achieve up to 99% reduction of naturally occurring bioburden. The intent of this approach is to reduce vegetative bioburden and prevent any “blooms” of bioburden during the process. Low-level disinfection may not control or eradicate resistant forms of microbial flora such as spores.

For high level disinfection, it is generally acceptable to achieve $\geq 99.99\%$ reduction of naturally occurring bioburden. The intent of this approach is to reduce vegetative bioburden, spores and fungi so as to provide a very clean material.

For sterilization, the focus changes from “reducing bioburden” on tissue to “predicting the probability of a non-sterile unit” resulting from the process. The probability of a non-sterile unit is more commonly referred to as a Sterility Assurance Level (SAL).

Generally, for grafts labeled “Sterile,” an SAL of 1×10^{-6} has been achieved by the process on the final tissue configuration. This is often referred to as a “Terminal Sterilization Process” because the tissue is in its final configuration and will not be further manipulated or packaged after sterilization is complete.

The level of disinfection or sterilization takes into account the amount of bioburden reduction and the type of bioburden being reduced. If the tissue bioburden is known to include spore-formers like *Bacillus sp.* or *Clostridium sp.*, the use of a general disinfectant may not provide significant reduction of the bioburden.

Capabilities or limitations of the microbial reduction potential of a process are often supported by literature searches, consultation with experts in the field, and/or process characterization.

1. Using Representative Challenge Microorganisms

Challenge microorganisms are often chosen to understand the effectiveness of individual steps of the overall process across multiple microorganism types. For example, a species from each primary category of microorganism may be selected:

- Gram negative bacilli (e.g., *E. coli*, *P. aeruginosa*, *Serratia species*)
- Gram positive bacilli – usually a spore-former (e.g., *Bacillus species*)
- Gram positive cocci (e.g., *Staphylococcus aureus*)
- Mold (e.g., *Aspergillus species*)
- Yeast (e.g., *Candida species*)
- Anaerobe (e.g., *Clostridium species* for a spore-former or *P. acnes* for a non-spore-former)

Additionally, it is common to add microorganisms that occur on tissue or in the environment, such as air-, surface- and water-borne microorganisms. In some cases, microorganisms can be selected to meet multiple criteria (e.g., *E. coli* may represent gram negative bacilli and may also be found on tissue).

When selecting microorganisms, it may be tempting to omit select microorganisms because they have not been previously demonstrated to be of concern. While this is an option, if a potentially pathogenic microorganism category emerges in the future, it may be necessary to perform additional evaluations with that microorganism type. It is usually best to initially evaluate a broad range of microorganism categories and species.

There are no specified criteria for selection of microorganisms in FDA documents related to tissue. Other documents, however, provide guidance regarding this topic. ISO Standards 14160 (12) and ISO 14937 (13) provide guidance on selecting appropriate microorganisms for evaluating a sterilization process. These concepts are similar for evaluating a disinfection process such as those commonly applied to tissue.

2. Using Microbial Screening Studies

Another option for selecting microorganisms is to implement a screening method for process-resistant microorganisms. This is often performed by applying the process or the process step to tissue, using a shorter time and/or lesser concentration than typically specified, then testing the

tissue for surviving microorganisms. Surviving microorganism types must then be included in the process validation.

3. Use of Microorganisms in Validation

When performing validations of a step or an overall process it may be possible to use initial test data to reduce the need for testing all microorganisms under consideration. Using only the more resistant microorganisms (for a worst-case challenge) allows for a greater number of process variables to be challenged with similar resources due to the reduction of replications and tissue samples involved compared to if all microorganisms needed to be evaluated.

Example: Initial research and development (R&D) testing or process characterization may indicate that Step B easily kills gram negative rods, strict anaerobes, gram positive cocci and yeasts. If all critical aspects of Step B (as determined by risk analysis and the initial R&D tests) remain the same, it may be possible to perform the validation of the step using only the more resistant microorganisms (i.e., a gram positive rod and a mold). Testing fewer microorganism types might then allow for testing of additional time points to optimize Step B for microbial reduction.

Note that the data used to reduce the number of microorganism types for Step B may not apply to other steps in the process because the mechanism of kill for other steps may be different. It is likely that this type of evaluation will need to be performed individually for each step in a process.

D. Determination of Microbiological Surveillance Components

Analysis of process characterization or validation data of an individual step or of the entire process can indicate that certain steps or certain aspects of a step in a process should be monitored (tested) at some established frequency. Every step of a process will not require monitoring on a routine basis unless there is little or no process validation in place. The criticality of a process step should be considered in selecting steps to be monitored routinely. Correctly established process monitors may give a more sensitive and accurate representation of finished tissue integrity because only a limited number can be tested.

Thorough process validation and data review can also demonstrate that there are aspects of the process which are comparable or better indicators of the microbiological status of the finished tissue than testing the finished tissue itself. Although this is not a common practice, it should not be ruled out as an option when substantial data are available to support it.

In performing this determination one should consider whether there is a terminal sterilization step in the process. Inclusion of a terminal sterilization step in a process may result in different surveillance components compared to a process that does not include terminal sterilization (e.g., aseptic processing only). Inclusion of a terminal sterilization step should never result in a loosely controlled process, but it may result in routine testing of fewer components due to the additional safety provided by the sterilization step.

Annexes E & F provide scenarios where microbiological surveillance might be applied.

E. Establishing Tissue Bioburden Criteria

Evaluation of process validation data can be used to establish bioburden specifications as applicable, and to understand the potential impact an excursion can have on the tissue. Risk analysis and risk management can be used to assist in setting bioburden criteria and addressing excursions. These may be established initially based on process validation data, and periodically evaluated to assure they are still properly established.

Annex E provides an example of establishing bioburden alert and action levels.

A thorough knowledge of the capability of the process can also assist in determining the microbiological acceptability of tissue coming into the process. A process that is not very robust may require more stringent rules regarding the microbiological status of tissue subjected to that process. A very robust process may allow for more flexibility regarding microbiological status. In current guidance (8), FDA recommends the following: “Discard all musculoskeletal HCT/Ps from a donor that has any musculoskeletal pre-processing cultures positive for *Clostridium*, *Streptococcus pyogenes* (group A strep), or any other microorganisms that you have determined to be difficult to eliminate, unless you have a terminal sterilization process validated to a sterility assurance level (SAL) of 10^{-6} .” This is reflected in AATB Standard K2.310 Pre-Sterilization/Pre-Disinfection Cultures.

F. Change control

Upon completion of a process step validation or a complete process validation it is critical that an effective change control system be established. Changes to any aspect of the process may alter the effectiveness of the process and must be evaluated carefully. Evaluations must be thorough and documented, and may require some degree of testing to verify assumptions made regarding the impact the change may have on the finished tissue.

V. METHODS FOR SAMPLING AND CULTURING

Many methods for sampling and culturing are available and it is not the intent of this guidance to specify that a particular method be used. The intent is to clearly explain some of the common methods being used and discuss their advantages and disadvantages. Whether 100% of the tissue is tested (e.g., recovery cultures or pre-processing cultures) or a percentage (post-processing or other types of cultures), these concepts will usually apply.

A. Sampling Methods

The term sampling methods refers to techniques and tests applied to the tissue in order to determine the numbers and/or types of microorganisms on the tissue.

1. Swabbing: Swabbing has been the most common sampling method for obtaining pre-processing cultures and has also been used to obtain post-processing cultures. Its advantages are a long history of use, the lack of equipment needed for the test, and the ease of training and use.

Swab culturing has historically been shown to have low accuracy, sensitivity, and reliability (14-25). Establishing quantifiable bioburden (in colony forming units per tissue) can be accomplished via filter-culturing and fluid-extraction techniques (14). However, obtaining

accurate quantifiable bioburden via swabbing can prove difficult due to the limitations of swabbing techniques and protocols often used (26).

A primary disadvantage to swabbing is lack of microbiological sensitivity. Data have been published regarding the low sensitivity of the swab method. Sensitivity of the swab method is both user and method dependent, and can be understood by evaluating use of swabs in the actual process. To accomplish this, a recovery efficiency test can be performed to determine the effectiveness of recovering microorganisms from the tissue when using a swab. See Section XII. Validation and Qualification of Test Methods at B. Test Method Validation, listing 1. Bioburden Recovery Efficiency.

2. Elution: The term elution in this context means that a fluid is used to remove (elute) microorganisms from the tissue after which the fluid is tested to determine the number and/or type of microorganisms present in the fluid.

Many methods can be employed in the elution technique and some are described below:

Extraction with surfactants: Extraction fluids (eluent) that contain surfactants (e.g., Fluid D as described in USP) might be used as they can result in a more complete removal of the microorganisms from the tissue. However, surfactants can often leave unacceptable residues on the tissue after the test, so this method will usually result in discarding the tissue that was used for testing unless a validated cleaning technique can be performed on the tissue.

Extraction with fluid: It's advised to use extraction fluids that do not leave residues on the tissue (e.g., saline) because the tissue used for testing can continue through processing and be released for clinical use. Removal of microorganisms might not be as complete due to the lack of surfactants, but since the tissue can be used after the test is performed it may result in allowing for more tissues to be tested.

Testing of tissues: Regardless of which type of extraction fluid is used, the tissues may be tested either individually or multiple tissues from the same donor can be combined. If tissue is tested individually, data are obtained which can demonstrate the consistency of the tissue bioburden on a tissue-by-tissue basis. Depending on use of results, combining multiple tissues from the same donor might be appropriate. Such results could be used to establish or monitor incoming bioburden but should not be used for tissue release to distribution. See Section IV. General Considerations For Microbiological Testing at E. Establishing Tissue Bioburden Criteria, and Section IX. Acceptance Criteria at B. Alert And Action Levels.

Much of this information is explained in ANSI/AAMI/ISO 11737-1 (27) and AAMI TIR 37-2007 (28). It is also important to determine the recovery efficiency of these methods, as previously described (29, 30).

3. Destructive Testing: Destructive testing refers to tissues immersed in a growth medium and incubated to determine if viable microorganisms are present on the tissue. It is often used in sterility tests. It is the most sensitive of tests in that it does not rely on removal of microorganisms from the tissue. However it does not allow for testing of a high percentage of tissue because the tissue must be discarded after testing. Destructive testing does not provide a count of microorganisms (quantitative test), it only provides a positive or negative result (qualitative test). It is common to characterize any growth that occurs (e.g., Gram stains, identification to genus and/or species, etc.).

4. Automated systems and rapid microbiological methods (RMM): These types of microbiological test systems are becoming more common and might be applicable to testing of tissue. In the end, they provide similar types of results as the methods described above, so extensive discussion is not needed here. It is important to ensure that the automated or rapid method used has the proper level of sensitivity and specificity so that the results gathered provide the information needed. In growth-based RMMs, an evaluation for inhibitory substances (e.g., growth promotion or a bacteriostasis/fungistasis test) is also required. See FDA draft guidance (31).

VI. NEUTRALIZATION

In any test system it must be demonstrated that proper neutralization of inhibitory substances has occurred. Inhibitory substances introduced by disinfected tissue may result in lower numbers of microorganisms being seen (for elution methods) or in false negative results (for destructive test or sterility test methods). Inhibition can also be naturally caused by viable or functional cells in the tissue being cultured (e.g., skin, cardiac and vascular tissue), so the fact that the tissue does not come into contact with antibiotics or inhibitory chemicals does not mean that the testing to demonstrate neutralization is unnecessary. Neutralization must be demonstrated with any type of sample (e.g., a piece of tissue, an extract of the tissue or a swab).

Validation of neutralization in a sterility test (i.e., destructive test) is usually called a Method Suitability test [aka bacteriostasis/fungistasis test (B/F test)]. The Method Suitability test procedures described in USP <71> (7) have traditionally been used with tissue allografts. This test does not determine the effectiveness of microorganism recovery, since microorganisms are not removed from the tissue. This test determines whether proper neutralization has occurred in the test system such that false negative test results do not occur.

Determination of proper neutralization and potential remedies for inhibitory substances are discussed in ANSI/AAMI/ISO 11737-1 (27), 11737-2 (32) and USP <71> (7) and USP <1227> (33).

There can be circumstances where inclusion of other microorganisms, in addition to those called out in the previously mentioned documents, may be appropriate. Evaluating this need might be accomplished by comparing the microorganisms that the tissue bank has experienced or those that are expected to occur (e.g., anaerobic microorganisms) with those to be used in the neutralization study to ensure that relevant, general microorganism types are included. Another example might be in testing skin to demonstrate that the microorganisms from the criteria list for skin are all capable of growing in the neutralized test system. The rationale for inclusion or exclusion of any additional microorganisms should be documented.

VII. TISSUES AND FLUIDS USED FOR TESTING

Various types of tissues and fluid should be tested, and must be representative of the different tissue types processed. Variation in bioburden count and inhibition are commonly encountered when testing different types of tissues (i.e., bone, soft tissue, cardiac, skin, etc.). Some common approaches to sampling are described below.

Sample Type	Description	Advantages	Disadvantages
Companion Tissue	Similar in bioburden to tissues in the batch	Use increases the quantity of available finished tissue	Obtaining sufficient sample size may be difficult; Not actual finished tissue
Finished Tissue Sample	Sample of finished tissue (fully processed, enclosed in its final container)	Direct analysis of finished tissue	Obtaining sufficient sample size may be difficult; reduces quantity of available finished tissue
Fluid Extraction	Fluid has had contact with entire batch of tissue	Assessment of entire batch of tissue	Debris from the tissue can clog the filter

For all sample types described above there are two test methods to select from. A quantitative test (i.e., bioburden) will provide a count of viable microorganisms from the tissue. The validation for a quantitative test is a recovery efficiency (discussed in Section XII. Validation and Qualification of Test Methods at B. Test Method Validation, listing 1. Bioburden Recovery Efficiency). A qualitative test (i.e., sterility) will provide a presence or absence result for viable microorganisms. The validation for a qualitative test is a method suitability test (also called a B/F test, discussed in Section VI. Neutralization).

A. Companion Tissue

Companion tissue refers to tissue which is recovered from the donor but which will not be used for transplantation. It can be comprised of portions of recovered tissue that are not acceptable for transplantation (i.e., not meeting tissue quality specifications such as discoloration, high porosity, tendon fiber separation, conduits with calcific atheroma, etc.), or portions trimmed from transplantable tissue during recovery and/or processing stages.

Companion tissue goes through every step of processing with tissue intended to become finished tissue (e.g., same processing events, containers, solutions, incubators, etc.). Because the tissue is destined for the same cleaning and disinfection process and is of the same type, it is reasonable to expect the bioburden type and numbers to be representative of the finished tissue. This is confirmed through validation or verification that the size/volume yields bioburden that, per unit area, is representative of the finished tissue. A rationale, supported by data, should be in place to address any differences in size between the companion tissue used for testing and the transplantable tissue. Companion tissue is discarded after testing.

See Annex G for an example when validating use of companion tissue.

B. Fluids

A fluid extraction refers to a fluid-based removal of microorganisms from tissues (i.e., elution) and performing microbiological testing on the fluid. These fluids may be tested to represent the microbiological quality of the tissues provided that proper validation has occurred (e.g., recovery efficiency or Method Suitability testing depending on the test to be performed).

Fluid extraction can be performed with any type of tissue (e.g., transplantable, non-transplantable, etc.) and at any point during the tissue process (e.g., early steps, intermediate, final packaging steps, final packaged tissues, etc.).

Fluid extractions taken from static rinses (e.g., transport tissue solutions) are typically relying on the long-term contact of the rinse fluid with the tissue whereby microorganisms are liberated from the tissue via non-mechanical means. Fluid extractions taken from static rinses are usually a method with higher variability associated with recovery efficiency and can be difficult to show repeatability.

Fluid extractions taken from mechanical rinses (e.g., in-process tissue steps, final extraction step prior to tissue packaging) are usually short rinse steps coupled with mechanical energy (e.g., shaking, stomaching, ultrasonics and vortexing) to liberate microorganisms into the fluid extraction. Mechanical rinsing will have less extraction efficiency variability than static rinses and can be validated for repeatability.

Considerations when validating a fluid extraction methodology are:

1. Worst-case attributes of extraction process
 - a. Worst-case attributes can be the maximum amount of tissue in the extraction step, shortest time of step (if a range is specified), lowest setting on mechanical component of the step or other variables determined during characterization studies.
2. Tissue types (e.g., bone, soft tissue, soft tissue with bone attached)
3. Tissue inoculation sites (if validated via the inoculation method)
4. Inoculum contact time (the amount of time to allow the inoculum to absorb prior to testing)
 - a. The higher the inoculum volume, the longer the contact time will need to be
5. Fluid extraction volume
6. Mechanical energy utilized for fluid extraction
7. Amount of time allowed for fluid extraction
8. Required neutralization for test method
9. Characterization surrounding the extraction methodology to understand variability associated with the method, tissue type and donor to donor variability
10. Appropriate number of replicates
11. Method of determining repeatability/acceptance criteria (e.g., recovery efficiency, calculations)

Validation of fluid extraction processes is usually based on the concept of recovery efficiency. Recovery efficiency details are outlined in Section XII. Validation and Qualification of Test Methods at B. Test Method Validation, listing 1. Bioburden Recovery Efficiency.

See Annex H for an example when validating a fluid extraction method, and Annex I for an example when calculating fluid extraction results.

C. Sample Size

It is not possible to establish a sample size representative of all situations. Sample size should be based on a documented rationale. Historically, 10% of a finished lot (considering variations in samples) has been a common quantity tested and appears to have functioned well. USP <71> (7), Table 3 provides some options on sample sizes for aseptically processed pharmaceutical

products. Under certain circumstances, a sample size of 10% of the finished batch is recommended for testing in each medium with a minimum sample size of four and a maximum of 10 in each medium. Table 2 provides options for whether each test sample can be split into two portions for testing (resulting in 10% of the finished batch being tested) or whether each test sample must be tested in its entirety in each medium (resulting in 20% of the finished batch being tested). Although the intent behind USP <71> (aseptically manufactured pharmaceuticals) meets the intent behind tissues which are not terminally sterilized, there must be some adaptation since in most cases a finished batch of tissue does not result in all pieces being equivalent in properties (e.g., size and shape).

Determination of sample size can be made in many ways.

Note that many statistical sampling methods only consider numbers and do not consider validation work, or controls and monitoring schemes. Process validation data should be able to assist in determining proper sample sizes, perhaps even better than purely statistical analyses. This approach will result in tissue banks using different sample sizes, and that is appropriate based on the level of validation performed and the number of controls and/or monitors in place.

For example: During a process validation it is noticed that the tissue bioburden after Step #3 is representative of the fully processed tissue bioburden. It is determined to use the rinse solution after Step #3 as an indication of the fully processed tissue bioburden. The recovery efficiency of the rinse solution is determined.

Concurrent testing of rinse solution from Step #3 and fully processed tissue from the same batch demonstrates consistent results, both in numbers and types of microorganisms. This concurrent testing is performed using tissue from donors having authorization for research use, where 100% of tissue from six batches of the same tissue type were tested after completion of processing. This evaluation was performed using different processing personnel and over six weeks of time.

In this situation the consistency of the results between testing the Step #3 rinse solution and the fully processed tissue allows for some flexibility in how much tissue is tested at the end of the process. If the Step #3 rinse solution is tested for every batch, that may allow for testing of only a few fully processed tissues at first (e.g., 3) and testing of no fully processed tissue after data is gathered over time (e.g., one year) if the consistency of the data continues.

This example does not provide a hard number of samples to be tested on a routine basis. Any number or percentage established in this guidance may be too restrictive for some and provide too much allowance for others, depending on the robustness of the quality system, process validation and other controls/monitors in place.

For terminally sterilized tissue grafts, the sample size situation may be different. In some cases (e.g., radiation sterilization) the sample sizes for some types of testing are established by the procedure being followed such as Method 1, Method 2 or VDmax (34, 35). For a process that is validated to a sterility assurance level of 10^{-6} , terminal sterilization should never replace or diminish the need for good overall process validation and good controls/monitoring of the process. However, if validated terminal sterilization is being used, it may allow for testing of fewer tissue samples on a routine basis, or may allow for more quickly reducing the quantity tested due to the additional safety provided in the sterilization process.

VIII. SAMPLING FREQUENCY

It is required to obtain data regarding the microbiological status of tissue from each donor prior to processing. Historically, the extent of the required data has ranged from testing some of the tissues from a donor (skin) to testing a sample of every tissue (cardiac and vascular) from a donor (pre-processing cultures).

Current requirements, see AATB Standard K2.310 (1), are that the sampling plan must provide an accurate microbiological representation of the tissues. This allows for flexibility to test all of the tissues from a donor (the default position) or to test a specific set (sampling) of tissues from the donor based on sufficient validation data and a documented rationale.

Regardless of the sampling plan details, it is required to obtain microbiological data on each donor prior to processing, see AATB Standard K2.310 (1). Whether this testing is qualitative (e.g., swab testing) or quantitative (e.g., extraction method), any method used must be followed by identification of the microorganisms. There is a classically accepted set of identification methods available (either automated or conventional methods), so the critical issue is that the sampling plan selected must adequately represent the clinically usable tissue.

Historically, it has been required to test a percentage of tissue post-processing. In the case of a (validated) *terminal sterilization* process, it is not necessary to perform pre-sterilization or post-sterilization tissue testing on a regular basis.

This concept is similar to that of sample size and is previously covered in the example under Sample Size.

IX. ACCEPTANCE CRITERIA

A. Specified microorganisms

The AATB Standards provide acceptance criteria for particular tissues and microorganisms. Those acceptance criteria (i.e., the list of specified microorganisms) are a minimum requirement and not meant to be all-inclusive. The numbers and types of microorganisms should be considered for each batch of tissue and the data should be used to determine their acceptability for release.

One option for addressing this concept is to establish acceptance criteria based on the results of the tissue bank's process validation. It may not be possible to establish a specific acceptance criterion for every microorganism of concern, but it may be possible to establish these criteria for some relevant microorganisms and include different microorganism types (e.g., Gram negative rod, Gram positive cocci, etc.).

Usually each microorganism type is included in a tissue process validation. Based on data obtained from the validation it is possible to determine how much of each microorganism type the process can effectively eliminate. These same numbers can be used to establish acceptance criteria for the microorganism types.

If a particular microorganism is demonstrated to consistently be on the tissue in numbers (amounts or with frequency) that cause concern, and if it is not clear whether the process validation covers this microorganism, then challenging the process using this specific microorganism may be necessary.

This does not require a full revalidation but can be performed using one microorganism included in the initial validation as a control along with the microorganism in question. It may also not require an evaluation of the entire process. Based on knowledge of the process, which the validation provides, it can be determined if the evaluation must be performed on the entire process or only a certain part(s) of the process.

B. Alert And Action Levels

Another aspect of acceptance criteria is the allowable quantity of microorganisms permitted on tissue pre-processing or post-processing. These values are often called alert and action levels. Alert and action levels will be different for pre-processing and post-processing evaluations. Pre-processing levels are based on process efficiency and post-processing levels are based on assessment of risk. It is not required that these levels be established when evaluating bioburden data (e.g., establishment of two levels can be appropriate if desired). Information is provided here regarding three levels to explain how they might be used as part of a bioburden monitoring system. Just as bioburden levels are commonly used for environmental monitoring, they should also be used for evaluation of tissue bioburden.

Validation of a process should generate data that verify the capability of the entire process to eliminate microorganism types. These data can be used to establish a bioburden level at which there should be concern that may not require corrective action (alert level) and a level where corrective action must occur (action level) as well as a level where it is known that the process is incapable of reducing the bioburden to the desired level (bioburden specification). Bioburden counts at these levels might vary widely depending on the process in place. A robust tissue process that provides many log reductions (e.g., demineralization process with acid and alcohol) could allow for higher pre-processing bioburden counts compared to a minimal tissue process that only has one or two log reductions (e.g., soft tissue process with detergents and antibiotics). Additionally, a validated terminal sterilization process (e.g., irradiation) might allow even higher alert and action level values.

There are no standard terms that must be used, nor are there standardized approaches to establishing bioburden levels. The concept of these levels however, is critical. Once the capability of a tissue process is understood, it will also be understood that there are bioburden levels that might overwhelm the process and render it ineffective. The purpose of establishing bioburden levels and trending bioburden data is to ensure that all tissue treated using the process is acceptable for transplantation. Bioburden levels should be established keeping this safety concept in mind.

Generally, the alert level can be established to demonstrate when a bioburden count is substantially above the typical counts obtained. This level might not require corrective action but might result in additional testing or a heightened awareness during review of subsequent test data.

The action level can be established to demonstrate when a bioburden count is set at a level low enough not to challenge the capability of the process. This level requires corrective action,

which often includes additional testing, and requires quarantine of tissue until the issue can be investigated and resolved.

Bioburden levels should be established using substantial data. It is commonly suggested that the data should also represent a long period of time (e.g., 6-12 months) to include seasonal or other variations that may occur. While the proper amount of data is being gathered it is appropriate to establish temporary levels, which also should be based on actual data.

At no time should bioburden alert and action levels be established randomly or arbitrarily, as this might result in failure of expectations of the process resulting in unsafe tissue, or an overreaction resulting in discard of tissue which could be rendered safe by the process.

As is the case with specified microorganisms previously discussed, if terminal sterilization is in place then supportive data from its validation studies must be taken into account when establishing bioburden levels.

X. CULTURE NEGATIVE RESULTS

Historically, obtaining culture negative results of processed tissue was often the primary, and in some cases the only, indication that the tissue was microbiologically acceptable for use. “Culture negative results” refers to tests performed where the results of the test are negative for growth (usually a destructive or “sterility” test).

Under current expectations, this approach is no longer acceptable. Culture negative results of processed tissue are meant to be a component of the overall process control system. Culture negative results are only useful in the context of proper process validation and validation of the test method performed, including evaluation of adequate neutralization studies for the test.

XI. ENVIRONMENTAL MONITORING

This section discusses general concepts and recommended practices regarding the establishment of environmental monitoring (EM) plans and interpretation of EM data. In the context of this chapter, use of the word “environment” includes all surfaces, water, personnel and the air in the area(s) being monitored.

Standardized values or requirements, cleanroom classification, and non-viable particulates are not described here. Guidance is already provided in national and international standards [e.g., USP <1116> (36), ISO 14644 series (37), and PDA TR13 (38)].

A. Introduction

Contamination in the environment (air, surfaces and water) has the potential to contaminate tissue during processing operations. Because of this, EM must be employed in any environment that can possibly have a microbiological impact on tissue. Note that the primary intent of EM is to evaluate the quality of the manufacturing environment and to demonstrate acceptable trends over time. EM data should always be reviewed and considered prior to making an HCTP

available for distribution, but an EM excursion does not necessarily mean that tissue has been impacted/affected.

There are few specific regulatory requirements relating to EM (39):

§ 1271.190(b)(1):

Facility cleaning and sanitation.

You must maintain any facility used in the manufacture of HCT/Ps in a clean, sanitary, and orderly manner, to prevent the introduction, transmission, or spread of communicable disease.

§ 1271.195(a) and (c):

Environmental control.

Where environmental conditions 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, you must adequately control environmental conditions and provide proper conditions for operations.

Environmental monitoring.

You must monitor environmental conditions where environmental conditions 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. Where appropriate, you must provide environmental monitoring for microorganisms.

Note that these requirements only state what must be accomplished, not how to accomplish it. Because of this, there is flexibility regarding how the requirements should be met. Some guidance is provided in different standards or documents and the more notable of these are provided in the following text.

Environmental control does not ensure acceptability of processed tissue because environmental control is not the sole aspect of an overall quality system. Demonstration of consistent, acceptable EM is usually the outcome of a well-established and well-implemented quality system. An exact or specific level of required “control” has not been defined. The requirement is that the level of control provided by the procedure consistently provides an environment that does not negatively impact the tissue. If EM data or tissue bioburden data demonstrate that the environment is impacting the tissue, the procedure and/or process must be updated to improve safety conditions. This also requires the evaluation of impact to tissue that may have been processed under questionable conditions.

B. Environment/Tissue Connection

The relationship between the microbiological status of the environment and the microbiological status of tissue is not always clear. This relationship, if any, will vary depending on a number of aspects, including but not limited to the:

- environment (level of classification);
- personnel in the environment;
- training program and staff adherence to it;
- amount of contact between the tissue and critical areas in the room;
- amount of time the tissue is exposed to the environment;
- processes being performed in the room and their impact on the environment; and

- effectiveness of cleaning protocols applied in the environment.

It cannot automatically be assumed that the microbiological status of the environment will have an impact on tissue. The level of impact that different aspects of the environment might have on tissue must be understood and sufficiently addressed. Since there is not an automatic association between the two, it should not be automatic that an excursion in the environment causes discard of the tissue. An EM excursion should always cause a documented investigation and determination of the potential impact on tissue, but it does not always follow that the tissue has been affected.

Due to the level of cleanliness in most processing rooms, it may be the case that the tissue may contaminate the environment rather than *vice versa*. In the early stages of tissue processing it might be more likely that the tissue would contaminate the environment, and in the later stages, that the environment might contaminate the tissue.

In general, sequential movement of tissue from the uncontrolled environment to cleaner environments, will necessitate stricter levels of environmental control and monitoring. During all such movements of tissue, strict segregation of donor lots shall be observed as well as thorough cleaning of the area between handling of tissue from different donors.

A clear definition of the activities that are conducted during each phase of the process and the associated environmental requirements for each phase of the process will often make the processor's approach more readily understood.

C. Temperature And Humidity Monitoring In The Tissue Processing Environment

In the United States, there are no standard requirements for temperature and humidity in the tissue processing environment. General guidance regarding acceptable ranges for temperature and humidity can be found [36, 37, 39 see 1271.195 (a)], however, there are no standard levels or values provided for tissue establishments. Tissue establishments must develop their own levels and values.

The primary purposes for temperature and humidity controls are for the control of contamination and cross-contamination, control of manufacturing conditions (tissue sensitivity), for the comfort of personnel, and/or for reduction of electrostatic charges (if this is critical to the tissue or if it poses a fire hazard).

For purposes of tissue processing, generally it would not be necessary to have tight specifications for temperature or humidity. However, it might be necessary to have a target specification and to routinely monitor one or the other. The rationale for temperature and humidity specifications or monitoring (or reasons for not needing them) must be documented.

When addressing temperature and humidity levels, consideration is given to operator comfort. If an operator is perspiring due to environmental conditions, they will be more likely to contaminate the environment with perspiration through attempts at wiping off the perspiration.

Also, certain types of microbes are more likely to thrive at high humidity levels (e.g., greater than 70%). Specifically, fungi could become a significant contributor to the environmental flora due to an increase in humidity in the working environment. These organisms in a high humidity

environment (especially where visible moisture is present) can rapidly grow and sporulate and contaminate the facility.

D. Tissue Sterilization Versus Aseptic Processing

Environmental controls and monitoring should be maintained to assure that processing conditions are controlled to the extent necessary to prevent risk of infectious disease transmission. For terminally sterilized tissue subjected to a validated sterilization technology, the controls must assure that *Bioburden* limits used to determine validation parameters and sterilization cycles are met. In the case of tissues not subject to a sterilization process, environmental controls and monitoring need to be established to control risk of adventitious *Bioburden* introduced during processing. In either case, controls should be adequate to prevent the risk of cross contamination.

E. Decontamination Effectiveness Studies for Cleanroom Surfaces

Disinfectant (cleaning agent) effectiveness studies are generally straightforward since there is usually one step involved (e.g., a spray or a wipe of a surface with one disinfectant). Standards are available which provide a good framework for evaluation of disinfectants [e.g., ASTM E2614-08 (40), USP <1072> (41), and AAMI TIR 12 (42)].

There are two phases to evaluating disinfectants. The first phase is usually performed by the disinfectant manufacturer, to determine the efficacy of the disinfectant against a panel of microorganisms, some of which may be considered “compliant” and some “non-compliant” when applied to tissue processing functions.

The second phase is usually performed by the user of the surface disinfectant (e.g., a tissue bank) against a selected panel of additional microorganisms, including types that have been recovered in the processing facility or from the tissue. In these tests, it is important to evaluate various surfaces on which the disinfectant will be used. Testing is usually performed on coupons of the various types of material to be decontaminated so that test microorganisms are not being introduced to the processing environment. This type of testing must include a neutralization study to ensure that media used for testing will allow growth of surviving microorganisms.

Title 21 CFR Part 1271 Subpart D, Current Good Tissue Practice (39) does not require that companies perform cleaning validation, only that they be able to demonstrate that their disinfection process is effective in preventing the potential contamination or cross-contamination of tissue. A tissue bank should have a documented rationale for the choice made regarding the disinfectant and any associated testing.

Other healthcare industries have different expectations. It is common for pharmaceutical companies to validate the cleaning process by properly performing cleanroom surface disinfectant effectiveness studies even though the manufacturer can provide information regarding effectiveness. Historically, medical device companies have referenced manufacturer information to justify use of a particular disinfectant, but this practice is evolving to be more consistent with the approach used by pharmaceutical companies.

In a situation where there is very little or no disinfection of tissue during tissue processing it might be more important for a tissue bank to perform the cleanroom surface disinfectant cleaning

validation themselves, using coupons of their surfaces and the microorganisms they carefully select.

It is not the intent of this document to establish a required log reduction for cleanroom surface disinfectants. Certainly, acceptance criteria must be established if a cleaning validation is to be performed, and the acceptance criteria must be determined by each tissue bank. Note that USP <1072> (41) targets at least a 3 log reduction of vegetative microorganisms and at least a 2 log reduction for bacterial spores.

F. Initial Qualification of Processing Areas

Whether the processing area is a classified cleanroom or controlled environment the same concepts apply, even though the requirements are stricter for a classified cleanroom. Although the requirements for particulates in a cleanroom are well established, that is not the case for viable microorganisms in the air or on surfaces. USP <1116> (36) provides guidance that, although it is only guidance, has proven to be attainable and generally acceptable to regulatory agencies. There is no need to require that tissue banks establish more rigorous requirements than those provided in USP. Requirements that are less rigorous might be allowable with written justification (e.g., terminal sterilization).

Additionally, there is no defined requirement regarding how much data must be obtained prior to initiation of use of the cleanroom. The quantity of data obtained for air and surface microorganisms should be sufficient to demonstrate consistent microbiological control of the area. This usually consists of demonstration over a period of time that the environmental monitoring test results meet the acceptability criteria established by the company, or that they are consistent and low if criteria have not yet been established. One approach would be monitoring over the course of an entire day and over the course of a week or two, including periods of inactivity.

Initially a tissue bank may not establish EM alert/action levels until monitoring data from the cleanrooms are obtained. In this instance, the acceptability criteria might be that the EM results be consistently low. Then when cleanroom use begins, if tissue testing is providing acceptable results, this indicates that the environment is not negatively impacting tissue.

USP <1116> (36) provides suggestions regarding contamination recovery rates in cleanrooms (see Tables 2 and 3). For example, an ISO 5 room classification a <1% contamination recovery rate for active air sample, settle plate, contact plate or swab, and glove or garment is advised. PDA TR13 (38) Table 1, provides a summary of microbial level suggestions which includes EU recommendations compared to USP recommendations. These suggestions (provided to the pharmaceutical industry) may be implemented in a tissue bank, but they should not be blindly implemented without data that suggests they are applicable.

It is wise to initially gather air and surface data over a period of time (to be determined by the tissue bank) with the cleanroom fully equipped but at rest (i.e., static or not in operation). This provides baseline data on the ability of the cleanroom to remain in control over time.

A second set of data can be obtained with the cleanroom in use (active or dynamic). The sampling plan for this data could be the same as that used with the cleanroom at rest. This data can be compared to the “at rest” data to determine the impact that people and processes have on the controlled environment.

The last step demonstrates the effect that people and processes have on the room over time. Generally it is wise to perform monitoring more frequently initially (e.g., with every processing session, once a day or once a week) to demonstrate control, followed by a reduction in the frequency for the long term (e.g., daily or weekly depending on the criticality of the process in the room and the quantity of data available). See the section entitled Frequency of Sampling for more information on this topic.

The decision to gather initial dynamic data while processing actual tissue or while processing surrogate tissue should be documented by the tissue bank.

Note that viable microorganism counts will usually increase when the cleanroom is active. There is not an expectation that the dynamic data be identical to the static data, but the dynamic data should still demonstrate that the room is in control.

G. Types of Tests Commonly Performed

Following are types of EM tests commonly performed and a basic description of each. For all EM tests performed it is important that the media types and incubation conditions are appropriate for the microorganisms that could be present in the environment.

1. Nonviable air (particulates): This test determines the number and size of particles in the cleanroom air. It is performed as part of cleanroom certification and should be repeated at a specified interval. Limits are established by national and international standards [e.g., ISO 14644 series (37) and USP <1116> (36)].

2. Viable air (microorganisms): This test determines the number of viable microorganisms in the air. Active air samplers are used to test a particular quantity of air (e.g., 10-100 m³) and impinge the microorganisms onto an agar surface that is incubated for growth. Passive air sampling consists of the use of an agar plate left open on a surface for a specified length of time (e.g., 2-4 hours) and incubated for growth.

No limits are established but some recommended levels are provided in USP <1116> (36). Company-specific levels are usually established after an initial data-gathering period (e.g., 6 months to one year).

3. Viable surface (microorganisms): This test determines the number of viable microorganisms on the surfaces in a cleanroom (e.g. tabletops and equipment). It is performed using agar plates (e.g., Rodac® or Hygicult®) where the agar is lightly pressed against the surface for a short time (e.g., 5-10 seconds) and incubated for growth. Cleaning of residual agar on the surface tested must be performed after such sampling. Other surfaces that will not have tissue contact (e.g., floors and walls) may also be tested; if used to check cleaning effectiveness, these areas may have different acceptance criteria due to the lack of tissue contact.

Swabbing is sometimes performed on irregular-shaped surfaces followed by removal of the microorganisms from the swabs (usually with a water-based solution), filtration of the solution, and plating and incubating for growth.

No limits are established but some recommended levels are provided in USP <1116> (36).

Establishment-specific levels are usually established after an initial data-gathering period (e.g., 6 months to one year).

4. Water (microorganisms): This test determines the number of viable microorganisms in water used for processing. It is usually performed using membrane filtration of a pre-determined quantity (e.g., 100 mL) followed by plating and incubation for growth. Testing should ensure the water meets required specifications for tissue processing operations and, where appropriate, must be sterile [39 see 1271.210 (b)].

5. Water (endotoxin): This test determines the number of endotoxin units (EUs) in a water system and is usually performed using the Limulus Amebocyte Lysate (LAL) test. Endotoxin comes from the cell walls of Gram negative microorganisms. The EU result of a water sample does not equate to a viable microorganism count because endotoxins can be present whether microorganisms are dead or alive. Endotoxin limits are published for different USP grades of water (e.g., USP sterile water for irrigation has a limit of 0.25 EU per mL) but limits should be established by the tissue bank based on historical values and intended use of the water.

6. Personnel (microorganisms): This test determines the number of microorganisms on personnel in the cleanroom (e.g., gowns and gloves). The time when sampling is performed (e.g., beginning of process/shift, in-process, and/or at end of process/shift) should be established and justified. It is usually performed using the same types of agar plates used in surface sampling (e.g., Rodac® or Hygicult®), or by using conventional agar plates. After touching the plates to sampling areas, the plates are incubated for growth. Microorganism levels are published for personnel [e.g., PDA TR13 (38), and USP <1116> (36)] but they should be established by the tissue bank based on historical values, and on the purpose for testing. There should be consideration of the potential for residual agar remaining on the sampled area, and covering or discarding the garb may be indicated.

H. Selection of Sampling Sites

Initially all surfaces and areas which may have tissue contact or exposure should be monitored to assist in establishing an environmental monitoring baseline. After initial data are gathered, the number of sites can often be reduced to those having greatest potential for critical impact on tissue.

Generally it is not necessary to perform routine EM on surfaces or areas not intended to have direct or indirect contact with tissue. For example it may be necessary to monitor the classified room where tissue packaging occurs, but may not be necessary to monitor the room where shipping boxes are packed for distribution.

I. Alert and Action Levels

Note that many of these concepts are similar to those described for determination of alert and action levels for tissue bioburden.

An EM excursion is said to occur when an EM value is above a specified level (e.g., alert and/or action level). It is important that alert and action levels are properly established so that appropriate action is triggered when necessary. It is not within the scope of this document to provide a recommended mathematical method to establish alert and action levels, however, some concepts provided in standards [e.g., PDA TR13 (38) and USP <1116> (36)] are shared.

Alert and action levels should not be established with a limited amount of data. Initial values can be established during the cleanroom qualification stage and the values should be revisited after more time has passed (e.g., several months to a year) in order to affix permanent values.

Typically, there is not a direct correlation between EM bioburden and tissue bioburden. Although EM results are a part of the overall control process, they are not a direct indicator of whether tissue is suitable for use. An excursion in EM results might initiate an investigation into the appropriateness of particular batches of tissue, and EM results should be considered as tissue is released. However, a higher than normal count from an air sample or from the floor of the cleanroom should not automatically result in discard of tissue. The EM program is used less for determination of tissue release and more for demonstration of continued control over the environment and recognition of shifts from the norm. Evaluation of an excursion of the level of control can affect the determination of tissue disposition on a case-by-case basis (i.e., voluntary recall or withdrawal). Because of this typical separation between EM bioburden and tissue bioburden, the idea of establishing an EM bioburden specification is not addressed, although a tissue impact assessment must be performed.

Alert Level:

It is generally agreed that an alert level indicates that microbial counts have increased outside of the norm, but not to a point where there is immediate concern for tissue processed in the affected environment. An investigation into the excursion can be initiated, and appropriate corrective actions taken. Such actions may include, but are not limited to, review of the cleaning protocol, re-cleaning and resampling affected areas, review of personnel protocol and activities, or review of the processing operation for unusual events.

Action Level:

A value at or above the action level indicates that the microbial counts are outside of the norm and that they might be at a point where tissue could be impacted. An investigation is required, including a root cause analysis, followed by appropriate corrective and preventive action, to include an evaluation of impact on processed tissue.

Determination of alert and action levels is always accomplished by some mathematical means. Whether those means are as simple as use of standard deviations and averages or as sophisticated as complex statistical calculations is not the point of this document. The important concept to grasp is that the levels should assist a tissue bank in understanding when the environment might be getting out of control or might be impacting tissue. This means that trending EM data is critical to maintenance of a cleanroom and to demonstration of continued control.

Often the exact cause of an EM excursion cannot be determined. This does not mean that nothing should be done. In these cases, those involved must make educated decisions regarding what the potential cause or causes might have been, and determine and implement reasonable action for those causes.

J. Trending

There is no specified requirement for when EM alert and action levels must be revised and recalculated. However a formal review to determine if the current levels are still applicable is necessary at some determined interval. While many companies reassess levels annually, each tissue bank must determine an appropriate frequency for itself.

Since alert levels in EM are used largely to determine if the environment is in a state of control, alert levels should be evaluated to assure that a departure from historical trends can be readily detected and acted upon. If alert levels are set too high, changes in trending from historical norms could be occurring for some time prior to the alert being exceeded. Often, excursions of this nature are hard to investigate and resolve because of extended time that has already passed. Trending of the EM values in these instances will often show a continuous drift upward toward the alert level.

K. When to Sample

EM samples can be taken prior to processing, during processing or after processing. Each option provides a different set of data for a different purpose.

EM samples taken prior to processing provide the tissue bank with information relating to the cleanliness of the area before introduction of equipment and tissue, and also provide information on what may have happened to the area since the last time it was cleaned (e.g., during periods of inactivity). These samples can be used to establish baseline EM data for the room in question.

EM samples taken during processing or after processing (but before cleaning) assist in understanding what the microbiological effects of personnel, equipment and tissue have been to the environment, as well as what affect those might have had on the tissue. When performed during processing, care must be taken to ensure that performing EM does not potentially cause contamination of the tissue. For example, it may not be wise to perform active air sampling directly over tissue during processing.

L. Frequency of Sampling

USP <1116> (36), Table 2, recommends testing in each operating shift for a Class 100 (ISO Class 5) room. It has been common for some tissue banks to perform EM while processing tissue from each donor or batch. EM testing performed during processing can be used to understand the effect that processing tissue has on the environment in addition to understanding how the environment might affect the tissue. The frequency of EM should be dictated by the type of tissue that's processed and the amount of data obtained to support the desired frequency.

A terminally sterilized tissue process may not require that EM be performed while processing tissue from each donor or batch because of the additional safety the sterilization process provides. Tissue being released under an aseptic process may require more frequent EM because of the greater potential impact the environment may have on the finished tissue.

Determination of the frequency of testing should begin with a risk analysis for the tissue and the process and an evaluation of the potential impact the environment may have on the finished tissue. Generally, all EM plans should begin with frequent testing until enough data are gathered to justify reducing the frequency. The minimum frequency permissible must be determined by the tissue bank based on potential risk, which is identified in a documented risk assessment analysis.

M. Typical culturing conditions

Culture conditions are provided in many standards and documents relating to EM [USP<1116> (36), (11)]. However, use of standard media (e.g., soybean casein digest medium) at standard incubation parameters (e.g., 20-25°C for not less than four days and up to seven days for molds and yeasts or 30-35°C for not less than two or three days and up to seven days for bacteria) is appropriate. Other incubation conditions can certainly be used. It is important that there be a rationale supporting the incubation conditions used (e.g. based on a particular standard or on validation data).

N. Interpreting EM Data

Since the primary purpose of EM is to evaluate the quality of the processing environment, it is critical that EM data be reviewed by appropriate personnel and trended to determine continued control.

Full identification of microorganisms can be beneficial when establishing an initial baseline, when evaluating the potential impact of a process change, or investigating an EM excursion. In an ISO Class 5 environment or other critical environment, full identification is expected (i.e., genus and species). However, it would not be necessary to identify all microorganisms obtained on a routine basis, especially if the results are within specification. There are many cases where colony morphology and a Gram stain provide sufficient information (e.g. when gathering data over the course of a year to establish a baseline) and other cases where merely having the microorganism count is acceptable (e.g. after years of data have already been gathered and no changes are occurring to the process). The level of identification performed should be determined by the purpose for gathering the data.

Interpretation of EM data will be more useful if performed with EM trends in mind. Trending of EM data will assist the company in understanding their EM baseline as well as identifying potential issues on the horizon.

O. Tissue Impact for EM Excursions

In the event of EM excursions, it is critical to determine the potential impact, if any, on tissue. It should not be automatically assumed that an EM excursion had an impact on tissue; rather, an investigation should determine whether an impact was likely.

Ideally, EM should not be the only monitor or control involved in day-to-day processing. The investigation of potential impact of an EM excursion on tissue should include more than the EM results; it should also include the results of the batch-to-batch or day-to-day in-process controls. It might be possible, based on the entire amount of data available, to determine that the EM excursion had no impact on tissue, even without any additional testing. Herein lies the benefit of proper process validation and determination of appropriate microbiological surveillance. Note that testing additional tissue for sterility in the event of an EM excursion should not be considered a default approach.

Example: An EM excursion is obtained from the touch plate of a processing technician's gloves. The alert level is established at 3 CFU, action level is set at 9, and the result is 10 CFU. Identification is performed and the microorganisms are determined to be two

different species of Staphylococcus. In the same processing session, the following additional controls and monitors are performed and found to be within specification:

Transport solution microbial count

EM of one surface and cleanroom air (settling plate during processing)

Negative controls of the processing solutions

Sterilization cycles for equipment

Process validation data indicates that the process is very effective at killing Staphylococcus microorganisms (it provides a 5.6 log reduction). The aseptic packaging process validation indicates that the technician in question can properly package the tissue without adding contamination. The touch plate of the gloves was performed post-processing and prior to packaging, and the technician changed gloves prior to the packaging step. Therefore, the packaging process is not suspect. Lastly, the technician does not have a history of EM excursions.

All available data suggests that the contaminated gloves would have potentially impacted tissue only at the processing stage, and not at the packaging stage. Also, the process has been demonstrated to reduce contamination of this microorganism at the levels in question.

If the tissue is released under aseptic processing (i.e., no terminal sterilization), finished tissue from the batch is tested (cultured). If all other pre-established release specifications are met, a risk assessment analysis must be performed and documented, and used to justify release of finished tissue.

If the bank is releasing tissue using terminal sterilization, there would likely not be a need to perform any additional testing based on the strength of the data that no additional contamination likely occurred, and based on the microbial reduction that terminal sterilization provides.

XII. VALIDATION AND QUALIFICATION OF TEST METHODS

A. Introduction

There are two important stages in evaluating test methods.

- Validation to ensure that the test is functioning properly and providing the desired data. This means demonstration that the test method is capable of providing consistent and correct results (e.g. if testing the tissue for anaerobic microorganisms, the data represent only anaerobes and not strict aerobes).
- Qualification to ensure that the test method is functioning properly for a specific tissue type. In this instance it is already known that the test method provides consistent and correct data (because #1 above has already been completed), but different tissue types may affect the test method (e.g., if residual antibiotics in soft tissue are present in the test system, contaminating microorganisms may not be able to replicate causing a false negative test). The term “verification” is often used interchangeably with “qualification”.

Although it is common to use the term “test method validation” for both aspects, it is best to distinguish the two aspects by using different terminology. In other industries, use of the terms

“test method validation” and “test method qualification” assist in distinguishing between them; these terms are also appropriate in the tissue industry.

B. Test Method Validation

In validating a test method the tissue industry is not very different from other industries. There are different parameters evaluated during the validation for a qualitative test versus a quantitative test. For example, qualitative methods generally require evaluation of fewer parameters (e.g., specificity, limit of detection, ruggedness/repeatability, and equivalence if applicable). By comparison a quantitative method may require evaluation of additional parameters such as accuracy, precision, limit of quantitation, linearity, and range.

Guidance is provided in three chapters of USP, depending on the type of validation needed. Below is a discussion of all three.

Note that in most cases it will not be necessary for a tissue bank to perform full validation of a microbiological test method. Examples of the need for a full test method validation are included in the discussions below.

1. Bioburden Recovery Efficiency

When tissue bioburden is low, the recovery efficiency test must be performed by inoculating the tissue with a known number of microorganisms followed by performing the test method, and enumerating the microorganisms. The selection of the microorganism(s) to use for inoculation can be based on those types expected or demonstrated to be on the tissue. Typically, a single microorganism is chosen for the test.

Note that the recovery efficiency test of a swab culture method involves two phases:

First: The removal of the microorganisms from the tissue onto the swab (the swabbing step)

Second: The removal of the microorganisms from the swab into the test system. This is accomplished by either:

- a. Direct plating of the swab onto agar plates (i.e., swabbing the agar plate with the swab to transfer the microorganisms from the swab to the plate), or
- b. Applying an extraction method to the swab to remove the microorganisms into a liquid which can be filtered, or plated and cultured.

Both phases should be evaluated to understand the sensitivity of the swab method. The removal of microorganisms from the tissue has already been explained above. The removal of microorganisms from the swab is similar except that the swab is inoculated rather than the tissue. Both phases can be evaluated in a single experiment, but if improvement is needed, the data will not be available to determine which phase of the test must be changed.

When determining a recovery efficiency using the inoculation method, the percent recovery is determined by dividing the number recovered in the test by the number placed onto the tissue and the result being multiplied by 100. A correction factor can be determined by calculating the reciprocal of the percent recovery with the percent as a decimal. Either a recovery efficiency or a correction factor can be used as they both provide the same answer when used to adjust bioburden.

Example:

Recovery Efficiency = (# Recovered in Test / # Placed onto Tissue) X 100

If:

Recovered in Test = 18 CFU and

Placed onto Tissue = 87 CFU

Then:

Recovery Efficiency = (18 / 87) X 100 = 20.7%

Correction Factor = 1 / Percent Recovery as a Decimal

If:

Percent Recovery = 20.7%

Then:

Correction Factor = 1 / 0.207 = 4.8

If it is expected or understood that the naturally occurring bioburden is not low, a repetitive rinse recovery efficiency may be performed rather than inoculating the tissue. This test is similar but the tissue is not inoculated with microorganisms; rather, the same tissue is swabbed multiple times. The goal is that the final count recovered from the tissue be significantly lower than the initial count, ideally zero. The percent recovery is determined by dividing the count obtained from the first swab by all counts obtained from all swabs.

Example:

Recovery Efficiency =

(# Recovered From First Swab / # Recovered From All Swabs) X 100

If:

Swab 1 = 23 CFU

Swab 2 = 5 CFU

Swab 3 = 0 CFU

Swab 4 = 0 CFU

Then:

Recovery Efficiency = (23 / 28) X 100 = 82.1%

The correction factor in this example would be: 1 / .821 = 1.2

2. USP <1223> Validation of Alternative Microbiological Methods

This chapter (43) describes validation of a test method that is an alternative to the standard test methods in USP. For example, a tissue bank may wish to employ a modified (7) sterility test, and to incubate for 7 rather than 14 days.

This chapter would not be applicable for adding a neutralizer in the sterility test media to overcome inhibition in the test system.

This chapter may be of limited use to tissue banking since many of the test methods used are already standardized by USP or AAMI/ISO. If an alternative test method would be

advantageous to the tissue bank however, this would be the proper USP chapter to follow. Additional guidance can also be found in PDA TR33 (44).

3. USP <1225> Validation of Compendial Procedures

This chapter (45) specifies requirements for information that must be gathered in order to submit a new test method for inclusion in USP. For example, a tissue bank would reference this chapter if it develops a new rapid microbiological test method and would like this method to be included in the next version of USP. This chapter provides general information about test method validation, although performance of all aspects of this chapter may be overkill for the more traditional methods used in the tissue industry.

4. USP <1226> Verification of Compendial Procedures

This chapter (46) provides information on the verification procedure to be applied when setting up testing specified in USP [e.g., USP <71> Sterility Tests (7)]. The chapter clarifies that it is not required to perform full validation for test procedures outlined in USP, rather it states to select relevant aspects from USP <1225> (45) for evaluation. Note that this chapter uses the term “verification” rather than validation. Use of “verification” is appropriate considering the scope of what is being done.

This same approach can be used for test procedures outlined in AAMI/ISO methods [e.g., 11737-1 (27) for bioburden testing and 11737-2 (32) for sterility testing].

C. Test Method Qualification

When test method qualification is being performed it is already known that the test method functions properly under typical circumstances (e.g. when testing non-inhibitory tissue types with simple configurations, or if the validation was performed using a tissue surrogate such as a plastic or stainless steel coupon). It is necessary, however, to demonstrate that the tissue being tested falls under those “typical” circumstances. If it is found that the tissue does not fall under those circumstances then the test method must be altered so that the test is valid for that tissue. Examples of common alterations are the addition of neutralizing substances to media to eliminate the effect of residuals (e.g., for bioburden or sterility testing) or the use of a specialized filter material (for membrane filtrations).

Most compendial methods include a qualification process. For example, USP <71> (7) on sterility testing contains details for performing a growth promotion test and a Method Suitability test (also called the bacteriostasis/fungistasis test or B/F test), which is the qualification study for that test. Other tests in USP also provide the necessary qualification steps for that method (sometimes called verification). The AAMI/ISO tests also provide guidance on appropriate qualification tests (e.g., recovery efficiency and test for inhibitory substances for bioburden and Method Suitability).

When tissue banks are using test methods provided in compendia, the associated qualification studies provided are usually sufficient. If the test method is not compendial, as with an alternative test method, then an appropriate qualification study must be determined and performed.

Qualification studies that confirm proper neutralization of the test article usually follow the same general concepts:

1. Perform the intended neutralization step
2. Perform the intended culturing step
3. Inoculate the filter or test media with a low number (e.g., <100 CFU) of microorganisms, followed by incubation
4. Compare the inoculated test sample results to controls which had no contact with the tissue

An example of a neutralization qualification study is found in USP <71> (7), in the “Method Suitability Test” section.

There is no established percent recovery considered acceptable by tissue banking professionals. In USP, values of 50% and 70% are considered acceptable, depending on the type of test being performed.

A common misconception is that if the graft has properties that interfere with the growth of microorganisms during testing, the graft will behave in the same manner when transplanted into a graft recipient. The fallacy of this logic is that the inhibition displayed by the graft during testing may be transient. When implanted into a recipient the inhibiting compound may be diluted out or neutralized, allowing for microorganisms to reproduce. Failure to appropriately verify the accuracy of culturing methods can potentially put at risk the safety of the graft recipient by allowing inadequately sterilized or disinfected tissue into the marketplace.

Generally, it is not required to characterize what is causing inhibition in a test. It is usually acceptable to simply demonstrate that neutralization is occurring. Characterization of the inhibitory substance might be recommended as part of an investigation if typical neutralization techniques are not providing acceptable results. Guidance on neutralization can be found in USP <61> (47), <71> (7) and <1227> (33).

See Annex J for an example of test method qualification.

XIII. TISSUE LABELING

A. Labeling

Labeling should be clear, simple and consistent so the end user can understand the treatment status of the finished tissue. In an effort to achieve this, the following options are provided by AATB for labeling regarding the microbial processing status of the tissue.

- Aseptically processed
- Sterile

A description of *aseptic processing* is provided in the definitions in this document.

For sterile labeling, it is expected that a validated SAL, with an appropriately justified SAL value, is justified and used (see the section entitled SAL and the definition for *terminal sterilization*). If the term *sterile* is used on labeling, immediately following it there should be a description of the sterilization process.

It is not a requirement to provide the SAL value on the labeling. Providing the SAL on the labeling has not been a practice in the medical device industry, the SAL is not necessary for the user to know.

Additionally, information regarding bacterial or viral reduction or clearance is not necessary, but can be described in supportive documentation, including validation data.

Variations to these labeling requirements may exist where required and/or approved by other jurisdictions/regulatory agencies outside the United States.

B. Sterility Assurance Level (SAL)

The term SAL generally must only be used in a situation where a sterilization process is being applied to the tissue in its final packaging. If a sterilization process has been applied to tissue, but the tissue is then packaged or manipulated in some other way, the SAL associated with the sterilization process has potentially been compromised and is no longer assured without additional validation work. In the situation where the tissue is somehow manipulated post-sterilization, the appropriate terms to use would be *aseptic processing*.

In *aseptic processing*, typical approaches are used to assure disinfection is appropriate (e.g., disinfection using washing and/or chemicals during processing).

The log reduction value of a process does not equal an SAL of the same value. For example, if a tissue process can provide a 6 log reduction of microorganisms, this does not equal a 10^{-6} SAL. As mentioned previously, the term SAL should not be used to describe sterility for validated tissue process that does not include *terminal sterilization*.

Typically, a minimum SAL of 10^{-6} is used for health care products labeled sterile, and this is the usual expectation for tissue as well. The sterilization validation will clearly identify that an SAL has been demonstrated, and this is the SAL that should be referenced in documentation supported by data.

In the United States, an ANSI/AAMI standard allows for some flexibility in the SAL requirement (10). If tissue is sensitive to the sterilization process there are criteria provided which allow use of a higher SAL (e.g., 10^{-3} , 10^{-4} or 10^{-5}), and a sterile claim can be made on labeling. Refer to the standard for details on how to use this option.

Realistically, regardless of the SAL value of the tissue, the cleanliness of the tissue upon opening the package is reduced to the cleanliness of the environment in which it is opened. At that point, the environment dictates the tissue cleanliness more than the SAL value while the allograft was in the packaging.

XIV. ANNEXES

A. Characterizing a Process

Scenario:	A feasibility study has been conducted in which a 30 minute soak of 100 grams
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	<p>of tissue in 0.1g/L Gentamicin solution results in <1 CFU gram negative organisms / 10 grams of tissue. The study has been repeated twice and has a high level of confidence that it will pass validation. The validation manager indicated that the process would have to be performed three times in order to demonstrate reproducibility. The intention is to perform the process a third and final time, and then transfer the process to production.</p>
Issues:	<p>The range has not been determined for antibiotic concentration, soak time, or quantity of tissue that will allow the process to achieve <1 CFU / 10 grams of tissue. Since there is no range for concentration, exposure time, and quantity of tissue, a specification range cannot be set by which the processing team can run the process. This would steer the processing team toward failure, because the processing step is set to be exactly a “30 minute soak in 0.1g/L Gentamicin solution for 100g of tissue.” The process will produce acceptable outcomes when performed; however it is so narrowly defined that production teams will be plagued with process deviations.</p>
Evaluation:	<p>After speaking to the production manager regarding processing capacity, a matrix study was performed that evaluated:</p> <p>Gentamicin concentration: 0.06 – .14 g/L Tissue weight: 100g – 300g Soak time: 30 – 360 minutes</p> <p>Minimum and maximum parameters for concentration, exposure time, and quantity of tissue produced the desired outcome of <1 CFU of Gram negative organisms / 10 g of tissue. The specifications that were written and validated as a result of characterizing the process were:</p> <p>Gentamicin concentration: 0.08 – .12 g/L Tissue weight: 150g – 250g Soak time: 60 – 300 minutes</p> <p>In expanding the processing range, a process specification was provided that production could manage and, when occasional process excursions occurred, data was available to help evaluate acceptability of affected tissue.</p> <p>In addition, QC sent the metrology group a memo asking them to determine the accuracy of production equipment used to measure the weights and times.</p>

B. Stepwise Approach to Process Validation

This annex describes the processing steps in a tissue process then provides items that were considered during process characterization. It illustrates how initial process characterization can simplify process validation.

1. Sonicate tissue in sterile water for 10 minutes

- a. Process of cleaning/decontaminating/sterilizing the equipment
 - i. Validated as a separate step rather than addressing it in process validation
 - b. Determination that 10 minutes provides the required results
 - i. Addressed in process characterization rather than in process validation
 - c. Determination of temperature requirements
 - i. Process characterization showed no considerable affect based on temperature. A predetermined temperature range will be used during process validation.
2. Soak tissue in antibiotic cocktail A for 25 minutes
 - a. Process of cleaning/decontaminating the equipment
 - i. Validated as a separate step rather than addressing it in process validation
 - b. Required antibiotic cocktail concentrations
 - i. Initial work was performed in process characterization and a concentration has been established for the process validation
 - c. Shelf life of antibiotic cocktail potency after preparation
 - i. Addressed in process characterization rather than in process validation
 - d. Determination that 25 minutes provides the required results to the tissue
 - i. Initial work was performed in process characterization but two time points (25 minutes and 40 minutes) will be used in the process validation to determine the optimal time
 - e. Determination of temperature requirements, if any
 - i. Addressed in process characterization rather than in process validation
 3. Soak tissue in antibiotic cocktail B for 15 minutes
 - a. Same as above for cocktail A
 4. Rinse tissue in sterile water for 15 minutes
 - a. Same as above for initial sterile water sonication
 5. Package tissue
 - a. Process of cleaning/decontaminating the equipment
 - i. Validated as a separate step rather than addressing it in process validation
 - b. Qualification of package sealer
 - i. Performed as separate qualification previous to the process validation
 - c. Package validation
 - i. Includes: Integrity/strength, tissue/package interactions during shipping and package shelf life:
 - a) Performed as separate validation previous to or concurrent with the process validation

C. Validation of an Entire Process

This annex demonstrates the importance of performing process characterization and/or validation on individual process steps prior to validating an entire process. Assuming that process characterization has not occurred, consider the following:

In validation of a process intended to reduce bioburden on tissue, the following steps are used:

1. Sonicate tissue in sterile water for 10 minutes
2. Soak tissue in antibiotic cocktail A for 25 minutes
3. Soak tissue in antibiotic cocktail B for 15 minutes
4. Rinse tissue in sterile water for 15 minutes
5. Package tissue

Inoculating tissue with 10^6 CFU of specified microorganisms and testing the tissue for those microorganisms at the end of the process may result in recovery of 0 CFU. In this instance, it is impossible to determine the full capability of the process.

Alternatively, this approach may result in a final recovery of 10^4 CFU of the microorganisms. In this instance, there is no data to suggest which steps of the process might be optimized. The following questions have not been answered:

1. Is 25 minutes of cocktail A too much time or too little?
2. Is 15 minutes of cocktail B too much time or too little?
3. What concentration of cocktails A and B must be used?
4. What is the acceptable range (variation) for concentration, time or temperature of the cocktails?

D. Limited Validation of Existing Process

Process Q, which is marketed by Company ABC, has been validated to provide a specified reduction of microorganisms and a specified physical effect on tissue.

If a tissue bank chooses to purchase and use this validated process on its own tissue, the process must be qualified for use:

1. in their establishment;
2. on their tissue; and
3. by their personnel.

This does not mean that an entire validation must be performed, but it may mean that verification should be performed to assure the validation performed by Company ABC is applicable to their tissue. The verification may include the following:

1. Perform and document a risk analysis to determine the critical steps in the process.
2. Determine worst-case microorganisms and worst-case loads to be tested. This may have already been determined by Company ABC.
3. Determine the acceptance criteria for the test. This may be established with assistance from Company ABC.
4. Verify that appropriate results are obtained when using this validated process (i.e., similar results as Company ABC are obtained).
 - a. Demonstrate the suitability of the test method to be used (e.g., B/F test, see Section VI. Neutralization).
 - b. Inoculate tissue with the microorganisms at the appropriate loads and apply the process to the tissue.
 - c. Perform the proper neutralization step and test to verify the effectiveness of the process in eliminating the microorganisms.
 - d. Compare these results to the published results of Company ABC.

E. Applying Microbiological Surveillance – Example 1

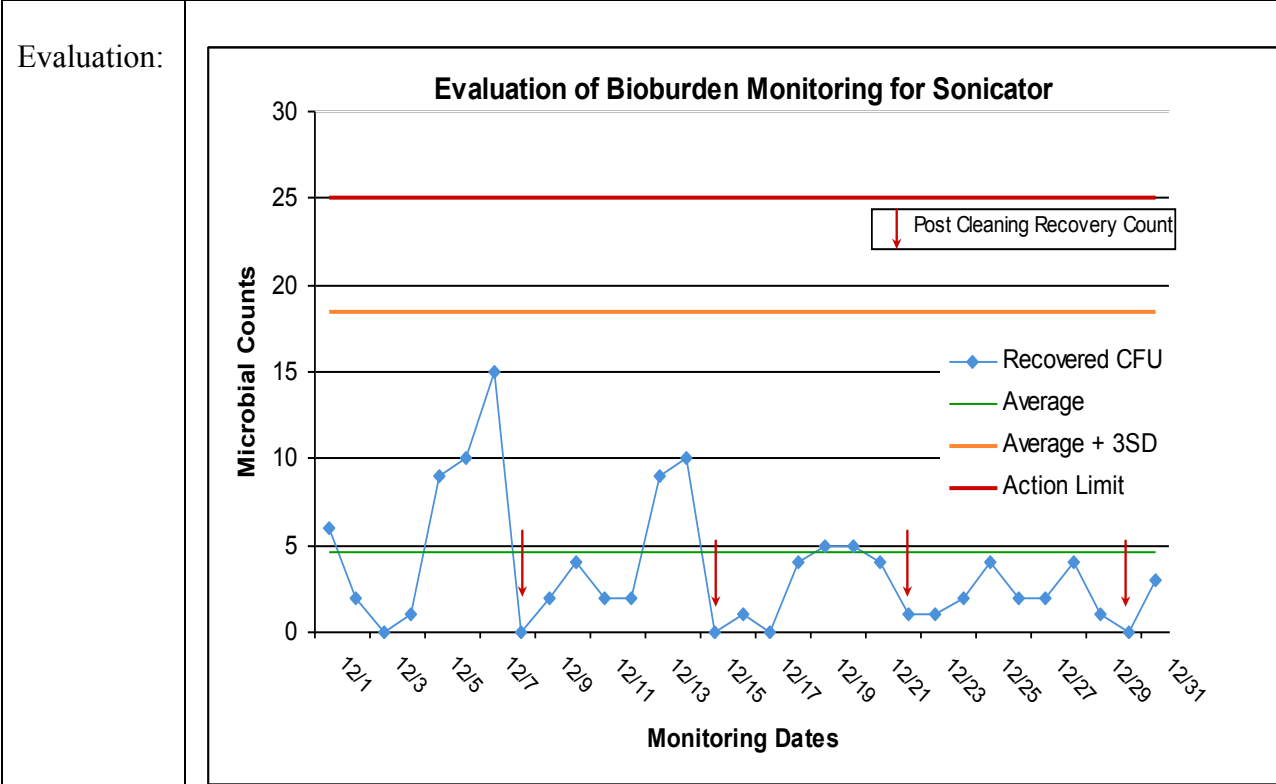
Scenario:	It was noted in the validation of the initial sterile water sonication step that the water is prone to contamination and growth after about four hours of use. It was also noted that the speed of contamination was somewhat variable; sometimes by four hours the water microbial count was 0 CFU per mL and other times it ranged between 10 and 25 CFU per mL. It was determined that up to 25 CFU per mL
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was acceptable, but it was suspected that the variability could be even more pronounced over time than it was during the validation. The water is changed and a simple cleaning is performed with every processing run, but the frequency of a thorough cleaning and of testing the water is in question.

It was also noted that none of the other process components were prone to microorganism growth and/or concentration change over the time period validated.

The initial test data would confirm whether there was a specific day of the week that should be monitored when the frequency was reduced to weekly or if the day of the week was irrelevant. After three months of weekly testing it would be determined if the frequency could be reduced to monthly.

Issues: It was determined, due to criticality of impact to tissue and based on the validation data, that the initial water sonication step should be monitored routinely. It was determined to monitor the water once per day for the first four weeks. This data would be used to set alert and action levels for the process, verify cleaning frequency for the equipment, and determine the frequency with which action levels are exceeded.



After plotting the data for one month of monitoring, the following observations were made:

- The reduction of the monitoring frequency to weekly is supported by the fact that 3 standard deviations (9%) of the values for the process fall below 18.5 CFU per mL and the action level is 25 CFU per mL.
- The cleaning frequency is appropriate given that the bioburden does not exceed

	<p>the action level during the interval between cleanings and the bioburden after cleaning is near zero in all instances.</p> <ul style="list-style-type: none"> • The process appears to be in a state of control in that after plotting the average plus 3 standard deviations (18.5) this value falls below the action limit (25 CFU) where a potential impact on the tissue could be expected. • The average plus 3 standard deviations (18.5) would be an appropriate alert level for indicating that the process might no longer be in a state of control while still allowing corrective action to be taken to restore a state of control before an impact on the tissue (action level) would be expected. • Data indicate that the process can be monitored weekly for the next three months (as planned) and that it should be performed sometime during the week, and not immediately after changing the water. Some of the data indicate that testing a day or two prior to the thorough clean provides some of the higher results, and this also seems logical. Thus the weekly samples will be pulled on day five or six after the thorough cleaning for the next three months, followed by a similar evaluation as described above. • In this situation a bioburden specification was not determined because there is not always a direct connection between environmental bioburden and tissue bioburden. Any value at or above the action level will be evaluated to determine whether there was likely impact to the tissue and what the resulting actions should be.
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F. Applying Microbiological Surveillance – Example 2

<p>Scenario:</p>	<p>In the initial validation of the last step of a process (Step F: final rinse of the batch of tissue in sterile water and sonicated for 10 minutes) it was discovered that if there were microorganisms remaining on some of the tissues after the process step (via sterility testing, aka destructive testing), the rinsate (the solution which remained after the sonication process) consistently contained the same microorganisms. This was determined because during the initial validation, plate count testing was performed on the water from the sonicator (post sonication) as well as sterility testing of the finished tissue (i.e., destructive testing).</p> <p>Based on this initial connection between the finished tissue and the Step F rinsate, it was determined to pay special attention to this situation during subsequent validation activities.</p>
<p>Issues:</p>	<p>In the validation activities, it was substantiated that the rinsate consistently contained the microorganisms which were present on the finished tissue (again based on rinsate plate count results compared to sterility testing (i.e., destructive testing) of finished tissue. It was noted that although some of the finished tissues would carry a particular microorganism, it would not be present on all of them. This means that testing a percentage of the finished tissue may or may not represent the entire batch of tissue. This information led the tissue bank to conclude that testing of the rinsate may actually be a better indicator of the microbiological nature of the batch of tissue than testing finished portions of tissue</p>

	from the batch.
Evaluation:	It was determined that for some period of time after the validation, side-by-side testing of both the finished tissue (sterility testing of 10% of the batch, aka destructive testing) and the Step F rinsate would be performed and trended. Based on the results of the testing over time it would be determined if the rinsate provides as sensitive or a more sensitive detection method for identifying the presence of microorganisms on tissue compared to sterility testing (i.e., destructive testing). The tissue bank may then have options regarding the necessity of testing finished tissue from each batch as an indication of the microbiological status of the batch.

G. Companion Tissue Validation Example

To qualify a companion tissue for end point culture testing, the following approach can be used:

1. Identify the largest and most difficult graft to disinfect and document the rationale for why it is worst case.
2. Identify the desired companion tissue size(s) for end point culture testing.
3. Validate a bioburden extraction method, by seeding the tissue with approximately 100-200 CFU of *Bacillus atrophaeus* or other appropriate organism from experience. Reference ISO 11737-1, Annex C (27) and AAMI TIR 37 (28).
 - a. Develop a recovery efficiency number to use to correct the bioburden count [(CFU recovered/CFU control plates)*100]
 - b. Perform this validation for the largest graft and the potential companion tissue
4. Perform bioburden testing on UNPROCESSED tissues, largest and potential companion samples.
 - a. The tissue may require debriding and non-chemical gross lipid removal to facilitate filtration of the extract for subsequent bioburden testing; pour plate is an alternative option to a filtration sample.
 - b. Unprocessed tissue is used to evaluate the bioburden equivalency between the largest and companion sample as unprocessed tissue is either culture negative or has very low bioburden which will make reproducible detection for a validation almost impossible.
 - c. It is recommended to evaluate bioburden from at least 10 different donors to account for donor derived variability.
 - d. Assess the bioburden from a companion sample(s) made from the same lot and type of tissue that will have the bioburden from the largest graft tested.
 - i. It's desirable to test at least three replicates of the companion and largest grafts per donor.
 - e. Normalize the corrected bioburden by surface area, mass or volume – provide rationale for its appropriateness.
5. Acceptance criteria
 - a. Recovery efficiency – it is desirable to have at least 50%, but this is not always achievable.
 - b. The normalized bioburden amount from the companion sample should be comparable to largest graft in the lot.
 - i. Comparable can be defined as but not limited to: within 1 log, 2 standard deviation or within 30%.

H. Validating a Fluid Extraction Method

This example uses a final rinse of transplantable tissue (i.e., cortical bone tissue) following a cleaning/disinfection process where all tissues were exposed to a mechanical-based extraction.

1. Pre-Validation

Establishment of the extraction method for a test should be based on appropriate characterization of the test variables. Examples of the variables to consider are:

- a. Time
- b. Temperature
- c. Extraction fluid (e.g., Fluid A, Fluid D, saline)
- d. Extraction type (e.g., orbital, stomaching, ultrasonic)
- e. Filter type (e.g., cellulose, polyethersulphone, nylon, hydrophobic edge)

The following example is based on evaluating and validating the recovery efficiency of the mechanical-based extraction selected. The tissue inoculation method was selected because historical data shows tissue bioburden at this stage is too low to use the repetitive recovery method of validating recovery efficiency.

- a. Utilizing a tissue inoculation method [Reference ISO 11737-1 Annex C (27)], determine recovery efficiency of fluid extraction methodology considering variables above.
- b. Add *Bacillus atrophaeus* spores using a target of 100 CFU per tissue tested to selected bone tissues (e.g., cortical rings) at the selected inoculation sites. Allow time to absorb, 10 minutes is generally sufficient, within a biological safety cabinet.
- c. At the time of inoculation, also inoculate agar plates with the same volume to determine the suspension titer.
- d. Test tissue that is not inoculated to understand naturally occurring bioburden on the tissue.
- e. Add inoculated ring(s) to rinse vessel with other cortical tissue (to represent a worst-case amount).
- f. Add solution and perform mechanical rinse step (worst-case parameters for volume, speed and time).
- g. Decant solution from tissue and filter solution using standard microbiological techniques, apply neutralization step (if applicable) and plate on appropriate media. Incubate plates in appropriate environment for appropriate amount of time [reference ISO 11737-1 (27) and USP<61> (47)].
 - i. Count colonies and determine recovery efficiency as a function of amount of microorganisms.
- h. Count colonies and determine recovery efficiency as a function of amount of microorganisms added to tissue vs. amount of microorganisms recovered on filter.
 - i. Ensure that the colonies counted are the challenge microorganism.
- i. Perform above test on the selected number of replicates to factor in system variability.
- j. Analyze data for variability using the selected approach.
- k. Define acceptance criteria for validation (overall recovery efficiency). Refer to pre-validation example immediately below.

2. Validation

- a. Perform recovery efficiency runs (e.g., $n \geq 3$ donors) using nominally defined variables (typical rinse procedure, tissue amounts, etc.) and the microbiological techniques outlined in pre-validation work.
- b. Compare determined recovery efficiency data from validation runs to acceptance criteria to demonstrate repeatability of fluid extraction methodology.
- c. Calculate correction factor to normalize the data for tracking purposes. Refer to validation example immediately below.

I. Fluid Extraction Calculation Example

1. Pre-Validation

- a. Worst-Case Extraction Parameters
- b. Establish Acceptance Criteria for Validation

Inoculum Check	CFU Count
Rep 1	90
Rep 2	98
Rep 3	92
Rep 4	91
Rep 5	101
Average \pm Std Dev	94 \pm 4

Test Article Recovery Runs	CFU Count	Recovery Efficiency	Bioburden CFU Correction Factor*
Rep 1	45	45 / 94 (x100) = 48%	1 / 0.42 = 2.4 *for use in quantitative testing
Rep 2	42	42 / 94 (x100) = 45%	
Rep 3	38	38 / 94 (x100) = 40%	
Rep 4	52	52 / 94 (x100) = 55%	
Rep 5	22	22 / 94 (x100) = 23%	
Average \pm Std Dev	40 \pm 11	42% \pm 12	

2. Validation

- a. Nominal Extraction Parameters
- b. Three Operator Runs
- c. Demonstrate Reproducibility of Extraction Methodology
- d. Target = All Validation Runs should average $\geq 42\%$; in this validation example it was determined that results should be equal to or better than the average of 42%

Pre-Validation Average Recovery Efficiency	Validation Run 1 Average Recovery Efficiency (5-10 samples)	Validation Run 2 Average Recovery Efficiency (5-10 samples)	Validation Run 3 Average Recovery Efficiency (5-10 samples)
42%	44%	52%	50%
Validation Result	Pass	Pass	Pass

Note: If a Validation Run fails, the pre-validation should be re-evaluated.

J. Test Method Qualification

<p>Scenario:</p>	<p>A process validation is being performed to determine the ability of a solution to reduce naturally occurring bioburden on a tissue by 99.9% (three logs). The solution being tested contains an antibiotic that is selective for Gram negative microorganisms.</p> <p>Data from a previous study is available where the bioburden of the tissue was identified. The predominant organisms are Gram negative facultative anaerobes, with less than 2% of the bioburden being fungi, Gram positive cocci and Gram positive rods.</p> <p>The test laboratory has already performed validation of the general bioburden test method for its use. There are additional tests that must be performed specific to this tissue and this bioburden reduction study to ensure that valid results are obtained.</p> <p>The process validation will consist of the following steps:</p> <ol style="list-style-type: none"> 1. Inoculating tissue with selected microorganisms 2. Treating some of the tissue with the intended process 3. Extracting the microorganisms remaining from both treated tissue and untreated tissue 4. Filtering the extracts through a 0.45 um filter 5. Placing the filter on trypticase soy agar (TSA) media plates 6. Incubating at 30-35°C for 48-96 hours 7. Counting the CFUs from the treated and untreated tissue media plates <p>The difference in the microorganism counts from the treated and untreated tissue will be used to determine the effectiveness of bioburden reduction.</p> <p>The physical removal of bioburden from the tissue (the bioburden extraction method) had been previously determined to be 62% using a repetitive recovery approach. This bioburden recovery method was reviewed and found appropriate to use for this bioburden reduction study.</p>
<p>Issues:</p>	<ol style="list-style-type: none"> 1. (Optimal media type) The media type and incubation conditions stated above have not been previously qualified for culturing the microorganisms to be used in the bioburden reduction study. It is desired to use one media type (TSA) and one incubation parameter (30-35°C for 48-96 hours) rather than using the media types and incubation parameters usually considered optimal for these microorganisms. 2. (Antibiotic neutralization) When the bioburden extraction is performed, residual antibiotics may also be extracted into the fluid. When the extraction fluid is filtered through a membrane filter, in addition to the microorganisms trapped on the filter, the residual antibiotics may also remain on the filter and inhibit microorganism growth. It must be demonstrated that the test method

	being used provides proper neutralization for growth of the microorganisms in question.
Evaluation:	<p>1. (Optimal media type) In order to assess the validity of the culturing conditions, three different Gram negative facultative anaerobes, a Gram positive rod, and a yeast (the same microorganisms which will be used in the process validation) are placed separately in quantities of 10-100 CFU onto both the optimal test media and the desired test media. The different media types are incubated as outlined in the table below and the colonies are counted.</p> <p>If, after incubating at the various conditions, the quantity of CFUs from the desired media and incubation conditions is comparable to the CFUs from the optimal media and incubation conditions, the desired media and incubation conditions may be considered valid. The tissue bank has established as acceptance criteria that the desired culturing condition CFUs must not be less than 70% of the optimal condition CFUs [per USP <1227> (33)].</p> <p>2. (Antibiotic neutralization) Neutralization is demonstrated by performing the bioburden extraction method on portions of tissue that have undergone the antibiotic soaking process. The extraction solution and the established number of rinses are filtered. As the final rinse is performed, the rinse solution is inoculated with 10-100 CFU of the same microorganisms as listed above. The filter is placed onto TSA and incubated at 30-35°C for 48-96 hours. As a positive control, a solution containing the same number of microorganisms is filtered and incubated. If after incubation, the number of recovered CFUs from the test samples and the controls are comparable (again to 70%), the neutralization method may be considered valid.</p> <p>Note that it is stated to inoculate <i>the final rinse</i> of the tissue extraction solution prior to filtering. If the tissue is directly inoculated, there are other variables involved that make the test results difficult to interpret.</p>

Organism	Optimal Culturing Conditions	Desired Culturing Conditions
Gram negative facultative anaerobes	BHI w/ 5% Sheep's Blood incubated at 30-35°C for 48-72 hours under aerobic and anaerobic conditions	TSA incubated at 30-35°C for 48-96 hours under aerobic conditions
Yeast	Potato dextrose agar incubated at 20-25°C for 48-72 hours	
Gram positive rod	TSA w/ 5% Sheep's Blood incubated at 30-35°C for 48-72 hours	

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Guidance Document

Evaluation of Body Cooling at Standard D5.400

[No. 7, version 2, December 9, 2013]

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*American Association of Tissue Banks
1320 Old Chain Bridge Road
Suite 450
McLean, Virginia 22101
(703) 827-9582 (703) 356-2198 Facsimile*

Additional copies of this *Guidance Document* are available from the AATB office. In addition, comments on this document may be submitted at any time to the AATB. The Association will review any comments received and revise the *Guidance Document* as appropriate. All requests and comments should be addressed to:

American Association of Tissue Banks
Suite 450
1320 Old Chain Bridge Road
McLean, Virginia 22101
www.aatb.org

For questions on the content of the document, please contact the AATB at:

(703) 827-9582 or (703) 356-2198 (Fax)

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Robert Hinely (co-editor)
Catherine H. Kamm (co-editor)
Daniel Schultz, MD (co-editor)
Scott A. Brubaker (co-editor, AATB liaison)

Kristen Brown
Wayne Daniels, DO
Patricia Darrigan
Gary Flanders
J. Dennis Hancock, MD
Michael Real
Mark Strong

Version 2 update:

Laurie Agle
Michael Gould, MD
Maria Leonard
Mike Real
Dan Schultz, MD
Randy White
Scott A. Brubaker

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AATB GUIDANCE DOCUMENT EVALUATION OF BODY COOLING

I. INTRODUCTION

Self-imposed limitations by tissue banking professionals regarding the time to recover tissue after donor death have existed in the United States for more than two decades. Mention of applying a time limit, and to maintain the body in a cold environment if there is a delay, is found in a publication endorsed by membership in 1984, via the inaugural edition of the AATB's *Standards for Tissue Banking* [1].¹ As it was then and it is now, time limits can depend on the type of tissue to be recovered, additional requirements related to body cooling, and expected functional utility of the tissue. Ideally, recovery should begin as soon as possible post asystole, however, many factors play a role in delays that occur before tissue recovery can begin. Untoward delay, especially in the absence of body cooling, has led to system failures resulting in transmission of bacterial infections (*Clostridium sordellii*) and the death of a tissue allograft recipient [2]. In this case, the donor body was not cooled for 19 hours after death, subjected to a short period of cooling (4 hours), and tissue recovery began approximately 23.5 hours after death [3]. Reports have shown bacterial contamination of tissues to be associated with, or due to, many factors including agonal state of the donor, prolonged intervals from death to recovery, delay of body cooling, pre-and post-mortem trauma, number of recovery personnel, length of recovery times, and variability in procedures [4,5]. Today, transporting a donor body to a dedicated tissue recovery site is commonplace and can cover a considerable distance from the hospital. One study addressed this and the possible warming and cooling rates of a donor body by performing tests on a gel-filled model [6]. Concerns abound regarding the proliferation of microorganisms after death so time to recovery and considerations for body cooling remain highly regarded.

A. History and Purpose

On March 18, 2010, an AATB Bulletin (No. 10-05) was issued that described changes to Standard D5.400 Time Limits for Tissue Recovery [7]. Where time limitations originally referred to when the donor body was not cooled for 15 “consecutive” hours, changes were made to limit when the donor body was not cooled for 15 “cumulative” hours. This change has resulted in interpretation that additional documentation is required. A perceived flaw of allowing up to 15 consecutive hours of non-cooling in some circumstances could theoretically allow for recovery of a donor's tissues to begin with literally only minutes of body cooling having occurred, yet the body was subjected to a non-cooled environment many hours but under 24 hours. The goal of this document is to provide definitions, examples of source documentation, strategies to document cooling intervals, and to provide guidance for various cautionary situations.

¹ In *Standards for Tissue Banking*. American Association of Tissue Banks. 1984; see Standard C1.352 which states “Tissues shall be retrieved as soon after death as is practical. In the event that tissue retrieval cannot be accomplished within hours of death, the remains shall be refrigerated. Specific time limits will vary with each tissue obtained and those time limits shall be at the discretion of the Tissue Bank Director. In order to ensure tissue quality and to avoid delay of funeral services, tissue retrieval should occur within 24 hours following time of death.”

An important aspect of this document includes considerations when assessing the time when the donor was subjected to cooling. An estimate of when the donor's body was subjected to cooling, when an estimate must be used, may be acceptable in certain scenarios. However, policy can differ among individual tissue banks whose Medical Director will ultimately determine donor suitability. Reliable information is expected so an informed decision regarding suitability of the donor can be made. Estimates should be avoided when determining when the body was first cooled after asystole.

The intent of Standard D5.400 [8, and below] is to mitigate and retard microbial proliferation by imposing time limitations and body cooling guidelines. The total time the body was not cooled must be considered when qualifying a deceased donor for suitability. It cannot be assumed that when a body is subjected to some cooling, that the body stays cooled when removed from that environment (and is no longer subjected to cooling).

This guidance was revised to reflect updating to the standard that clarifies the time when recovery begins and that subsequent steps must proceed without delay. To support this, a definition for *Skin Prep* was created for *Standards* and included in this guidance.

The standard, revised twice, is recreated here (with all amendments):

SECTION D - ACQUISITION OF TISSUE: AUTHORIZATION, INFORMED CONSENT, DONOR SCREENING, AND TISSUE RECOVERY AND COLLECTION

D5.000 RECOVERY AND COLLECTION POLICIES AND PROCEDURES

D5.400 Time Limits for Postmortem Tissue Recovery

When Recovery of tissue has begun, subsequent recovery steps must proceed without delay.

- (C, V) Cardiac and vascular tissue *Recovery* and *Processing* time limits (i.e., *Warm* and *Cold Ischemic Times*, *Disinfection Times*, and the *Perfusion Time* [specific to vascular tissues]) shall be established by each individual tissue bank; however, the following upper time limits for initiation of *Recovery* of specific tissue types shall not be exceeded.
- (C) *Warm Ischemic Time* (C) shall not exceed 24 hours from *Asystole* if the body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of *Asystole*. The time limit shall not exceed 15 hours if the body was not cooled or refrigerated. If the body is cooled for a period of time then not cooled for a period of time, the time period the body is not cooled cannot exceed 15 ~~consecutive~~ cumulative hours.
- (V) 1) *Perfusion Time* shall not exceed 12 hours from *Asystole*; and
2) *Warm Ischemic Time* (V) shall not exceed 24 hours from *Asystole* if the body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of *Asystole*. The time limit shall not exceed 15 hours if the body was not cooled or refrigerated. If the body is cooled for a period of time then not cooled for a period of time, the time period the body is not cooled cannot exceed 15 ~~consecutive~~ cumulative hours.

(MS, OA, S)

~~Tissue excision~~ *The Skin Prep* shall ~~commence~~ *begin* within 24 hours of *Asystole* provided the body was cooled (e.g., application of sufficient amounts of wet ice or a cooling blanket, cold weather conditions) or refrigerated within 12 hours of *Asystole*. ~~Tissue excision~~ *The Skin Prep* shall ~~commence~~ *begin* within 15 hours of death if the deceased donor has not been cooled or refrigerated. If the body is cooled for a period of time then not cooled for a period of time, the time period the body is not cooled cannot exceed 15 ~~consecutive~~ *cumulative* hours.

B. Definitions

The following definitions are used in this Guidance Document:

Asystole: The reference time for cardiac death. A documented pronounced time of death is used as ‘asystole’ when life-saving procedures have been attempted and there were signs of, or documentation of recent life (e.g., witnessed event, agonal respirations, pulseless electrical activity). If a death was not witnessed, ‘asystole’ must be determined by the last time known alive (LKA). Asystole will be ‘cross clamp time’ if the tissue donor was also a solid organ donor.

Body Cooling: The placement of a donor body in conditions of cold environment (e.g., mechanical refrigeration such as a morgue cooler, use of wet ice placed on or next to the body of the deceased, or exposure to comparable environmental conditions).

Last Known Alive (LKA): For an un-witnessed death, the last time known alive is the worst-case time used to establish when asystole could have occurred. This includes the time the person was seen or heard, or when they performed an action supported by a record. This would suffice as an equivocal time of having cardiac rhythm or respirations.

Medical Discretion: Under certain circumstances, a written and scientifically rationalized decision by a Medical Director can allow or disallow a particular scenario

Skin Prep: The application of antiseptic solution to decontaminate the skin. This is a continuous process that is performed without delay between steps; it does not include shaving hair, although this can be done if preferred. The manufacturer’s written recommendations must be followed, including that the antiseptic agent should remain in place for the full time.

Source: A written or oral record considered reliable that can be used to support the documentation of when a body was cooled or removed from cooling. A source must be documented. A few examples of source information can include a: Morgue Log Book; Hospital Security Log; a health care professional identified by name, or a specific staff person from the Medical Examiner’s office.

II. RELEVANT SCENARIOS

Q1. I found the cooling date and time as it appears in the hospital morgue logbook. Do I need to note in donor records that the information came from the logbook?

A1. Yes, the source of the information must be noted, whether the communication was from a written record or obtained verbally.

Q2. The morgue's handwritten logbook shows the donor body entered the morgue refrigerator at 0400. The facility's electronic chart describes the donor was taken to the morgue at 0315. Which time do I use and do I need to justify my answer?

A2. The time of 0400 should be used and described as a "worst-case scenario."

Q3. I have a hospital death notification form that shows the body was transferred from the patient's room at 1050 and taken to the morgue. Should I use 1050 for the start of the cooling time?

A3. No. Verification of entry into morgue refrigeration should be sought. If no further documentation exists, a verbal confirmation from a hospital source should be obtained. The name of the individual or the document providing this information must be noted in the donor file. In any case, if this time of entry into cooling will be estimated, this must be noted and, depending on criticality of the information in regard to limits to recovery time, it should be communicated to a responsible person at the tissue bank that will determine donor suitability.

Q4. It is summer time. The hospital does not have a morgue. A hospital representative states they placed bags of ice next to the donor's torso, however there is no documentation by medical staff that supports this. The body is found with bags containing ice in place as expected. Would a verbal time from the hospital staff be appropriate to use?

A4. Yes, the verbal information, including the source of the information can be used and must be documented. If source documents exist that describe measures taken to cool the body, they are preferred.

Q5. The hospital has a morgue logbook that only shows the date the donor was placed in morgue refrigeration. Can I use an approximate cooling time based on conversations with hospital staff?

A5. Yes. Document the verbal source of the information. A notation that the log simply states they "were placed in morgue refrigeration with no time assigned" can be noted but confirmation of the estimation of the time is expected. Otherwise, a worst-case scenario should be used. Example documentation could be: "J. Doe, Security Officer, estimated body to have been placed in the morgue cooler at 0015."

Q6. I am aware that our ME office removes bodies from morgue refrigeration for short intervals to complete their forensic data gathering. Do I need to document each interval to establish cumulative cooling time?

A6. No. It is recognized there will be in and out times by the ME or pathologist for short intervals. Documentation of such time intervals is considered beyond the intent of documenting the 15 cumulative hours of no body cooling. It is acceptable to use the entire ME interval as cooled time, despite intermittent, brief removals for x-rays, exams, specimen collection, etc. The intent of the change, from “consecutive” to “cumulative” regarding 15 hours when no body cooling occurs, did not include an expectation to add excessive documentation requirements that can promote errors. However, adequate documentation is expected so *relevant* periods (i.e. an autopsy), when no body cooling occurred can be realized.

Q7. The hospital has documented in and out cooling times of the donor. The body was transported to the Medical Examiner’s (ME) office, which I know is 30 minutes away. The ME doesn’t document in and out times and no one in that office has documentation regarding when this donor was taken in and out of cooling, however they follow a standardized work protocol. The ME staff reports bodies are routinely removed from cooling at 0800, however, the autopsy may not begin for 2-3 hours. Can I piece together cooling times based on common sense and the practice the ME follows?

A7. It is best practice is to show due diligence to find the information from either documentation or via interview. If neither is available, then an estimation of times can be utilized. It should be noted that the times are estimates. Example of Documentation: “Factual cooling times at the ME office are unavailable. Times are estimates based on the coroner’s stated practice per J. Doe, ME staff.” See the following example of a documentation method:

Asystole: Date 3/15/11 Time 1900

Donor Cooling:

Date In	Time In	Date Out	Time Out	Total Non-Cooled Time	Source (list for In Time / Out Time)
3/15/11	2000	3/16/11	0800	1 hour	Trans. Sheet/J. Doe, ME Staff
3/16/11	1300	3/16/11	1700	5 hours	J. Doe/Trans Sheet
				Total 6 hours estimated	

Q8. Can cooling the body using wet ice during transportation be counted towards additional cooling time?

A8. Yes. Utilizing bags of wet ice placed along the lateral aspect of the torso and between or on top of the thighs can serve the purpose of cooling the body. Documentation of this should include the name and title of the person who reported the times this was done and the number of ice bags used.

Q9. Does a death occurring in a cold environment (a decedent lying in a snow bank, or a hanging that occurred in a park during the winter and at night) allow for discretion and consideration as “cooled time?”

A9. Yes. Medical director discretion, documentation of known environmental temperatures (via the internet for weather sites for that locale, or other references) can be utilized to show the body was subjected to cool temperatures. Allowances for temperature should be documented with supportive, written rationale.

Q10. Can discretion be used when evaluating acceptability when a calculated postmortem interval has minimally exceeded the 15 hours uncooled time or tissue recovery time limits (i.e., Skin Prep)?

A10. Yes, however, this scenario would require comprehensive documentation by the Medical Director, possibly in consultation with a knowledgeable physician such as a pathologist or Medical Examiner to rationalize why the time intervals are inaccurately exceeded by the worst case estimations, or failure to account for comparable conditions to wet ice cooling. Discretion, for example, can include exposure to cold temperatures due to the environment. Discretion could include providing evidence of a shorter postmortem interval by the Medical Examiner or medical personnel observations (e.g. degrees of algor, rigor, livor, a core body temperature taken) at the time of their assessment.

Q11. Considering that the body cooling parameters are met, what is the expectation for the timing of tissue recovery when the skin preparation process overlaps the 15- or 24-hour time limits for recovery?

A11. The *Skin Prep* is performed with the same diligence as used for operative procedures, allows for maximum antisepsis, and occurs without interruptions. The recovery in such situations immediately follows the skin preparation.

Q12. Why is the death note and/or pronouncement note not sufficient documentation for time of Asystole for some donors?

A12. Time of pronouncement/Time of death may be different from time of *Asystole* depending on the scenario:

- a) The donor is ‘Do Not Resuscitate/Comfort Measures Only’ status prior to death on a unit without cardiac monitoring.

- b) The donor was hospitalized, cared for in a nursing home or in hospice (at home or at a facility) for several days prior to death. The only documentation provided regarding care of the donor within 24 hours of death is the pronouncement note.
- c) Conflicting times of death in care records vs. death records. Actual Time of Death/Last Seen Alive time is unclear.
- d) The donor is an organ donor. Pronouncement time and time of death is the time of brain death. *Asystole* is the time of cross clamp (clinical death).
- e) The death was not witnessed and the decedent was simply found and pronounced. Use of “Last Known Alive” time as defined in this Guidance Document ensures the donor was recovered within acceptable time limits.

III. SPECIAL CONSIDERATIONS

Donors who appear, based on reported asystole, LKA, or body cooling, to be within appropriate time requirements may have signs of accelerated post-mortem interval (decomposition). This can manifest as unexplained skin slippage, unexplained green discoloration (often seen first in the right lower quadrant of the abdomen), unexplained bloating, or putrefactive odor. These accelerated postmortem changes usually arise from hyperthermia due to inordinately warm environmental conditions, or underlying bodily conditions (e.g. a significant infection, brain lesion, or drugs leading to altered temperature regulation). Accelerated postmortem decomposition may also occur when exposed to environments of high bioburden near death (e.g. drowning in dirty water). Observation of changes such as those described above must be documented at physical assessment.

IV. SAMPLE DOCUMENTATION METHODS

Example I

	Source	Date	Time (Military)	Non-Cooled Time
Asystole (see definition)	<i>Pronouncement</i>	<i>4/11/2011</i>	<i>2300</i>	
Cooling Start	<i>M. Doe, RN</i>	<i>4/12/2011</i>	<i>0523</i>	
Cooling End	<i>Transport Sheet</i>	<i>4/12/2011</i>	<i>1315</i>	
				<i>6hrs23mins</i>
Cooling Start				
Cooling End				

Example II

Date/Time of Asystole:		Cooled? Y N		Total Time from Asystole to Recovery: _____Hrs. _____Mins.	
Cooling Information	Date	Time	Calculated Time Out of Cooling		Source of information
Cooling Started			Elapsed Time from Death to Cooling: _____Hrs. _____Mins.		
Out					
In			_____Hrs.	_____Mins.	
Out					
In			_____Hrs.	_____Mins.	
Out					
Initial Incision			_____Hrs.	_____Mins.	
Total Calculated time out of cooling (must be less than 15 hours)			_____Hrs.	_____Mins.	

Example III

Asystole: Date _____ Time _____

Donor Cooling:

Date In	Time In	Date Out	Time Out	Total Non-Cooled Time	Source (list for In Time / Out Time)
				Total ___hours estimated	

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Guidance Document

Effective Quality Assurance of the Donor Risk Assessment Interview

*Version 2
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*Eye Bank Association of America
Suite 1010
1015 18th Street, NW
Washington, District of Columbia 20036
(202) 775-4999 (202) 429-6036 Facsimile*

*American Association of Tissue Banks
Suite 450
1320 Old Chain Bridge Road
McLean, Virginia 22101
(703) 827-9582 (703) 356-2198 Facsimile*

*Association of Organ Procurement Organizations
Suite 300
8500 Leesburg Pike
Vienna, Virginia 22182
(703) 556-4242 (703) 556-4852 Facsimile*

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AATB:

Dave Fronk
Carrie Hartill
Paul Kostiak
Patty Malone
Tim Maye
Karen Norman
Kathy Pearson
Greg Ray
Scott A. Brubaker - Coordinator

AOPO:

Emily Goldbloom
Bruce Nicely
Jacquelyn Warn
Brenda Welsch
Loretta White
Julie Zabloski

EBAA:

Jennifer DeMatteo
Kenneth Manger

***AATB/AOPO/EBAA GUIDANCE DOCUMENT
EFFECTIVE QUALITY ASSURANCE OF THE DRAI***

I. INTRODUCTION

An essential safety element of *tissue* donor screening and ultimately the determination of a deceased *donor's eligibility* is the administration and completion of the *donor risk assessment interview* (DRAI). This guidance document describes components and considerations for developing and implementing an effective *quality assurance program (QA Program)* process for the DRAI.

The DRAI *record* is considered a *relevant medical record* used to determine initial and final *donor eligibility*. Two methods exist to obtain information required to complete the DRAI and each generates a concurrent *record* of the information gathered. Interviews may be conducted face to face, often in a hospital setting for a potential organ/tissue donor, but, more often, the interview is conducted by telephone for a potential tissue donor. For each method, the expectation is that a knowledgeable person regarding the donor's relevant medical history and social behavior is identified and interviewed for the DRAI. In all cases, the interview is conducted according to *standard operating procedures (SOPs)* and concurrently documented using a standardized form to ensure all requirements of the SOP are addressed.

Note: For the purposes of this guidance, the term "*tissue bank*" includes an eye bank, an organ procurement organization, or a tissue bank (but not a tissue bank that handles reproductive tissue only). When used for the first time in the body of this document, a term is italicized if a definition for it appears in section "B. Definitions and Acronyms."

A. Executive Summary

This guidance document provides expectations and describes best practice for managing an effective QA Program that provides a high level of assurance the DRAI process is being performed consistently as intended.

The QA Program must include all of the following:

- comprehensive SOPs;
- staff qualification, training, and *competency assessment and verification*;
- *quality control* of the documented *record* of the interview;
- an internal *audit* program which includes the performance of periodic assessment of the effectiveness of the SOP and compliance with the SOP; and
- corrective and preventive action as warranted.

Recommendations included in this consensus document represent the collective expertise of many procurement professionals. The definitions, regulatory expectations, components of a QA Program, and reference documents are provided for use by all professionals performing these functions, or entities for which these functions are performed. An effective QA Program as described in this guidance document is expected to be in place.

B. Definitions and Acronyms

These definitions originate from current standards of the AATB and the EBAA, except where noted:

AUDIT – A documented review of procedures, records, personnel functions, equipment, materials, facilities, and/or suppliers to evaluate adherence to the written *SOPM*, standards, applicable laws and regulations.

COMPETENCY – The ability of an employee to acceptably perform tasks for which he/she has been trained.

COMPETENCY ASSESSMENT – The evaluation of the ability of an employee to acceptably perform tasks for which he/she has been trained.

DEVIATION – An event that is a departure from a procedure or normal practice.

DONOR ELIGIBILITY— Determination made based on donor screening and testing for relevant communicable disease agents and diseases (This definition is derived from § 1271.45(b).

DONOR RISK ASSESSMENT INTERVIEW (aka Medical History Interview, Medical/Social History Questionnaire, or Uniform Donor History Questionnaire/UDHQ) – A documented dialogue in person or by telephone with an individual or individuals who would be knowledgeable of the donor’s relevant medical history and social behavior. For example, this may be: the donor, if living; the next of kin; the nearest available relative; a member of the donor’s household; other individual with an affinity relationship (e.g., caretaker, friend, significant life partner); and/or the primary treating physician. Alternatively, a living donor may complete a written questionnaire. The relevant social history is elicited by questions regarding certain activities or behaviors that are considered to place such an individual at increased risk for a relevant communicable disease agent or disease (RCDAD).

PROCEDURE – A series of steps which, when followed, are designed to result in a specific outcome.

QUALIFIED - Deemed competent by a recognized authority.

QUALITY – The conformance of tissue or a process with pre-established specifications or standards.

QUALITY ASSURANCE (QA) PROGRAM – The policies and environment required to meet standards of quality and safety, and provide confidence that the processes and tissue consistently

conform to quality requirements.

QUALITY CONTROL (QC) – Specific tests or activities defined by the *QA Program* to be performed to monitor authorization/informed consent, donor screening, recovery, processing, preservation and storage, tissue quality, and test accuracy. These may include but are not limited to, performance evaluations, inspection, testing, and controls used to determine the accuracy and reliability of the tissue bank’s equipment and operational procedures, as well as the monitoring of supplies, reagents, equipment, and facilities.

RECALL – An action taken by a tissue bank to locate and retrieve tissue from distribution and dispensary inventories. This includes withdrawals; see <http://www.fda.gov/Safety/Recalls/ucm165546.htm>

RECORD - Information that is inscribed on a tangible medium or that is stored in an electronic or other medium and is retrievable in perceivable form.

RECOVERY —Tissue surgically removed from a donor that is intended for use in human transplantation, therapy, research or education.

RELEVANT MEDICAL RECORDS – a collection of documents including a current *Donor Risk Assessment Interview*, a physical assessment/physical examination of the donor, laboratory test results (in addition to results of testing for required relevant communicable disease agents), relevant donor records, existing coroner and autopsy reports, as well as information obtained from any source or records which may pertain to donor eligibility regarding high risk behaviors, and clinical signs and symptoms for any relevant communicable disease agent or disease (RCDAD), and/or treatments related to medical conditions suggestive of such risk.

RESOLUTION – Adjustment, clarification, and/or correction of practices and/or procedures that results in compliance with the *SOPM* and/or standards.

STANDARD OPERATING PROCEDURES MANUAL (SOPM) – A group of standard operating procedures (SOPs) detailing the specific policies of a tissue bank and the procedures used by the staff/personnel. This includes, but is not limited to, procedures to: assess donor eligibility; recovery; processing; quarantine; release to inventory; labeling; storage; distribution; and recalling tissue.

TISSUE (aka human cell, tissue and cellular and tissue based products (HCT/Ps)) – A functional group of cells. The term is used collectively to indicate both cells and tissue, and includes ocular tissue.

TISSUE BANK (aka Tissue Establishment) – An entity that provides or engages in one or more services involving donated ocular and/or conventional tissue from living or deceased individuals for transplantation purposes. These services include assessing donor eligibility, recovery, processing, storage, labeling, and distribution of tissue.

VERIFICATION – The confirmation by examination and provision of objective evidence that

specified requirements have been fulfilled.

Acronyms:

AATB – American Association of Tissue Banks
aka – also known as
AOPO – Association of Organ Procurement Organizations
AST – American Society of Transplantation
ASTS - American Society of Transplant Surgeons
CDC – Centers for Disease Prevention and Control
CFR – Code of Federal Regulations
DRAI – donor risk assessment interview
EBAA – Eye Bank Association of America
FDA – United States Food and Drug Administration
HCT/Ps – human cell, tissue and cellular and tissue-based products
HBV – hepatitis B virus
HCV - hepatitis C virus
HIV - human immunodeficiency virus
HRSA – Health Resources and Services Administration
NATCO – The Organization for Transplant Professionals
NCHS – National Center for Health Statistics
QA – quality assurance
OPTN – Organ Procurement and Transplantation Network
QC – quality control
RCDAD - relevant communicable disease agent or disease
SOP - standard operating procedure
SOPM – standard operating procedures manual
TSEs - Transmissible Spongiform Encephalopathy(ies)
UDHQ - Uniform Donor History Questionnaire
UNOS – United Network for Organ Sharing
vCJD – variant Creutzfeldt-Jakob disease
WNV – West Nile virus

II. Regulatory Expectations

A. Federal

An evaluation of applicable FDA regulations at 21 CFR Part 1271 and related guidance for human cell, tissue, and cellular and tissue-based products (HCT/Ps) reveals relevant headings that can be applied to functions when performing the DRAI (aka FDA’s “donor medical history interview,” a donor screening function). A list of relevant requirements and a summary of expectations are provided in Appendix A.

1. Recommendations

- Develop your SOPM to reflect the following:

- the documented record of the interview is made concurrently by the interviewer performing the steps;
 - the documented *record* is the *relevant medical record* and is retained and/or shared; and
 - if made, the audio recording of the DRAI is used for *quality* review purposes only, and is not intended to be the documented record that's retained and/or shared.
- The interview must be conducted in accordance with the SOP.
 - Staff members who administer the DRAI must be *qualified*, be provided with appropriate training, and designated as “authorized” to perform the task.
 - Regularly scheduled assessments of all personnel shall be performed to verify compliance with the SOP.
 - The documented record is expected to accurately reflect the DRAI event.
 - A QA program must include sampling plans that verify the process used, whether the DRAI is recorded or not.
 - When an audio recording is made, an adequate QA sampling policy and *procedure* for reviewing and comparing the written or electronic record to the audio recording of the DRAI must be developed.
 - After sampling has occurred, changes made to any records already shared must be communicated in a timely manner.
 - The decision to retain the audio recording on file and the retention timeframe must be determined by each tissue establishment based on the tissue establishment's use of the recording in determining donor eligibility.

If the audio recording is not used for donor eligibility determination:

- Time periods selected should be reasonable for your operations and tied to quality control measures (e.g., see C. Quality Control, 1. Sampling Plan). The SOPM should include a description that when the record is produced concurrently with the voice recording, and a robust sampling plan is used after recordings are made, there is no need to retain the audio recording for an extended period of time.

If the audio recording is used for donor eligibility determination:

- The retention time period selected must be 10 years from the time of creation.

- The written agreement/contract between a tissue bank receiving donor tissue and the establishment that performs the DRAI on their behalf should ensure that responsibilities are clearly described and understood in regard to activities performed.

III. Components of a Quality Assurance Program

A. Standard Operating Procedures

Development of an effective, practical SOP is critical. The DRAI takes place when the interviewee may be distraught due to the recent death of the potential donor. This situation presents particular challenges to the interviewer if the SOP is written in a restrictive manner (e.g., requiring that the interview material be read verbatim).

While it is critical to gather all the relevant information required in the DRAI, a well-designed SOP and questionnaire can greatly assist both parties in the interview process. The DRAI is intended to be an interactive conversation (dialogue) designed to collect pertinent information. The use of ‘capture’ questions limits repetitious questioning and can quickly elicit required information. A capture question asks a broad question leading to more specific questioning only if needed.

Note: A group of donation and transplantation professionals representing AOPO, EBAA, NATCO, HRSA, OPTN/UNOS, AST, ASTS, NCHS, CDC, FDA and AATB have developed a uniform donor history questionnaire structured to address challenges when conducting the DRAI. The capture question approach described above is used and is preferred. It is recommended that all agencies performing DRAI activities evaluate this questionnaire for adoption into their processes and, as appropriate, adjust SOPs and staff training accordingly.

B. Staff Qualification, Training and Competency

The DRAI shall be performed by staff members who have sufficient qualifications, which equates to completion of a formal training program and documented *competency assessments*. To remain *qualified*, interviewer knowledge must be updated when new or revised policies and procedures are implemented.

Effective training of personnel performing DRAI activities is another area of opportunity for assuring the *quality* of the information gathered during the DRAI process. Interviewers are faced with many challenges during this process and should be trained to be sensitive to a number of factors. These include the:

- need to provide empathy to the donor family member(s) or other person interviewed;
- sensitive nature of many questions;
- criticality in obtaining the best information possible to facilitate donor eligibility determination;

- accuracy in completion of the documented record of the interview; and
- management of the interview process when an interviewee desires to limit the questions or the length of time spent on the DRAI.

A varied and challenging number of ‘priorities’ are present in the DRAI process; therefore, it is important to include in training programs for staff, not only the SOP content but also the perspective of the stakeholders in this process. Of particular importance is providing information related to the reason for, and intent of, each question as this may not be intuitive to the interviewer. In the absence of this understanding, interviewers might rephrase the question and miss the intent of a question’s assessment of risk. For example, this can include intent behind questions related to geography and travel during certain periods of time (i.e., related to risk associated with vCJD). As part of their training, personnel shall be made aware of the consequences of the improper performance of their specific jobs.

Discussion of ‘lessons learned’ is effective in maintaining the learning culture. Material for these discussions can be gathered from inside the organization, from reports of problems encountered by other agencies, as well as from audit findings where interviews may not have been completed as required or planned.

Competency assessments shall be conducted by organizations to ensure that the behavior, knowledge, skill, and ability of personnel performing the DRAI align with expectations including criteria of regulations, standards, and SOPs. Competency *verification* shall be done prior to personnel performing the DRAI role independently and should be performed on a recurring basis (such as annually). Recommendations include the use of tools and methods such as:

- observation and assessment of on-site or recorded performance of the DRAI personnel. These reviews can include mock DRAI scenarios and actual DRAIs (recorded or live);
- use of a competency assessment checklist to include all expectations required to complete a comprehensive DRAI. Such expectations should include that the interviewer:
 - provides proper instruction to the interviewee at the start;
 - asks all required questions;
 - executes the intent of the questions;
 - appropriately probes and follows up on responses during the DRAI, as needed; and
 - documents relevant responses accurately.
- clearly defined thresholds for competency. Data should be collected for error tracking and performance trends;
- improvement plans for personnel that have not achieved or retained an acceptable level of competence;
- competency exams to demonstrate knowledge and understanding for the questions and

their intended purpose; and

- inclusion of competency *verification* documentation in the individual's training record.

C. **Quality Control**

Quality Control activities shall be described in the SOPM and consist of a timely review of documented records soon after interviews are conducted. This may include direct observation of the administration of the DRAI, listening to audio recordings, and review of the documentation of the DRAI. The intent of quality control measures is to determine if the documented record:

- complies with the established SOP;
- accurately reflects information obtained from the interviewee; and
- is complete and legible.

Note: An audio recording of the dialogue that takes place for the DRAI is not mentioned in, or required by, FDA regulations or guidance, and is not required by standards of the AATB [1], AOPO [2] or EBAA [3]. Because some *tissue banks* record DRAIs in addition to concurrently completing a record, these practices need to be managed using appropriate quality assurance concepts.

Quality Control activities are usually structured and planned based on a confidence level for the process. Therefore, a number of variables should be considered in order to provide confidence in the documented record created concurrently during the course of the interview. Variables that should be taken into account include:

- experience with the current DRAI form and associated SOP;
- interviewer training;
- past results of quality control measures; and
- other quality assurance activities where *deviations* from *procedure* versus desired outcome have been identified.

In the event the DRAI is not completed in accordance with the SOP, the timely performance of corrective measures is essential. Any need to re-contact the interviewee to clarify responses or to obtain missing information should be done as soon as possible.

1. **Sampling Plan**

A sampling plan must be used to conduct the quality control program. An effective sampling plan takes into account certain variables (e.g., number of donors, assurance level) that determine an adequate sample size. Sampling plans should be applied to ensure that the sample includes multiple interviewers, that each interviewer is sampled periodically, and if there have been changes in the SOP or the DRAI, sampling may need to be increased. Routine reviews of this

activity should not be used as a substitute for competency assessment. All Quality Control activities must be documented including identification of which records were sampled, whether the activity was acceptable or, if deviations are noted, what immediate corrections were made. If applicable, a description of any long-term corrective actions should be included.

Considerations for **internal** process sampling include:

- select a short period of time, such as within 30 (thirty) days from date of performance, to prevent recurrence of any identified deviation;
- identify a satisfactory, representative number from all interviews done during this time period. See http://guidebook.dcma.mil/226/tools_links_file/stat-sample.htm where this type of sampling plan is provided:

Total # of Donor Records	# of Donor Records to Review
2 – 150	13
151 – 280	20
281 – 500	29

An additional reference for developing an acceptance sampling system is the American National Standards Sampling Procedures and Tables for Inspection by Attributes (ANSI/ASQ Z1.4-2008).

- the number of interviews each interviewer has completed during this established time and sample each person;
- frequency and sample size may need to be increased when there have been any changes in the SOP or DRAI form, or when a deviation has been identified; and
- interviewers that are newly authorized may require more frequent sampling at onset of performing these activities.

Determination of a sampling plan (schedule) must be documented and the rationale justified. The sampling plan should be robust and as data and experience is gathered, a step-wise adjustment in the sampling frequency may be justified.

Note: An audio recording of the DRAI is not required. . When an audio recording is used as a quality assurance tool, its retention status should be defined in policy and in your written agreement/contract. If an audio recording is utilized to make the donor eligibility determination, it is considered to be a relevant medical record and retained accordingly.

Considerations for **external** process sampling may include the components described above for an internal process. For example, the frequency of the audit and sample size may be modified to reflect the length of time since last audit, availability of recordings, as well as previous audit findings (this includes deviations).

D. Audit

A robust audit program should be designed to periodically assess the ongoing effectiveness of several areas of activity related to the DRAI process. Audit results will provide information on the adequacy of SOPs from the perspective of meeting external requirements (regulations or accrediting body standards). Audits also check internal processes such as compliance with SOPs, quality control, training activities, and competency assessments.

Audits are performed on a planned basis and their frequency is usually determined as part of an overall, internal audit program. Audits include all aspects of the DRAI process. They are typically performed at least once per year by someone not directly involved in the process. The results of past audits as well as the current state of compliance should be considered in determining the need to increase the frequency of audits to ensure the stability of the program.

Audits may include random observations of actual conducted interviews and/or the review of audio recordings of interviews in comparison with the concurrent record. See ‘III. C. 1. Sampling Plan’ above. Consideration should also be given to ensure that the audit program ensures that each interviewer is included. Findings from these audit activities, indicating evidence of compliance or the need for correction, must be documented to demonstrate adequate review and reflect the scope of the audit activity. The quality assurance audit process is not intended to replace quality control activities.

1. Examples

- Upon reviewing an audio recording of the DRAI, it is determined that the interviewer failed to ask the interviewee, “In the past 5 years has the donor had sex in exchange for money or drugs?” The interviewer documented a “no” response to this question on the written DRAI and the tissue was ultimately distributed for transplantation.
 - In this instance, in the absence of other information addressing such high risk behavior, the donor determination was incomplete. The tissue bank that released the tissue would submit an HCT/P Deviation Report to FDA, providing a synopsis of the occurrence, detailing the root cause, and delineating corrective actions to be performed. Corrective actions could include: contacting the interviewee again to ask the question, *recall* of the tissue, -re-training the interviewer, and an audit of other past interviews performed by the interviewer. Reporting to state agencies and accrediting bodies may also need to occur, as applicable.
- Upon reviewing an audio recording of the DRAI, it is determined that the interviewer inappropriately paraphrased a question. For example, the tissue bank’s DRAI includes the question, “Was the donor or any of his/her blood relatives diagnosed with or been told they were at risk for Creutzfeldt-Jakob Disease or variant Creutzfeldt-Jakob Disease?” The interviewer actually asked the interviewee, “Did the donor ever have mad cow disease?” The interviewer documented a “no” response to this question on the DRAI and the tissue was ultimately distributed for transplantation.
 - FDA guidance states that if the person interviewed “is not familiar with the term “Creutzfeldt-Jakob Disease” or “variant Creutzfeldt-Jakob Disease,” you may try

to describe those in layman's terms. If the person being interviewed is still not familiar with those terms, you may consider the lack of familiarity with those terms as a negative response to questions using those terms." In this instance, the interviewer did not first ask about "Creutzfeldt-Jakob Disease" or "variant Creutzfeldt-Jakob Disease" and did not ask about the donor's blood relatives, so this risk was not assessed as required. The tissue bank that released the tissue would submit an HCT/P Deviation Report to FDA, providing a synopsis of the occurrence, detailing the root cause, and delineating corrective actions to be performed. Corrective actions could include: contacting the interviewee again to ask the question, *recall* of the tissue, re-training the interviewer, and an audit of other past interviews performed by the interviewer. Reporting to state agencies and accrediting bodies may also need to occur, as applicable.

- While observing the interview process in real time, it is determined that the interviewer omitted part of a question. For example, the tissue bank's DRAI includes the question, "Has the donor ever used a needle to inject drugs into his/her veins, muscles, or under the skin for non-medical use?" The interviewer actually asked the question, "Has the donor ever used a needle to inject drugs?" The interviewer documented a "no" response to this question on the DRAI and the tissue was ultimately distributed for transplantation.
 - In this instance, the essence of the question was actually asked. It can be argued that the question that was asked was actually more inclusive than the question on the DRAI. For example, if the donor ever injected drugs for a medical purpose, that would be captured in this question. Moreover, the question asked simply queries if the donor ever used a needle to inject drugs, so a negative response would rule out needing to determine the route. If the interviewee provided a "yes" response, then further clarification would be needed. The interviewer provided a "no" response" so no reporting to any regulatory agency or accrediting body would be necessary. For this example, documentation justifying this decision should be maintained in donor records and shared if applicable. Corrective action necessitates re-training the interviewer and possibly performing an audit of other past interviews performed by the interviewer.
- Upon reviewing an audio recording of the DRAI and comparing it to the DRAI record, it is determined that the interviewer failed to accurately document the interviewee's actual response. For example, the tissue bank's DRAI includes the question, "Did the donor drink alcohol?" The interviewee reported that the donor drank 4 beers each night, but the interviewer documented the response as "no." The tissue was ultimately distributed for transplantation.
 - In this instance, given that the additional medical information does not indicate an increased risk for a relevant communicable disease agent or disease, no HCT/P Deviation Report need be submitted. However, the tissue bank releasing the tissue should document justification why the error is not relevant to disease transmission. The tissue bank would still need to document its findings in their QA report and treat it as a deviation, along with any corrective action(s) it deems necessary, such as re-training the interviewer and possibly performing an audit of other past interviews performed by the interviewer.

Note: Corrected DRAI records need to be shared appropriately, and without delay, with all tissue banks involved with recovery of tissue, or receipt of tissue, from the donor.

E. Corrective and Preventive Action

Quality assurance should also include documented investigations, corrective actions and effectiveness checks when deviations from SOP, regulations, or standards related to the DRAI process are identified. Deviations can be identified:

- during quality control activities;
- as the result of audits or inspections; and
- via feedback from entities with whom the documented record has been shared.

An effective corrective action plan should address immediate action to be taken to rectify the deviation and consider process improvement to prevent recurrence. Effectiveness checks should be performed to confirm that corrective actions have been effective in eliminating the root cause of the deviation. In addition, if a deviation is seen during routine quality control sampling or audit, the sample size may be increased until the corrective action is deemed effective.

The scale and scope of a corrective action plan will depend on factors such as severity and extent of deviation. Severity is best considered from the perspective of the use of the DRAI information in determining final donor eligibility. Extent may be a factor of multiple interviewers and/or length of time the deviations have been identified as occurring.

If quality control activities are performed in a timely manner as described above, the length of time and extent of the deviation is likely to be limited. It may be necessary to prioritize aspects of the investigation based on the risk posed. Risks include inappropriate donor eligibility determination, potential for communicable disease transmission, and/or *recall* of tissue grafts. If the deviation is determined to be extensive, additional resources may be necessary to complete the plan in a timely manner.

Examples of corrective action activities (*resolutions*) may include:

- Notifying without delay all tissue banks that have received the DRAI and reaching agreement on any necessary follow-up actions (e.g., providing frequent updates as action plans are implemented, sharing additional or corrected information, etc.).
- Identifying the need to re-contact interviewees if the intent of the DRAI was not met, or if information provided by the interviewee appears to have been misunderstood or incorrectly recorded by the interviewer.
- Development of a plan to re-contact the interviewee(s) or obtain missing information. Plans should include actions to be taken if there is difficulty locating the person or if she/he is unable or unwilling to assist in clarifying or providing information. If initial attempts to correct or clarify information are unsuccessful, other viable options include:

an inquiry with the primary care physician of the donor; locating another knowledgeable person; or, the use of a private investigator to locate the original interviewee.

- Evaluating existing processes to identify the root cause of a deviation. Training and retraining is often identified as a root cause and/or corrective action and care should be taken to assure that if retraining is determined to be the appropriate corrective action, effectiveness checks are performed and confirm that this was root cause rather than the underlying SOP or process.
- While every effort should be made to obtain information required from the DRAI, in the event it is not possible, a risk assessment should be performed for each case. This risk assessment should be completed in collaboration with the tissue processor(s) that determines donor eligibility. A careful review of additional records may provide missing, or clarify questionable, information.
- When a deviation is discovered, an investigation must be performed to determine the scope of the problem. Depending on the circumstances/results of the investigation, a planned audit of other interviews performed by that interviewer may be indicated.

1. Timely Notification

Timely notification is critical. When tissue associated with a deviation related to the DRAI have been distributed for transplant, the tissue processor has a time frame of no more than 45 (forty-five) days to report the incident to FDA under HCT/P Biological Product Deviation reporting requirements. Actions required prior to submission of this report include obtaining additional information and performing a health hazard (risk) assessment. If it is not possible to resolve or address the deviation and the associated risks, further actions may be necessary (e.g., disposition of the tissue remaining in quarantine or inventory, a recall may be indicated for tissues that were already distributed for transplant).

IV. Appendix

A. Federal Expectations [4, 5, 6, 7] and Summary

Subpart C - Donor Eligibility Final Rule

§ 1271.3 How does FDA define important terms in this part?

(n) *Donor medical history interview*

(s) *Relevant medical records*

§ 1271.50 How do I determine whether a donor is eligible?

(a) *Determination based on screening and testing.*

(b) *Eligible donor.*

§ 1271.55 What records must accompany an HCT/P after the donor-eligibility determination is complete; and what records must I retain?

(a) *Accompanying records.*

(b) *Summary of records.*

- (d) *Record retention requirements*
- § 1271.75 How do I screen a donor?
 - (a) *All donors.*
 - (d) *Ineligible donors.*

HCT/P Donor Eligibility Final Guidance

IV. DONOR SCREENING (§ 1271.75)

- C. What sources of information do I review?
- E. What risk factors or conditions do I look for when screening a donor?

Subpart D – Current Good Tissue Practice Final Rule

§ 1271.150 Current good tissue practice requirements.

- (a) *General.*
- (b) *Core CGTP requirements.*
- (c) *Compliance with applicable requirements*
 - (1) *Manufacturing arrangements*

§ 1271.160 Establishment and maintenance of a quality program.

- (a) *General.*
- (b) *Audits.*

§ 1271.170 Personnel.

- (a) *General.*
- (b) *Competent performance of functions.*
- (c) *Training.*

§ 1271.180 Procedures.

- (a) *General.*
- (b) *Review and approval.*
- (c) *Availability.*
- (d) *Standard procedures.*

§ 1271.270 Records.

- (a) *General.*
- (b) *Records management system.*
- (c) *Methods of retention.*
- (d) *Length of retention.*
- (e) *Contracts and agreements.*

Current Good Tissue Practice Final Guidance

III. CGTP REQUIREMENTS (§ 1271.150)

- C. How Do I Ensure that Another Establishment with Which I Have a Contract, Agreement or Other Arrangement Complies with CGTP Requirements?
- D. What Steps Should I Take if I Become Aware and Then Determine that the Establishment Performing Any Step in Manufacture for Me is No Longer in Compliance with Part 1271?

V. ESTABLISHMENT AND MAINTENANCE OF A QUALITY PROGRAM (§ 1271.160)

- A. What is a Quality Program?
- B. Which Establishments Must Establish and Maintain a Quality Program?

- C. What is the Role of the Quality Program Regarding Procedures?
- D. What Must I Do When Information is Received From Sources Outside the Establishment, and What Must I Do with this Information?
- E. With Whom Must an Establishment Share Information Pertaining to the Possible Contamination of or Potential for Transmission of Communicable Disease by an HCT/P?
- F. How Can a Quality Program Ensure that Appropriate Corrective Actions Related to Core CGTP Requirements Are Taken, When Necessary?
- G. What Must the Quality Program Ensure Regarding Personnel?
- H. How Does the Quality Program Ensure that Appropriate Monitoring Systems Are in Place?
- I. When HCT/P Deviations Occur, What is the Role of the Quality Program?
- J. What Are the Requirements for Performing Quality Audits of Your Establishment?
- K. Will FDA Review the Quality Audit During Inspection of the Establishment?

VI. PERSONNEL (§ 1271.170)

- A. What Are the Specific Requirements for Personnel at HCT/P Establishments?
- B. How Would I Ensure that Personnel Have the Necessary Education, Experience and Training to Perform Their Job?

VII. PROCEDURES (§ 1271.180)

- C. May I Use Procedures From Established Industry Standards?

XII. RECOVERY (§ 1271.215)

- B. What Are Some Ways that a Recovery Establishment Could Ensure that HCT/Ps Are Recovered 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?
- D. What Are Ways in Which a Processor Receiving HCT/Ps From a Recovery Establishment Under Contract with the Processor Could Verify the Identity of the Donor and Could Ensure That the Donor Records Are From the Same Donor as the HCT/Ps?

XIX. RECORDS (§ 1271.270)

- A. What are the General Requirements for Records?
- B. What Kind of Records Management System Must I Have?
- C. What Are Acceptable Methods of Record Retention?
- D. For How Long Must I Retain my HCT/P Manufacturing Records?
- E. What Records of Contracts and Agreements Must I Maintain?

In summary, regulatory requirements include:

- Tissue donors must be screened for relevant communicable disease and disease agents (RCDADs) and a donor must be determined ineligible who is identified as having a risk factor for, or clinical evidence of, any RCDAD (HIV types 1 & 2, HBV, HCV, human TSEs, *T. pallidum* (syphilis), WNV, vaccinia, sepsis, and risk associated with xenotransplantation).
- Donor eligibility determinations, including donor screening, are considered “core CGTP” requirements and includes contracts, agreements or other arrangements with parties that

perform these functions on behalf of a tissue establishment.

- A quality program must be in place that addresses all core CGTP requirements. Expected functions that must be covered:
 - Establishing and maintaining appropriate procedures relating to core CGTP requirements, and ensuring compliance with respect to such procedures, including review, approval, and revision;
 - Ensuring that procedures exist for documenting information related to core CGTP requirements;
 - Ensuring that appropriate corrective actions relating to core CGTP requirements, including re-audits of activities where deviations have been identified, are taken and documented.
 - Verifying corrective actions to ensure actions taken have been effective and are in compliance with CGTP. Where appropriate, corrective actions must include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence.
 - Ensuring proper training and education of personnel involved in activities related to core CGTP requirements;
 - Establishing and maintaining appropriate monitoring systems as necessary to comply with requirements;
 - Investigating and documenting deviations (and trends) relating to core CGTP requirements. Each investigation must include a review and evaluation of the deviation, efforts made to determine the cause, and the implementation of corrective action(s) to prevent recurrence.

- A quality audit of activities related to core CGTP requirements must be periodically performed for review by management.

- An establishment that performs functions on your behalf must have a quality program that addresses these operations, and it's expected that periodic compliance audits of the establishment are performed. During the audit, you should consider reviewing a representative sample of the donor medical history interview records that were previously provided by the recovery establishment to confirm their accuracy by checking with the source of the information.

- A recommendation is that contracts, agreements or other arrangements describe the responsibilities of all parties. When donor eligibility is determined following a review of records obtained by another establishment, the contract, agreement or other arrangement should specifically identify what records will be obtained, in what format they will be provided, responsibilities for record retention and access, and if the reviewing firm will convey donor eligibility conclusions back to the firm that collected the information.

- Regarding personnel, a sufficient number to ensure compliance with requirements is expected; they must have the necessary education, experience, and training to ensure competent performance of their assigned functions; they can perform only those activities for which they are *qualified* and authorized; and all personnel must be trained, and

retrained as necessary, so they perform their assigned responsibilities adequately.

- Procedures must be established and maintained to meet core CGTP requirements for related steps that the tissue establishment personnel perform. You must design these procedures to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable disease.
- Before implementation of procedures, a responsible person must review and approve them, and procedures must be readily accessible to personnel in the area where the operations to which they relate are performed.
- A “donor medical history interview” must be obtained and it is considered a “relevant medical record.”
- A review of “relevant medical records” must occur. When review of the donor medical history interview is performed you should make inquiries when circumstances indicate that follow-up information might be relevant.
- SOPs must be established and maintained to assure review of relevant medical records is properly conducted.
- SOPs must ensure records, such as the donor medical history interview, are current, complete and reliable as well as accurate, indelible, and legible.
- Records must be maintained concurrently with the performance of each required step and must be as detailed as necessary to provide a complete history of the work performed. Any requirement where an action can be documented involves the creation of a record, which is subject to the requirements for records.
- If other records are “available” and they can include information pertaining to risk factors for relevant communicable disease (e.g., social behavior, treatments), you should make inquiries to obtain all relevant information.
- “Available” means that a record or information exists, or is pending, and can be obtained through due diligence, within a reasonable amount of time. A “reasonable” amount of time is a period of time that would allow for the collection of important information without compromising the utility of the tissue.
- The initial tissue establishment that performed the donor medical history interview should document the findings. The establishment that makes the HCT/P available for distribution should review the records of the findings to make sure that all release criteria (including donor eligibility) were met, and would retain the documented findings.
- You must establish and maintain a records management system. Records must be maintained in such a way as to facilitate review of the HCT/Ps history before making tissue allografts available for distribution. The regulations do not specify the details of a

records management system, but you should organize your records in a useful manner in accordance with the requirements in this section. The recovery establishment must maintain copies of all transferred records and organize them in its records management system.

- You may retain required records as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Equipment that is necessary to make the records available and legible, such as computer and reader equipment, must be readily available. Records stored in electronic systems must be backed up.
- Records must be retained for 10 years after their creation, or at least 10 years after the date of administration of an HCT/P, or if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest.
- A list of the responsibilities of any establishment that performs a manufacturing step for you should be maintained and this should ensure that responsibilities are understood. For-cause and random comparisons of documentation should be performed.
- If non-compliance by a contractor is discovered, you must take reasonable steps to ensure the establishment develops a corrective action plan and you should review the plan and verify that corrective actions have been taken under the establishment's quality program.

V. References

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3. *Medical Standards*, EBAA, Washington, DC, current edition
4. U.S. Department of Health and Human Services, Food and Drug Administration, Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products; Final Rule (69 FR 29785, May 25, 2004).
5. U.S. Department of Health and Human Services, Food and Drug Administration, Final Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), August 8, 2007.
6. U.S. Department of Health and Human Services, Food and Drug Administration, Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement; Final Rule (69 FR 68612, November 24, 2004).
7. U.S. Department of Health and Human Services, Food and Drug Administration, Final Guidance for Industry, Current Good Tissue Practice (CGTP) and Additional

Requirements for Manufacturers of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), December 2011.



Implementation Guidance Document

Uniform Donor Risk Assessment Interview Forms

*Version 2
May 20, 2015*

*Eye Bank Association of America
Suite 1010
1015 18th Street, NW
Washington, District of Columbia 20036
(202) 775-4999 (202) 429-6036 Facsimile*

*American Association of Tissue Banks
Suite 320
8200 Greensboro Drive
McLean, Virginia 22102
(703) 827-9582 (703) 356-2198 Facsimile*

*Association of Organ Procurement Organizations
Suite 300
8500 Leesburg Pike
Vienna, Virginia 22182
(703) 556-4242 (703) 556-4852 Facsimile*

Dedication

The project to create this *Implementation Guidance Document, Donor Risk Assessment Interview Forms*, and support documents is dedicated to all organ, tissue and eye donation professionals involved in communicating directly with donor family members and others to obtain information used to assess a donor's eligibility. These documents have been created to assist with performing this challenging and important part of the donation assessment that requires not only a thorough understanding of technical screening requirements but also compassion, patience, and empathy when interacting with acutely bereaved individuals. Providing this service is personally demanding in a number of ways, and you are recognized for your dedication and sacrifices. The important role you fulfill results in successful transplantation for many.

Respectfully,
Your colleagues

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Scott A. Brubaker (co-editor, AATB liaison)
Amanda Nerone (co-editor)
Stephanie Willson (co-editor, CDC/NCHS)

Paula Applegate
Melissa Bendel
Brian Bricker
Karen Cameron
Jacob Chrzanowski
Jennifer DeMatteo
Peter Dow
Jennifer Drago
Susan Grunow
Arnitha Lim
Bruce Nicely
Nicholas Nuttall
Jami Otis
Ashlee Parra
Diana Ponce-Martel
Reva Riggins
Heather Shank-Givens
Julie Zabloski

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IMPLEMENTATION GUIDANCE DOCUMENT UNIFORM DONOR RISK ASSESSMENT INTERVIEW FORMS

I. INTRODUCTION

Organ, tissue, and eye (OTE) donation and transplantation professionals have long understood the value of collecting relevant medical, behavioral risk, and travel history information about potential donors to assess infectious disease risk as well as determine factors that can affect the quality of an organ or utility of the tissue. Testing today is greatly improved and valuable, both for detecting infectious diseases and understanding expected organ function, however, gaps remain (i.e., testing ‘window periods,’ health history that assists with predicting long term organ functionality) that can be filled by collecting accurate information from a proxy (or proxies) providing information on behalf of the OTE donor. In the past, OTE donor medical and behavioral risk questionnaires have not been studied to assess interviewee comprehension or interviewer perspectives on the functionality of formats, and these are known to be a root cause of mistakes. After reports of the successful development of a qualified blood donor questionnaire, the OTE donation community started a project to develop similar tools for screening donors for transplantation. To develop these tools, lessons learned from the blood donation community’s experiences were used as well as knowledge and experience from our own professionals involved with interviewing recently grieving donor family members or others in close relationship to the donor.

This *Implementation Guidance Document* outlines expectations and contains useful descriptions and references for the person administering any of the *Uniform Donor Risk Assessment Interview* (DRAI) forms (i.e., Donor >12 years old, Child Donor ≤12 years old, and Birth Mother). Following these instructions and utilization of support documents (see Support Tools) should promote uniformity in donor screening activities and optimize donation outcomes.

To access components and considerations for developing and implementing an effective quality assurance program for personnel performing the DRAI process, refer to the current version of the AATB-EBAA-AOPO Guidance Document titled “*Effective Quality Assurance of the Donor Risk Assessment Interview.*”

A. History and Purpose

The UDHQ-OTE Project was an acronym used for the development of a **Uniform Donor History Questionnaire for Organ, Tissue, and Eye** donors. This project was conceptualized in late 2006 and became a major effort involving experienced professionals from organ, tissue, and eye donation organizations and related associations, as well as government agencies. Its purpose was to create qualified, uniform donor history questionnaires, one for a child donor and one for an adult donor, with supporting documents for use by OTE donation professionals when screening for risks and applying policies used to determine donor eligibility. Supporting documents include this *Implementation Guidance Document*, references, and a flowchart for each interview question.

Historically, questionnaires used to screen OTE donors in the United States (US) and Canada have had problems similar to those identified at the turn of the century by blood donation professionals in North America. These include:

- content and formats that have never been formally evaluated for effectiveness;
- inclusion of questions that are not necessary and can act as distractors;
- incorporation of many long, often compound, questions;
- use of terminology and word phrases that the general public may not comprehend; and
- lack of standardization among organizations, which affects tissue and eye bank quality program review processes and interpretation of answers by organ transplant professionals.

During 2007, a multi-organizational UDHQ-OTE Task Force was formed to begin work on a consensus questionnaire based on screening requirements of regulations and professional standards, best practices from the vast amount of experiences of members, and new concepts learned from the development in the US of a universal blood donor questionnaire, as well as one for donors of cellular therapy products. This new Task Force met periodically by conference call over the next three years. On December 1, 2010 the Task Force released a draft version of a questionnaire to be used for an OTE donor >12 years old, as well as one for a child donor, and requested constructive comments from professionals and the public. Incorporation of these questionnaires can prove to streamline this critical donor risk assessment process and increase satisfaction of all stakeholders involved in providing donor information (the interviewees), those administering the interviews, and those who review the answers to the donor risk assessment questions. These tools are expected to:

- optimize identification of eligible donors;
- minimize errors due to inaccurate rule out;
- accurately identify an organ donor risk designation; and
- reduce complexity to facilitate comprehension by a bereaved interviewee.

The questions were designed to meet requirements and expectations of state, national and international regulations, laws, policies and/or standards. The concept surrounding how the interview can be done has been optimized by use of broad-based *filter questions*, a process that assists with a respondent's understanding of the questions. Further questioning to identify specific risk is only performed when indicated. Sub-questions were developed to gather appropriate, supportive information about the risk being evaluated.

In April 2011, a steering committee, the "UDHQ Stakeholder Review Group," was formed to review more than 500 comments received during the comment period and to finalize the forms. This group included representatives from appropriate government agencies such as FDA/CBER, HRSA, CDC and NCHS, as well as two OPTN/UNOS committees (DTAC, and the OPO Committee), and professional societies, namely, AATB, AOPO, EBAA, NATCO, AST, and ASTS. A few members of the UDHQ Task Force completed the membership of this review

group. They finalized a new draft version of the Uniform DRAI for a donor >12 years old after careful consideration of comments received. Officials from FDA/CBER offered a few final comments for improvement that were incorporated so the form was sure to meet federal expectations when screening human donors of cells and/or tissues. This next version was made available for use on May 7, 2012 by the professional donation and transplantation societies above. Updates to questions occurred in early 2013 to ensure the Uniform DRAI for a donor >12 years old meets expectations of the “*PHS Guideline for Reducing Human Immunodeficiency Virus, Hepatitis B Virus, and Hepatitis C Virus Transmission Through Organ Transplantation.*”

The Uniform DRAI for a donor >12 years old was further scrutinized throughout 2013 by the foremost authority regarding development of effective public health and behavioral history surveys in the US. Professionals from the CDC’s National Center for Health Statistics (NCHS) performed a series of cognitive interviewing studies using a final draft version of the ‘adult’ donor questionnaire. This science-based, qualitative evaluation of the questions was funded by the Office of Blood, Organ and Other Tissue Safety at CDC, via an Interagency Agreement. Authored by Stephanie Willson PhD, a report is available from NCHS: *Cognitive Evaluation of the Donor Risk Assessment Interview (DRAI): Results of Interviews Conducted April – December, 2013.*

The UDHQ Stakeholder Review Group was reformed and, using the report from NCHS, they finalized versions of three DRAI forms released on September 10, 2014:

- *Uniform DRAI - Donor greater than 12 yrs old;*
- *Uniform DRAI - Child Donor less than or equal to 12 yrs old; and*
- *Uniform DRAI - Birth Mother.*

A few support documents/tools have also been issued:

- *Implementation Guidance Document, Uniform Donor Risk Assessment Interview Forms;*
- *Effective Quality Assurance of the Donor Risk Assessment Interview;*
- *Uniform DRAI - Requirements Crosswalk Documents; and*
- Question flowcharts.

An online portal hosted by AATB (at www.aatb.org) is planned to collect constructive suggestions from users. This information will be reviewed regularly by a Stakeholder Review Group and changes made where appropriate. Periodic updates may also occur when any change is announced to requirements (e.g., to policies, regulations, guidance, or standards). If using the Uniform DRAI forms, adherence to published updates is expected.

B. Abbreviations

The following abbreviations are used in this Guidance Document:

AOPO – Association of Organ Procurement Organizations
AATB – American Association of Tissue Banks
AST – American Society of Transplantation
ASTS – American Society of Transplant Surgeons
CBER – Center for Biologics Evaluation and Research

CAN/CSA – Canada/Canadian Standards Association
CDC – Centers for Disease Control and Prevention
CTO – cell, tissue, and organ
DRAI – Donor Risk Assessment Interview
DTAC – Disease Transmission Advisory Committee
EBAA - Eye Bank Association of America
FDA – US Food and Drug Administration
HHS – Health and Human Services
HRSA – Health Resources and Services Administration
LEP – Limited English Proficiency
NATCO – “The organization for transplant professionals”
NCHS - National Center for Health Statistics (a division within CDC)
OPO – organ procurement organization
OPTN – Organ Procurement and Transplantation Network
OTE – organ, tissue, and eye
PHS – Public Health Service
UDHQ – Uniform Donor History Questionnaire
UNOS – United Network for Organ Sharing
US – United States
yrs - years

C. Definitions

As used in this Guidance Document, the following definitions apply:

Donor Risk Assessment Interview (DRAI) – (aka Medical History Interview - FDA) A documented dialogue in person or by telephone with an individual or individuals who would be knowledgeable of the donor’s relevant medical history and social behavior (i.e., a *knowledgeable person*). Alternatively, a living donor may complete a written questionnaire. The relevant social history is elicited by questions regarding certain activities or behaviors that are considered to place such an individual at increased risk for a relevant communicable disease agent or disease (RCDAD).

Filter question – A question asked in order to determine if further questioning is necessary to assess risk.

Knowledgeable person – the person interviewed which can be the donor, if living; the next of kin; the nearest available relative; a member of the donor’s household; other individual with an affinity relationship (e.g., caretaker, friend, significant life partner); and/or the primary treating physician, who would be familiar with the donor’s relevant medical history and social behavior.

II. ORGANIZATIONAL CONSIDERATIONS

A. Compliance Expectations

1. Acceptable Alterations to the Form

Users of the Uniform DRAI forms are strongly discouraged from changing the content or order of any questions, preambles to questions, or the format designed to enhance flow and mental time travel. Alteration of the form removes the ability to apply qualitative analysis findings by NCHS because the interview tool is different from the tested version. Versions with revisions outside the scope listed below may not be presented as a “Uniform DRAI.” Only the following changes are considered acceptable for an organization to title/refer to their DRAI form as a “Uniform DRAI”:

- The name/title of the form can be changed, however, the establishment’s policies and/or procedures should contain a reference that describes the new title’s link to the respective Uniform DRAI form.
- There is space provided in the header on page one to insert the logo of the program using the form as well as their address. Alternative styles can be used to document this information, but provision of the identity of the program is required. Adding information to the area before the first preamble is allowed.
- Information on page one that provides the name of a second person interviewed and their contact information can be adjusted to meet local needs.
- The sequence of questions must remain unaltered, however, individual questions can be removed if not required for that donation. For example;
 - if eye tissue only can be donated and no organs or other tissues, questions not required for eye donation can be selectively removed; and
 - if a test kit being used for HIV-1 **Ab** testing is labeled to include HIV-1 Group O, the questioning associated with HIV-1 Group O risk can be removed.
- If any new questions are added, they can only be inserted before the first numbered question or after the last numbered question.
- Follow-up questioning for a “yes” response to a filter question can include more directions (i.e., in *italics*) for the interviewer to follow. For example, “*If this occurred within the past 12 months ask:*” could be added if it applies, however, eligibility requirements must be met.
- On the Uniform DRAI – Child donor ≤12 years old, a different format or process can be used for instructions at question number 1, however, the actual questions at “1a.” and “1a(i).” cannot be changed. For more information, see Section III. The Interview Form, part C. Special Consideration for a Donor ≤12 years old.
- The Uniform DRAI - Child donor ≤12 years old and the Uniform DRAI - Birth Mother can be combined into a single document, if local policy describes it.

2. Unique Circumstances

Although this guidance document addresses many scenarios, it's not possible to represent all of them. When unique circumstances arise, local policy should provide guidance that meets relevant requirements and there may be a need to consult with, for example, the institution's medical director or the appropriate manager on call.

3. Form Updates

Compliance with published updates of the Uniform DRAI forms is expected within the deadline announced.

B. Local Policies/Procedures

1. Living Donation

The category of "living donor" may include (but is not limited to) a living organ donor or organ donation from an individual in the context of imminent death (e.g., mechanical ventilation willingly discontinued by the patient being treated), reproductive tissue donors, and other tissue donation (e.g., placenta for amnion, skin from abdominoplasty, surgical bone donation, etc.). For these donations, the donor would provide directly their medical, behavioral and travel history. Local policy should dictate how current the living donor's DRAI must be, relative to the donation event, but it is recommended that this donor screening step occurs close to the donation date. Procedural considerations should include how the interview with a living donor must be conducted. If a prospective donor is allowed to self-administer the DRAI questionnaire, consultation with professional staff (such as a donation coordinator) must occur to ensure a dialogue so questions are understood and answers are interpreted correctly.

2. When to Stop the Interview Process

Policy should be established with consideration of written agreements/contracts of local organizations involved in the donation and procurement/recovery process. Direction needs to be clear for organs versus tissue/eye and/or research scenarios. If individual local policy allows, the interview may be stopped for a tissue or eye donor if a definitive risk is identified that indicates the donor is not eligible.

3. Alternative Languages

In order to collect accurate relevant medical, behavioral risk and travel history information about the potential donor, the knowledgeable person must be able to understand and respond to the questions being asked. If it is determined during the conversation with the knowledgeable person that they have a Limited English Proficiency (LEP), every reasonable effort should be made to ensure that the opportunity for donation is provided such as utilization of:

- a professional interpreter service;
- staff fluent in the language; and/or

- a family member or friend of the family to translate.

Regarding use of an alternative language form, see section III., part B. Format and Use.

C. Electronic Use of the Form

The Uniform DRAI forms can be formatted as electronic files, however, the software program used must be capable of providing an audit trail to account for any revisions to the original, concurrent documentation. Note: A fillable PDF (Adobe® Systems Incorporated) version does not meet this expectation. As with all electronic records, the DRAI tool should be programmed to the same security and verification standards. Version identification should be visible on the electronic system (or printed, if applicable) on the screen (or paper). Programming of questions and response choices (e.g., “yes”, “no”, “N/A”) should include audit capabilities for verification of the documenter. If built within an existing electronic documentation system, the DRAI will carry the same expectation for validation of any modifications or enhancements. Policies must be in place if the electronic system is not used and a backup plan must be in place if the electronic system is not working.

D. Approval of Changes

To promote compliance to regulations, laws, standards and policies, any changes to the Uniform DRAI forms must be approved prior to use. Local policy should include notification and/or approval steps (e.g., with a tissue processor making the determination of final donor eligibility/suitability).

E. Document Control

Organizations should implement a plan consistent with their management of internal forms and documents. This may include, but not be limited to:

- naming the document;
- identifying an implementation date;
- assigning a version number;
- approving each version with signatures;
- requiring regular review and training of the form; and
- archiving former versions.

Organizations must have a method to ensure that staff has access to the current version of the form, whether electronic or paper.

III. THE INTERVIEW FORMS

A. Important Concepts and Expectations

- The Uniform DRAI forms are tools designed to optimize the process used to gather relevant information from the knowledgeable person(s) identified to provide medical, behavioral, and travel history for a deceased donor. This tool can also be adapted for use with a living donor of an organ or tissue.
- These interview tools are not intended to assist with policy decisions in all scenarios. For example, actions to take after answers and information have been provided in the Final Questions are at the discretion of users.
- Uniform DRAI forms must be completed concurrently while performing the interview in the question order provided and according to local policies and procedures.
- The questions are designed to meet requirements and expectations of state, national and international regulations, laws, policies and/or standards. If donor criteria between users differ, this can promote confusion, and jeopardize the process uniformity to which donation and transplantation stakeholders have agreed is best.
- Each question is constructed to be as short as possible but with the ability to gather necessary information to cover requirements. Although kept to a minimum, there are a few questions where screening redundancy occurs. Entirely restricting screening for risk to one possibility does not always occur and this is deliberate (i.e., risks related to travel). This allows for interviewees to remember diseases, surgeries, procedures etc. that they may not have thought of with the initial question.
- Use of “she/he*” in questions is intentional to consistently remind the interviewer to mix the appropriate pronoun with other terms with which the interviewee can relate: the donor’s given name; their nickname; or by inserting “your” father, mother, husband, wife, sister, brother, daughter, son, or child (as indicated). By using this approach, the interviewer is afforded real-time instructions throughout administration of the questionnaire, versus simply using “the donor” or “the deceased” to lead off questions.
- The Uniform DRAI forms use the *filter question* approach, which covers a broad topic initially, and when an affirmative answer is given, provides follow-up sub-questions that must also be asked to elicit additional, necessary information/details. Since specific donor eligibility criteria may vary from one facility to another, an affirmative response to some questions may require consultation with the facility’s policies.
- A few questions and preambles include examples to educate the interviewee regarding risk being assessed. For instance, after communicating with officials at FDA, a *filter question* can be used to initially assess sexual risk but only when “sexual activity,” “sex,” or “sexual act” has been defined first for the interviewee. Considering the sensitive nature of this topic, an acceptable preamble and question were developed for each of the

Uniform DRAIs. Additionally, providing examples of these terms aids in reducing the number of questions considered intrusive.

- Our nation's foremost authority on health history and behavioral risk surveys, the National Center for Health Statistics (NCHS), a division of the CDC, analyzed the original DRAI form for a Donor >12 years old. Their qualitative evaluation used cognitive interviewing techniques that included bereaved persons. Users are strongly discouraged from changing any questions, preambles to questions, or question order used on the Uniform DRAI forms because doing so removes the ability to apply findings by NCHS to an adulterated form. If any questions are added, they can only be inserted before the first question or after the last question. The name of the forms can be changed and users are encouraged to identify the form with their name, address, and logo. Refer to section II., part A. Compliance Expectations above.
- Questioning begins with current and recent history, and sequentially proceeds through the past 12 months, past 5 years, then EVER. This mental time travel order is known to enhance the interviewee's ability to recall.

B. Format and Use

A format was selected for the Uniform DRAI forms from a variety of styles. The following points are considered to enhance use, and concepts described in the *Effective QA of the DRAI Guidance Document* and garnered from the *Cognitive Evaluation of the Donor Risk Assessment Interview (DRAI): Results of Interviews Conducted April – December, 2013* apply:

- A quiet area for both the interviewer and interviewee(s) is desired so questions and responses can be clearly heard, and privacy is preferred to maintain confidentiality.
- All *filter questions* are designed to be asked first. In paper format, they appear in the left-hand column.
- Questions must not be skipped unless directed to do so by the questionnaire.
- To optimize interviewee recall, questions are designed to be read in numbered order.
- Questions should be read in their entirety and as written. Specific word choices were intentionally made and further developed after the original DRAI form was tested using cognitive interviewing techniques. Reading questions verbatim is not a requirement unless directed by your internal policy and procedures, but it is highly encouraged.
- Each Uniform DRAI form is intended to facilitate an interactive conversation (dialogue) designed to collect and document pertinent information, but a consistent intent of the questions regarding specific risk must be communicated to interviewees if not read verbatim. Rephrasing questions is discouraged and may miss the intent of a question's assessment of risk.
- In paper format, the No - Yes answer selections are arranged in the middle column vertically instead of horizontally to avoid confusion. If a Yes response is received, sub-questions that must be asked next appear directly across from the Yes selection to promote ease of flow.

- The format provides more space in the column to the right for documenting detailed information for the sub-questions.
- Lines can be added to facilitate documentation for sub-questions and spacing between questions can be adjusted to meet local needs.
- Documentation of answers to sub-questions can be provided in a horizontal fashion instead of vertically. Example: when documenting “What kind?, Where?, and When?” for travel or residency outside the US or Canada, documentation methods can align across the answer area. This may only be practicable for some questions.
- Questions periodically contain instructions to the interviewer that are not read to the interviewee. These appear as text in *italics*.
- The preambles appear in bold type to enhance visibility to the interviewer and are intended to be read to the interviewee to preface questioning. The preambles are part of each Uniform DRAI form and their style was studied when assessing comprehension.
- Time periods (i.e., past 12 months, past 5 years, and EVER) appear in bold type to stress relevance to the interviewer.
- When relevant risk history is known by the interviewee, it must be captured, but there can be instances when an “I don’t know” answer is initially given to a question. It’s important to remind the interviewee(s) to answer to the best of their knowledge. If the answer is again “I don’t know,” then ask “Do you have actual knowledge of...” (be sure to repeat the question in a format that fits the question). Local policies and training should describe how to handle this scenario.
- In cases where the interviewee repeatedly answers “I don’t know,” the interviewer needs to assess if someone else must be interviewed.
- If more than one person is interviewed, refer to local policy for documenting answers to questions.
- If it is determined that an additional person is needed to answer specific questions, document that determination in the “Additional Notes” section. Document which question(s) the second person answered.
- When interviewing one knowledgeable person for two or more donors, or for more than one history (i.e., interviewing a parent about her/his children, or interviewing a child about her/his parents), the interview can be conducted simultaneously, if consistent with organizational policy/procedure.
- Responses should be documented with sufficient detail. Local policies and procedures must define how responses to sub-questions will be documented on the Uniform DRAI.
- Use of a translated form (alternative language) is encouraged when indicated and Compliance Expectations must be met. Refer to section II., part B., listing 3. on page 12.
- Local policy and interviewer training/education should address documentation practices when responses to questions are provided using slang or other descriptions. This can occur for an affirmative (yes) response (e.g., yeah, yep, absolutely, I believe so, etc.) or

for a negative (no) response (e.g., never, nah, he wouldn't do that, I really don't think so, not to my knowledge, etc.).

- Follow good documentation practices as outlined in local policies. Elements may include handwritten or electronic entries (i.e., requirements for use/non-use of N/A boxes, documentation for use/non-use of multiple Uniform DRAI forms).

C. Special Considerations for a Donor ≤ 12 years old

- If a child donor's history includes being fed breast milk in the past 12 months and it was sourced from a person other than the birth mother, local policy should be established to assess risk. Consideration could include whether the breast milk originated from an establishment accredited by the Human Milk Banking Association of North America. Their standards include screening donors for high-risk behavior and testing donors for relevant communicable diseases. Donated milk is pasteurized using validated methods to remove potentially harmful bacteria and viruses. See <https://www.hmbana.org> for more information.
- The Uniform DRAI – Child donor ≤ 12 years old uses EVER in referencing a time period in filter questions. If a yes answer is given, further questioning often begins with “when,” however, “how long ago” could be substituted for “when.”
- Scenarios can occur when a child donor ≤ 12 years old has been continuously hospitalized since birth. In this scenario, the Uniform DRAI – Child donor ≤ 12 years old is not required to be completed, however, the donor's relevant medical records at the hospital shall be used to assess the medical and behavioral history risks required for donor screening per guidance, policies and standards. Note that when completing the Uniform DRAI – Birth Mother form under such circumstances, the otherwise optional interview question regarding family history of CJD must be asked. If the Uniform DRAI – Birth Mother form is not completed in this circumstance (i.e., child's age > 18 months but ≤ 12 yrs, and has not been fed breast milk in past 12 months), the otherwise optional interview question regarding family history of CJD must be asked and documented. The timing of this interview can be adjusted to meet local needs or for certain scenarios. For example, this interview can occur before, during, or after the process when the Document of Authorization is completed.
- Local policy could address a scenario where the child donor is older than 5 years and was fed breast milk within the past 12 months.

D. Special Considerations for the Birth Mother Assessment

Scenarios can arise where the birth mother of a deceased child donor was a surrogate mother or the birth mother received Assisted Reproductive Technology (ART) procedures such as embryo transfers or artificial insemination that resulted in the child donor's birth. Questions regarding risk for communicable disease should be directed toward the woman who had carried the child, independent from the manner in which she was impregnated.

IV. SUPPORT TOOLS

A. Flowcharts for Questions

Flowcharts are provided for questions on the Uniform DRAI forms to guide the interviewer through the interview process and they can also be used for quality assurance purposes. They are intended as a resource that, where indicated, may be revised by programs to reflect local policy as long as eligibility decisions are not made less strict than those indicated by relevant requirements. Users of the Uniform DRAI forms should have policies and procedures that describe acceptable methods for gathering necessary information when a response to a question indicates follow-up is needed. The flowchart for each question can be tailored to meet local policy, when applicable.

Each question is a separate flowchart, and each one contains the following information:

- Question: Question number and the question.
- Donor Eligibility: Provides additional information regarding eligibility considerations
- Note: an optional field related to the specific question.
- Flowchart: Uses standard flow-charting symbols.
 - Square/Rectangle = statement
 - Diamond = question/decision point (Uniform DRAI questions are within red diamonds)
 - Oval = action
 - Arrow = move to next question

Each question ends with an arrow that indicates to “move to the next question,” however, programs must follow their own policies and procedures concerning eligibility determinations based on information collected (which may indicate the donor is not eligible). A condition or history that is not an absolute rule-out can be directed to “Consult your policy.”

B. Uniform DRAI Requirements Crosswalk Documents

Uniform DRAI Requirements Crosswalk documents are available that provide the relationship between questions on each Uniform DRAI form with donor screening expectations from applicable federal regulations, guidance and policies, as well as state laws and professional standards. These documents are updated when any requirements change or when the forms are updated for other reasons.

C. Effective Quality Assurance of the DRAI (AOPO-EBAA-AATB Guidance Document)

This multi-agency guidance document provides expectations and describes best practice for managing an effective Quality Assurance Program that provides a high level of assurance the DRAI process is being performed consistently as intended. It contains direction regarding

components of the program such as: standard operating procedures; staff qualifications, training and competency; sampling plans for quality control measures; auditing examples; and corrective and preventive action including timely notification. The current version can be accessed on the websites of AOPO, EBAA, and AATB.

V. REFERENCES

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Uniform DRAI – Child donor less than or equal to 12 yrs old (current version)

Uniform DRAI - Birth Mother (current version)

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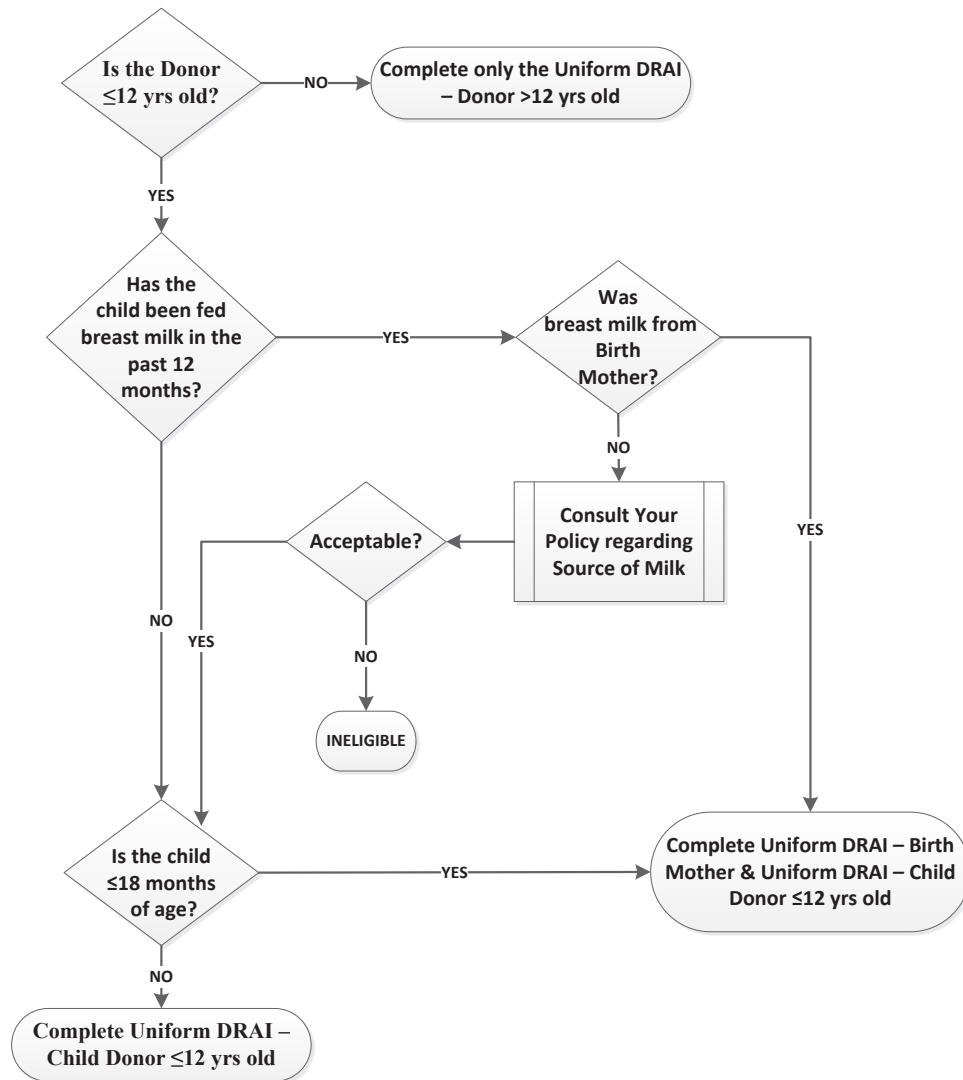
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VI. APPENDIX

A. Child Donor – Form Selection/Decision Flowchart



Note: If the child had been continuously hospitalized since birth, a *Uniform DRAI - Child Donor <=12 yrs old* form does not need to be completed, however, Question #27 must be answered when completing the *Uniform DRAI - Birth Mother* form. If this latter form is also not completed (i.e., child's age >18 months but <=12 yrs, and has not been fed breast milk in past 12 months), the otherwise optional interview question regarding family history of CJD must be asked and documented.

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American Association of Tissue Banks®

8200 Greensboro Drive
Suite 320
McLean, VA 22102
703.827.9582
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About the cover: Scanning electron micrograph of freeze-dried decellularized cancellous bone, taken with a Carl Zeiss Sigma FESEM, magnification 99x. Colorization has been used to accentuate the porous structure of the bone.

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