



# *Guidance Document*

## *Qualification of Packaging and Validation of Shipping/Transport Procedures*

*[No. 9, October 23, 2017]*

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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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**AATB GUIDANCE DOCUMENT**  
***Qualification of Packaging and Validation of Shipping/Transport Procedures***

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**I. INTRODUCTION**

The need to qualify packaging systems used for tissue for transplant is required in AATB's *Standards for Tissue Banking*. There is also a requirement that procedures must be properly validated for transporting tissue and when distributing finished tissue. This guidance was developed to address requirements for packaging used to protect tissue stored and transported in various states such as refrigerated, frozen, lyophilized, dehydrated, cryopreserved, or preserved by another suitable method. For accreditation purposes, a tissue bank's *Quality Assurance Program* should demonstrate compliance to the expectations described in this guidance document. This guidance also standardizes terminology for use by accredited institutions, and references are provided to widely recognized guidelines and requirements used by other professions.

**A. Scope**

This document provides instructions for qualifying tissue packaging systems. Requirements for validating packages at relevant points in the handling of tissue include initial use at recovery or acquisition, through interim stages of tissue processing, then to final packaging. The validation of procedures used to transport tissue is a key element for protection of tissue and is included in the scope of this guidance. This document uses the terms shipping and transport interchangeably.

This document does not cover requirements for labeling or address the use of donor, tissue identification numbers. For detailed expectations for labeling, refer to relevant sections in AATB *Standards*.

**B. Illustrations and Definitions**

**1. Illustrations**

Five figures are provided below for visual representation to aid in the understanding of the concepts of the topics discussed in this document and may not represent the only method available.

Figure 1: Typical Tissue Packaging Systems: Recovery/Acquisition Assembly

Figure 2: Typical Tissue Packaging System: Inner Packaging Assembly

Figure 3a: Typical Transport Container with Refrigerant

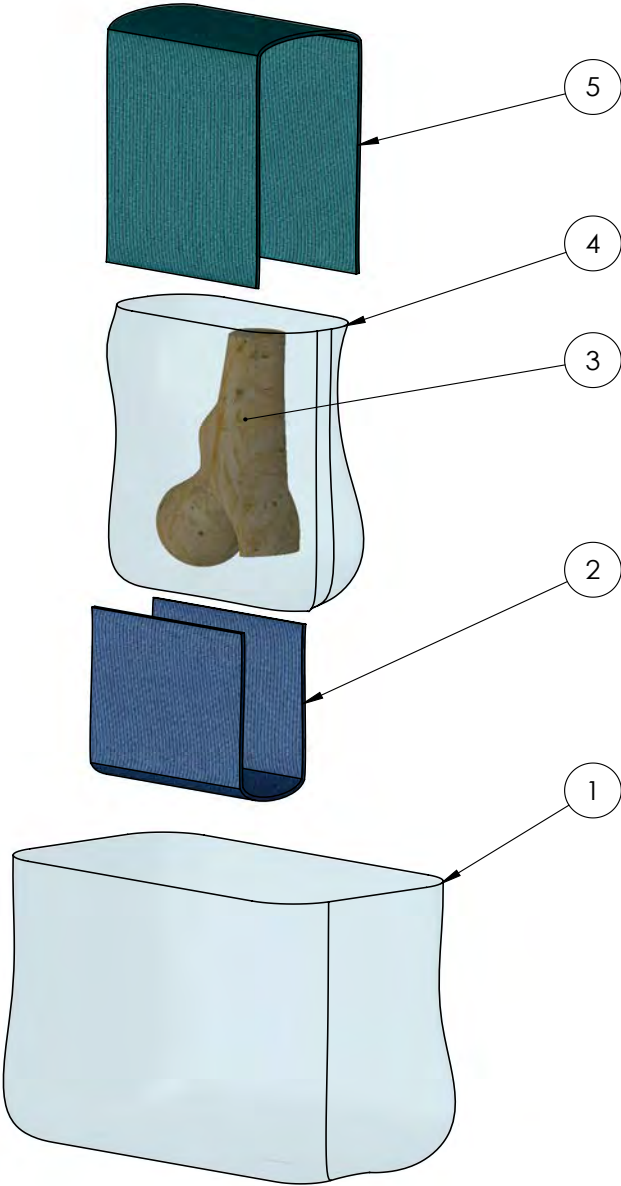
Figure 3b: Typical Transport Container without Refrigerant

Figure 4: Flowchart of Final Packaging System Testing

**Figure 1: Typical Tissue/NAM Packaging Systems: Recovery/Aquisition Assembly**

Note: Other tissue/NAM packaging systems compliant with packaging guidelines may be acceptable.

For labeling, refer to AATB Standards for Tissue Banking



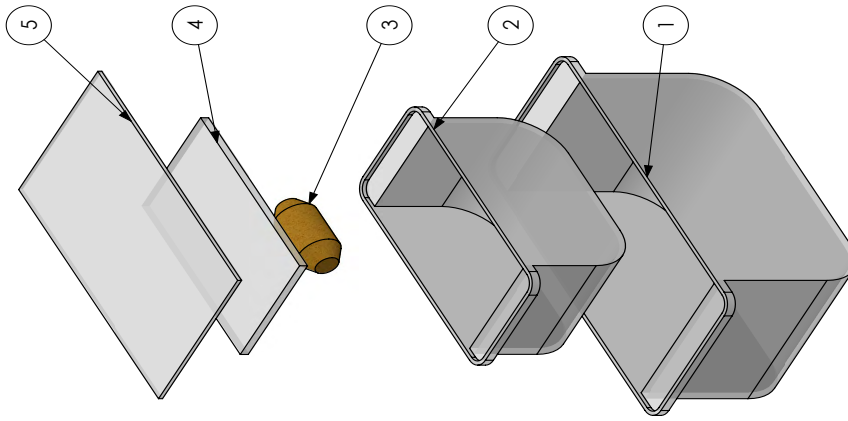
**Primary packaging closed according to AATB Standards**

**\*Refer to definitions provided in the guidance document**

PART #	DESCRIPTION
1	ADDITIONAL PROTECTIVE PACKAGING
2	SECONDARY PACKAGING
3	TISSUE/NAM
4	PRIMARY PACKAGING (INNER MOISTURE BARRIER)
5	PROTECTIVE PACKAGE (INNER WRAPPING)

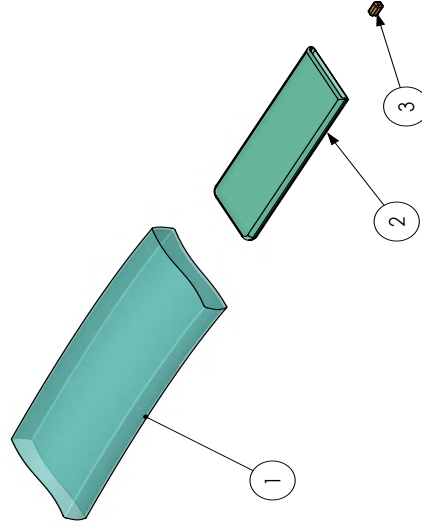
**Figure 2: Typical Finished Tissue Packaging System: Inner Packaging Assembly**  
 Note: Other finished tissue packaging systems compliant with packaging guidelines may be acceptable.  
 For labeling, refer to AATB Standards for Tissue Banking

**Rigid packaging example for finished tissue product (single tissue in two-layer sterile barrier system)**



PART #	DESCRIPTION
1	STERILE BARRIER
2	PRIMARY PACKAGE (RIGID)
3	TISSUE
4	PRIMARY PACKAGE (LID)
5	STERILE BARRIER LID

**Flexible packaging example for finished tissue product (single tissue in two-layer sterile barrier system)**



PART #	DESCRIPTION
1	SECONDARY PACKAGE (OUTER POUCH)
2	PRIMARY PACKAGING (INNER TISSUE POUCH)
3	TISSUE

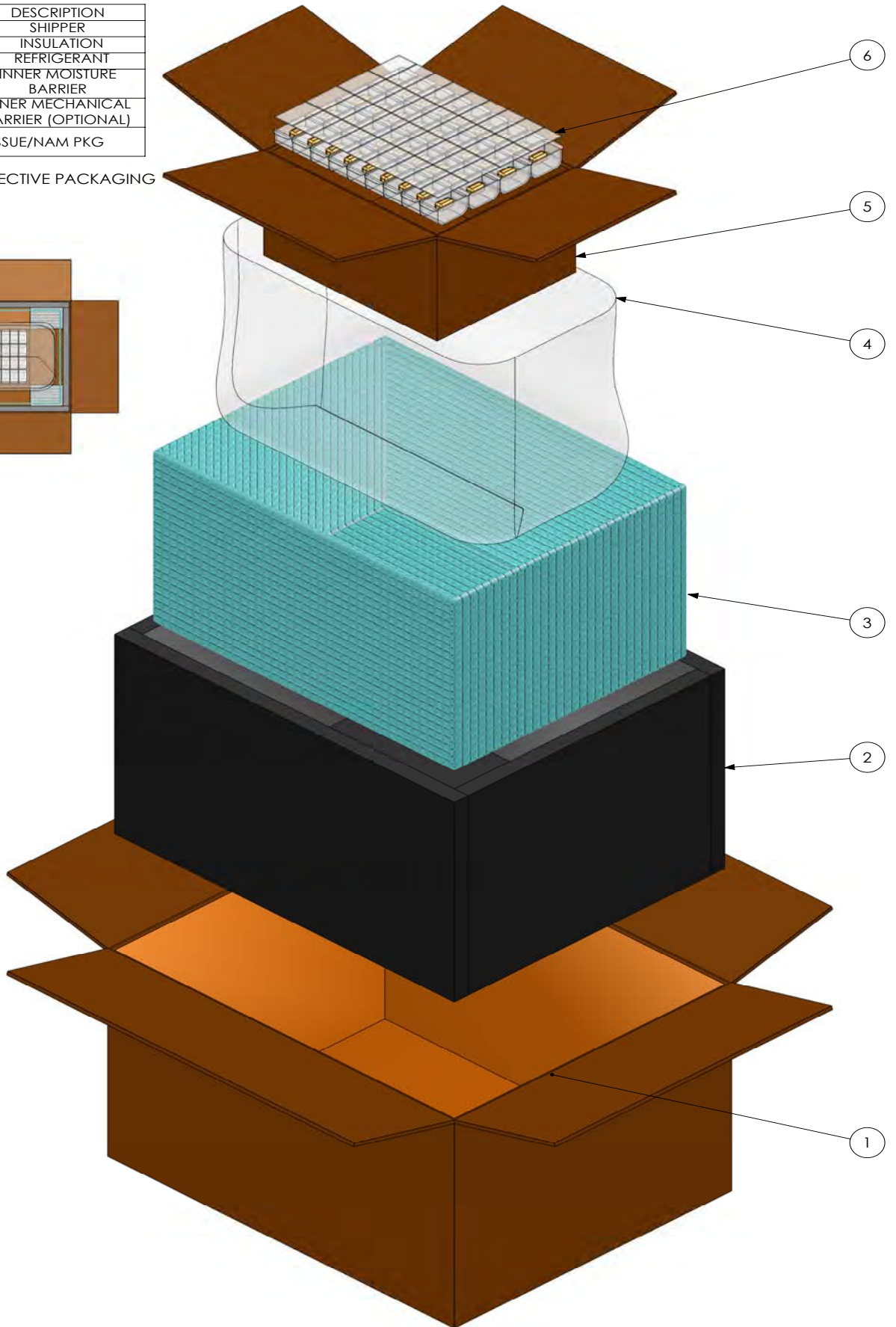
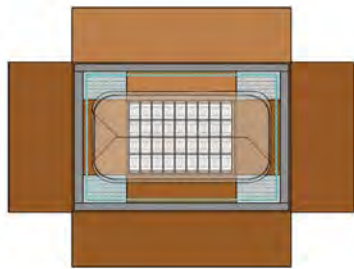


**Figure 3a: Typical Transport Container with Refrigerant**

Note: Other transport container options compliant with packaging guidelines may be acceptable. For labeling, refer to AATB Standards for Tissue Banking

PART #	DESCRIPTION
1	SHIPPER
2	INSULATION
3	REFRIGERANT
4*	INNER MOISTURE BARRIER
5*	INNER MECHANICAL BARRIER (OPTIONAL)
6	TISSUE/NAM PKG

\*ADDITIONAL PROTECTIVE PACKAGING



**Figure 3b: Typical Transport Container without Refrigerant**

Note: Other transport container options compliant with packaging guidelines may be acceptable.  
For labeling, refer to AATB Standards for Tissue Banking

PART #	DESCRIPTION
1	Shipper
2	Packaging Void Fill, e.g. Foam Peanuts
3	Packaged Tissue

\*For labeling, see AATB standards # # #

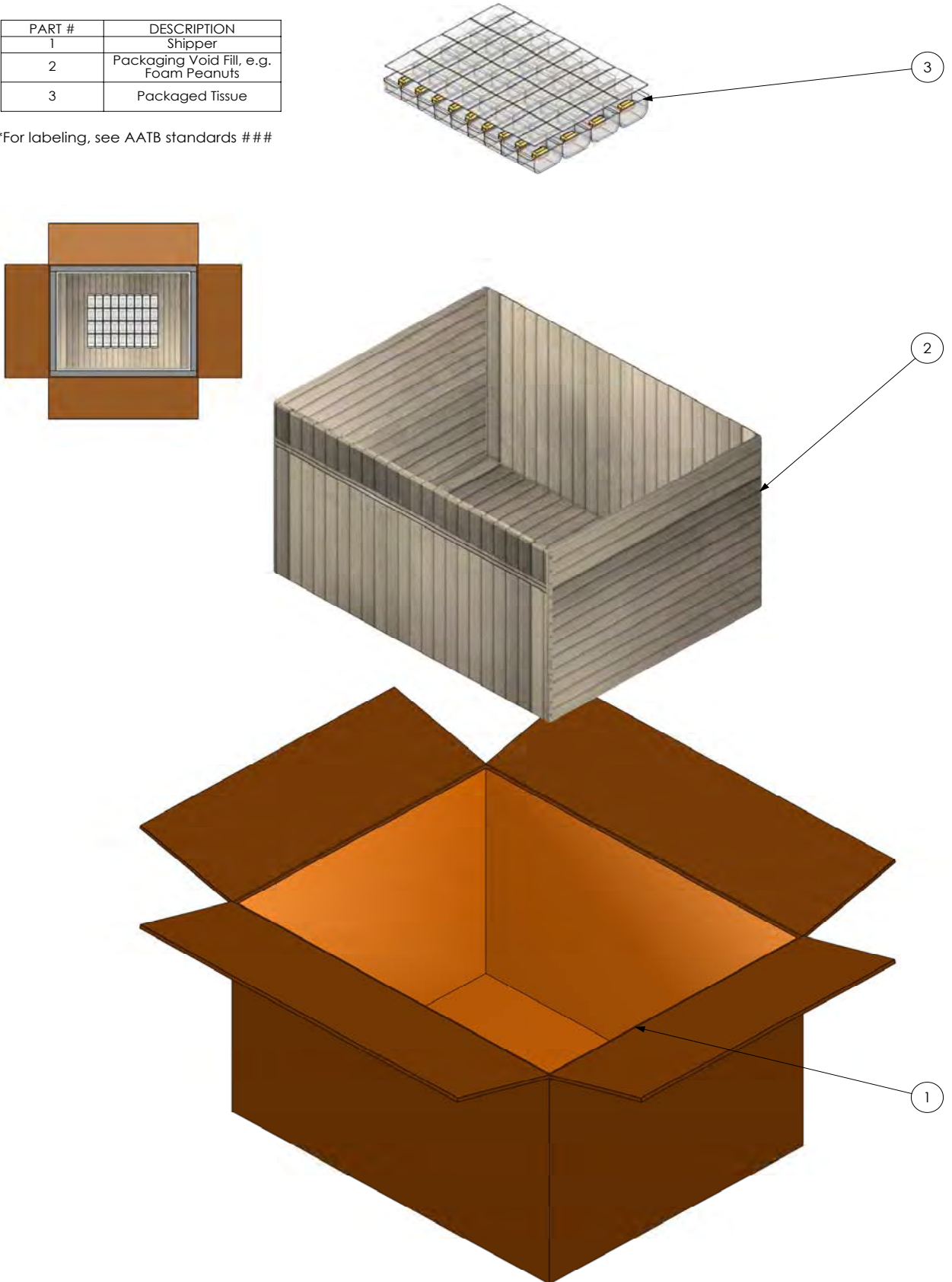
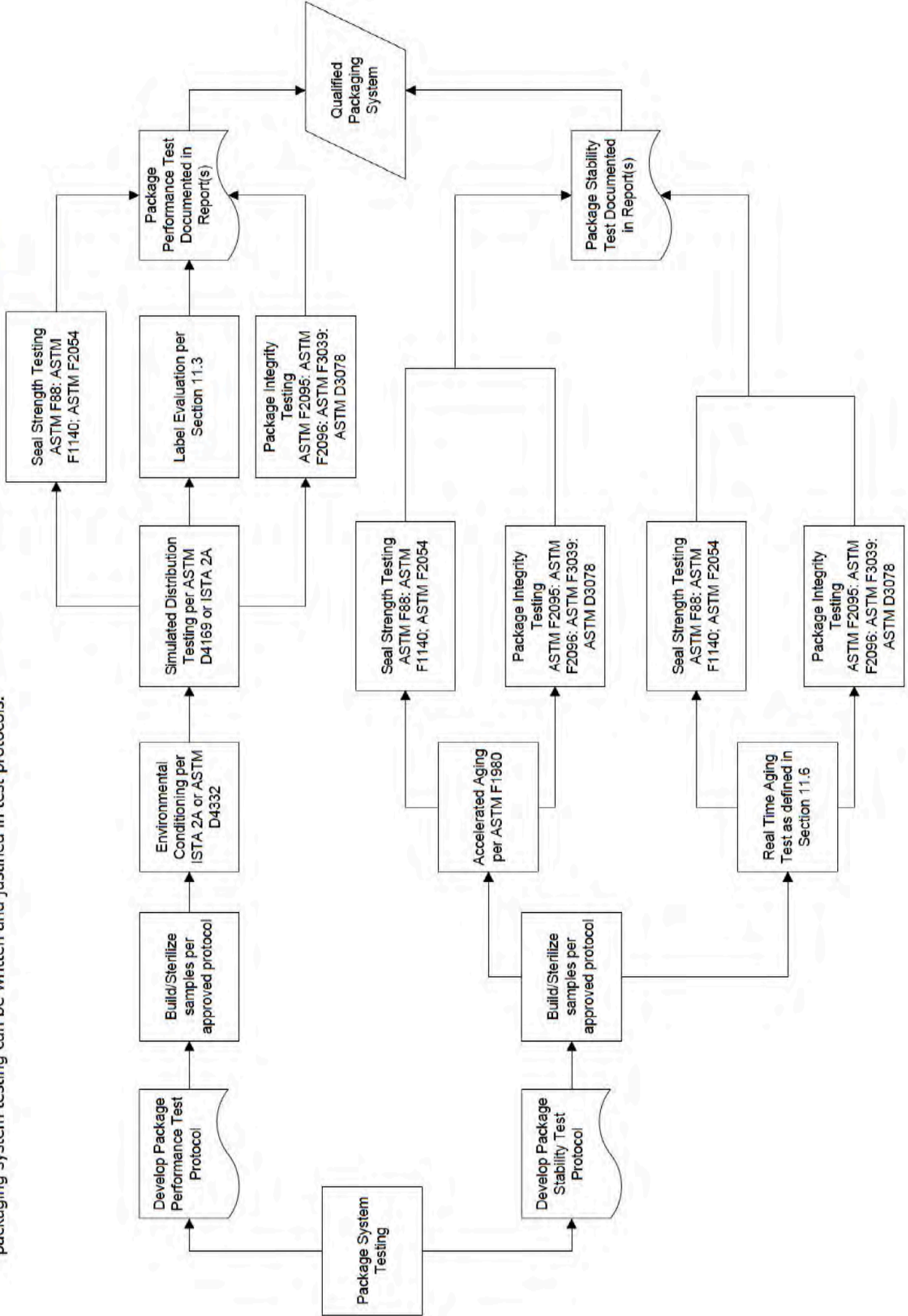


Figure 4: Flowchart of Final Packaging System Testing

## Typical Flowchart of Performance Testing of the Packaging System for Finished Tissue Packaging

Note: This process flow should be used for packaging system testing, which typically begins after package process validation is initiated. This flowchart does not apply to tissue packaged at recovery or for in-process packaging. Modifications that differ from the typical packaging system testing can be written and justified in test protocols.



## 2. Definitions

Words that are defined here also appear in italics throughout the document. 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 “*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 this document, the following terms *shall* be defined as follows:

**Accelerated aging (package):** A technique to simulate the effects of time on the packaging (with or without tissue, as deemed necessary) by subjecting it to elevated temperatures in a controlled environment representative of controlled environment storage conditions.

**Acquisition (BT):** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Additional protective packaging:** Layers beyond the *primary package* and *secondary package* as deemed necessary to protect the *sterile barrier system* during storage, transport and handling.

**Aseptic presentation:** Introduction and transfer of contents from a package using conditions and procedures that exclude microbial contamination (adapted from ISO 11607).

**Aseptic processing:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms

**Bias:** A systematic error that contributes to the difference between the mean of a large number of test results and an accepted reference value (see ASTM Form & Style Manual).

**Change control:** Assessment and determination of the appropriateness of a proposed alteration to the packaging, a procedure or a process.

**Closure:** Means used to close a package where no seal is formed (adapted from ISO 11607).

**Finished tissue:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Fully verified:** 100% inspection that ensures all critical quality aspects of an output have been met.

**Label:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms

**Microbial barrier:** Property of the *sterile barrier system* that prevents the ingress and/or egress of microorganisms under specified conditions (from ASTM F17-2008).

**Microbiological contamination (of packaged tissue):** The entry of viable microorganisms into a finished package due to lack of or loss of *package integrity* (from ASTM F17-2008).

**Package integrity:** The physical capability of a given package to protect its contents with the desired level of protection over a defined period of service; for example, as a barrier to physical, microbiological, or chemical challenges (from ASTM F17-2008).

**Packaging material:** Any material used in the fabrication or sealing of a package or packaging.

**Packaging system:** The combination of *primary package*, *secondary package*, and *additional protective packaging*, as deemed necessary.

**Precision:** The closeness of agreement between test results obtained under prescribed conditions (see ASTM Form & Style Manual).

**Preformed:** A package or *sterile barrier system* that is supplied partially assembled for filling and final *closure* or sealing (for example, pouches, bags, trays and open reusable containers).

**Primary package:** Layer of packaging in direct contact with tissue.

**Process controls:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Processing:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Qualification:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Quality:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Quality Assurance (QA) Program:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Real time aging:** Storage time of packaging (with or without tissue, as deemed necessary) at nominal or normal storage conditions of the product or tissue.

**Recovery:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Repeatability:** Conditions where independent test results are obtained with the same method on identical test items in the same laboratory by the same operator using the same equipment within short intervals of time (from ASTM E177-2014).

**Reproducibility:** Conditions where test results are obtained with the same method on identical test items in different laboratories with different operators using different equipment (from ASTM E177-2014).

**Safety:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Seal integrity:** Characteristics of the seal, which ensures it prevents the ingress of microorganisms under specified conditions; this is demonstrated under test conditions which consider aspects including but not limited to processes relevant to the sterilization, handling, distribution, transport, and storage.

**Seal strength:** Force per unit width of seal required to separate progressively a flexible material from a rigid material or another flexible material, under the conditions of test. A measure of the mechanical strength of the bond between sealed materials of a package.

**Secondary package:** The barrier that surrounds the *primary package* (e.g., the *tissue* can be *sterile tissue* inside, *aseptically processed tissue*, *recovered*, or *acquired tissue*.) Refer to Figures 1 and 2.

**Stability testing:** Provision of evidence that demonstrates how the quality of a substance or product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light.

**Sterile:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Sterile barrier system:** Minimum package that prevents the ingress of microorganisms and allows aseptic presentation of tissue at point of use.

**Sterilization (tissue):** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Sterilization (package):** A validated process used to render packaging *sterile*.

**Sterilization compatibility:** Attributes of the packaging material and/or system that allow it to both withstand the sterilization process and attain the required conditions for sterilization within the preformed package or sterile barrier system. For guidance refer to AAMI TIR 17 Compatibility of materials to sterilization.

**Tissue:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Transport system:** The combination of the *packaging system* and the container utilized to transport tissue.

**Validation (general):** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

**Validation (process):** Documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications (ISO 11607-2:2006).

**Verification:** Reference AATB *Standards for Tissue Banking* at A2.000 Definitions of Terms.

## ***II. QUALITY SYSTEMS AND DOCUMENTATION***

The activities described in this document shall be carried out within a formal quality system, in accordance with FDA 21 CFR Part 1271 and FDA 21 CFR Part 820.

Demonstration of compliance with these packaging guidelines is expected to be documented. This documentation includes, but is not limited to, protocols, performance data, test results, and tissue records. All documentation shall contain traceable signatures and documented *change controls*.

Conditions under which the *packaging materials* or *performed* packages are stored and used should be established, controlled and recorded. Traceability of test or process equipment, process conditions, operators, and materials used shall be maintained.

All documentation, including applicable standards and industry specifications, shall be maintained for a specified retention period. The retention period shall consider factors such as regulatory requirements, expiry date, life cycle and traceability of the tissue.

### **III. TEST METHODS AND SAMPLING PLANS**

#### **A. Test Methods**

Packaging test methods to be used should be evaluated and *validated*.

- This determination of suitability for use should be based on the type of package selected, the purpose and characteristics. The physical properties and interactions with *tissue* and other components should be considered during this evaluation.
- Test methods for packaging vary based on a variety of characteristics of the package, the intended use and the configuration selected.
- Test method *validations* include measures of repeatability and reproducibility created through inter-laboratory studies, wherever possible.
- A list of frequently used test methods for packaging, and whether or not they have a *precision* and *bias* statement, is available in ISO 11607-01, Annex B with a discussion of potentially applicable test methods in ISO 16775, Annex A, Annex C, and Annex O.

#### **B. Sampling Plans**

- Sampling plans need to be constructed based on confidence requirements that will provide reasonable assurance the process is robust and consistent.
- Sampling plans and methods should be established, be adequate for their intended use, and be based on a valid statistical rationale.
- For further guidance on considerations for sampling plans, see ISO 11607-01, Section 4.3 with more details found in ISO 16775, Annex L, ASQ/ANSI Quality Control Standards (Z1.4 & Z1.9).

### **IV. GENERAL REQUIREMENTS FOR PACKAGING**

Prior to use, qualified packaging shall be stored at the *tissue bank* in accordance with manufacturers' instructions, unless *qualified/validated* for intended use or storage. Every proposed package should be shown to be suitable for its intended use:

- it should adequately protect the *tissue* throughout the process until time of use;
- it should be compatible with the *tissue* and any *processing materials* contained within the package;
- if it may be in direct contact with tissue it should be composed of packaging materials that are considered nontoxic and safe for use with the *tissue* or device;
- if the system has performance features, the assembled packaging container closure system should be shown to function properly. For instance, if the tissue is labeled *sterile* it must maintain *sterility* until time of use, if the package is used for *tissue* in process it must be able to be opened without damaging the contents, if the package is used to present the contents at point of use it must be able to deliver it aseptically. Considerations for user requirements should be included when performance features are being designed;
- it should be compatible with chosen type of sterilization process and cycle parameters.

The process of using the intended packaging should be validated, including any equipment used. Package performance testing should be performed on the output of this validated process

Note: Section V contains guidance on assessing suitability for intended use, Section VII on Validating the Packaging Process and Section VIII on Package Performance Testing.

There are essentially three stages where packaging is utilized, requirements may be specific to the stage where the package is intended to be used:

- recovery/acquisition - the critical requirement of this packaging is that it prevents cross contamination and damage to the tissue when in transit from the site of recovery or delivery of birth tissue, to the tissue bank processor or institution acquiring the tissue.
- processing/manufacturing - this packaging must continue to prevent cross-contamination and protect the contents through processing steps, over an extended time to expiry.
- final packaging - this packaging must protect the contents through storage and transport, and permit *aseptic presentation* at time of use. For further guidance on packaging and common *packaging materials* used see Annex B.

## **V. ASSESSING SUITABILITY FOR INTENDED USE**

The process of determination of suitability for intended use is multi step. First, basic requirements should be established by the tissue bank. Packaging materials and packages selected should have a demonstrated capability for meeting those requirements. Next the packaging process should be *validated* using these *packaging materials*. The outputs of that packaging process should then undergo package performance testing to confirm that the packaging is suitable for its specific intended use.



All *packaging materials* and packages should:

- be made of known and traceable *packaging materials*, and provided by qualified suppliers (see K1.300 Purchasing Controls in AATB *Standards for Tissue Banking*);
- be nontoxic, non leaching into the *tissue*. This consideration is especially important for those packaging components which may be in direct contact with the *tissue*, but it is also applicable to any component from which substances may migrate into the *tissue* (e.g., an ink or adhesive);
- have a demonstrated ability to meet the specified physical properties such as basis weight or thickness, dimensional measurement, seal strength, tear or puncture resistance;
- be capable of opening in an aseptic manner without damage to contents;
- provide the *tissue* with adequate protection from factors (e.g., temperature, moisture, distribution environment) that can cause degradation in the quality of the *tissue* until its expiration date. Both duration *and* conditions of storage and transport should be considered;
- protect the tissue from exposure to external contaminants, by maintaining *package integrity* after it is sealed. Potential key considerations are the need for puncture resistance if *tissue* and/or inner layers of packaging are abrasive; if the contents are wet it is important to determine that seals will not be compromised by the presence of the fluid;
- have a demonstrated ability to prevent the ingress of microorganisms under test conditions which consider *sterilization* process, distribution, handling and storage; and
- allow for and be compatible with the *sterilization* processes utilized in the processing and/or sterilization of the tissue. If packaging is to be sterilized prior to use, the packaging should be capable of sterilization in that method as well. For further information on sterilization considerations see ISO 11607-01, Section 5.3 along with some helpful information in ISO 16775, Annex B.
- *labels* or *labeling material* that come in direct contact with *tissue* *should* be nontoxic, non-leaching materials.
- application of *labels* must not damage package or its contents. Pointed writing instruments that could abrade packaging components *should* not be used.
- *labels* must remain intact and legible throughout any sterilization, storage, or transportation.

## **VI. DESIGN AND DEVELOPMENT**

There *shall* be documented procedures for the design and development of packaging.

The design must protect and maintain integrity of the *tissue* and package until time of use, as well as prevent contamination and permit *aseptic presentation* of *tissue*.

Design and development *should* consider many factors, including but not limited to:

- user requirements;
- weight, size, and shape of the *tissue*. Any sharp edges or protrusions must be considered.
- use of fluids (e.g., reagents, preservatives);
- sensitivity of the *packaging material* and the *tissue* to environmental conditions such as light, moisture, shock, and temperature;
- storage and transport, both duration and conditions;
- *sterilization* compatibility;
- special packaging requirements such as housing specific items together, if multiple layers of packaging are used they must be compatible and not damage each other;
- protection requirements of *tissue*, and temperature stability requirements;
- labeling requirements, including identification of tissue, traceability, expiration, storage requirements and directions for use. Include appropriate identifiers. Refer to Section G Labeling in AATB *Standards for Tissue Banking*. For a medical device containing *tissue*, refer to FDA Final Guidance: Unique Device Identification System Small Entity Compliance Guide, issued 8/13/2014.
- conditions of loading and processing requirements;
- fit of *tissue* and other components into the packaging and whether the package is able to meet critical dimension and tolerance; and
- when available, historical use and data for similar packaging.

For further information on Design Inputs see ISO 16775, Annex J.

## **VII. PACKAGING PROCESS VALIDATION**

### **A. General**

Sterile barrier system manufacturing processes shall be validated. This should include processes that take place at a supplier site such as the manufacture of preformed sterile barrier systems. Deviations shall be documented, reviewed and resulting actions approved by persons responsible for validation.

Process validation shall include, at a minimum, an installation qualification, an operational qualification, and a performance qualification, typically in that order. Qualification and validation requirements *should* be determined based on consideration of risk to *safety* and *quality*.

In special circumstances or re-validation processes, the validation sequence may differ and an explanation shall be documented.

Worst case *shall* be defined and have a documented rationale. Worst case can be defined in many different ways depending on the study being performed (minimum sealing temperature, sterilized at the maximum dose, heaviest tissue, minimum/maximum amount of dry ice, etc.). The study parameters *must* be defined by the tissue bank based on the risk to the attribute being assessed and a rationale *must* be documented. (See K1.200 Qualification, Verification, and Validation Requirements).

When similar *sterile barrier system* manufacturing processes are *validated*, a rationale for establishing similarities among *finished tissue* types and identifying the worst-case *sterile barrier system shall* be documented.

Sampling plans *shall* be based on a statistically valid rationale.

## **B. Installation Qualification (IQ)**

The equipment used for sealing *should* be correctly installed and appropriate for intended use. Installation qualification considerations may include but are not limited to the following:

- verification of design features. Manufactured parts meet requirements of the design. Design modifications are to be documented and a rationale for deviations documented and approved. Verification of manufacturer's compliance to tolerances and critical features.
- verify supplier documentation, prints, drawings, and operation and maintenance manuals when available.
- installation of utilities (e.g., electrical power, compressed air (gas) pressure). Equipment should be challenged to recover after sudden loss of a utility, such as a power outage or loss of air pressure.
- environmental conditions such as cleanliness, temperature, humidity, and lighting should be documented and verified as acceptable for use.
- safety features should be addressed, and challenged as applicable. This may include application of warning labels or installation of guards designed for use in pinch point or hot locations.
- operation and preventive maintenance procedures should be established and training conducted and documented.

Any critical function should be controlled and monitored. Where any critical function is equipped with alarms for monitoring parameter limits of operation, the installation qualification should include challenging sensors or other instrumentation linked to control monitoring systems.

Critical process instruments, sensors, displays, controllers, etc. shall be certified as calibrated and have ongoing documented calibration requirements. The calibration interval must be current when any validation activities are performed.

Validation of software-hardware interfaces should include challenging a system to demonstrate it operates as designed and performs the intended functions. Reliability and accuracy, especially if data is collected, can be critical, for example in a case where inspection acceptance and traceability records are affected.

### **C. Operational Qualification (OQ)**

Process parameters are to be established during the Operation Qualification using upper and lower process limits. These parameters are expected to produce packages complying to specification under different and anticipated conditions of manufacture.

Packages formed must meet established acceptance criteria. In establishing acceptance criteria the quality properties to be considered include but are not limited to:

- the package is produced with seals of a specified seal strength and dimension (e.g., width);
- the seals do not contain channels or open seals. Seals should be continuous to enable seal integrity (Note: For packages that contain tissue in solution or dried, it is particularly important to assess that it neither affects seal integrity nor prevents effective seal closure from occurring); and
- the processing of packages does not cause punctures, tears, material delamination or separation.

### **D. Performance Qualification (PQ)**

The performance qualification is run to provide an effective demonstration that the installed equipment and established operating parameters consistently produce packages that meet established acceptance criteria. Any requirements for environmental conditions, e.g. cleanliness, temperature range, humidity, *should* be defined and met. Use of control and monitoring systems as well as documented procedures and specifications challenged in the OQ must be used in the PQ.

A statistically valid sampling plan rationale should be established and be able to determine variability within runs. A minimum of three production runs *must* be performed to measure reproducibility and repeatability. The PQ runs *should* use packages containing actual or simulated *tissue*.

Over multiple runs at nominal operational parameters established in the OQ, packaging specification/acceptance criteria must be met and the process is to be demonstrated as capable and in control.

Operational procedures such as work shifts and personnel changes, equipment setups, material lot changeovers and tooling may be considered as ways to challenge the OQ established conditions and determine the success of quality outcomes.

### **E. Formal Approval of the Process Validation and Ongoing Control and Monitoring**

Each qualification stage requires a documented review and formal approval of the validation activities.

The outcome of the *validation* is the identification of critical process parameters that are monitored to demonstrate control within those parameters and compliance to package quality requirements.

For guidance when revalidation activities may be appropriate, see Section XI.

## **VIII. PACKAGE PERFORMANCE TESTING**

The package designed to maintain the sterile barrier is considered the *sterile barrier system*. *Secondary* and *additional protective packaging* may be employed to protect the *sterile barrier system*, provide labeling and/or facilitate presentation. Lastly, transport containers permit safe and effective transport. For information on evaluation of transport containers see Section IX. For guidance on generating a final packaging system validation protocol, see ISO 11607-2 for performance requirements with reference notes in ISO 16775, Annex I. In this guidance document, see Figure 4 Typical Flowchart of Performance Testing of the Packaging System for Finished Tissue Packaging.

### **A. Conditions of Use**

Performance testing protocols should be drafted based on the anticipated conditions of use. Packaging used for recovery/acquisition, during processing/manufacturing or for *finished tissue*; may all be different in form and have different design requirements to meet.

### **B. Effects of Sterilization**

Effects of sterilization must be evaluated:

- Testing shall be done after the designated sterilization cycle. If multiple sterilization cycles are allowed, performance testing of the packaging must be done after the maximum number of cycles. This applies to terminally sterilized tissue as well as those for which packaging materials are sterilized prior to packaging.
- The labeling, if present during sterilization, must not adversely affect the sterilization process.

### **C. Sample Requirements**

- Package performance testing shall be conducted on the worst-case *sterile barrier system* produced at the specified process limits of sealing and after exposure to all the specified *sterilization* processes and transportation simulation. For further discussion of worst case see ISO 11607-1, Section 6.3 with further help from ISO 16775, Annex H. study parameters must be defined by the tissue bank based on the risk to the attribute being assessed; rationale must be documented. (see K1.200 Qualification, Verification, and Validation Requirements)

- Actual tissue or simulated tissue that adequately challenges the packaging system is to be used during *validations*. Justification for sample selection should be included as part of the protocol development process and/or reporting.

#### **D. Test Requirements/Sterile Barrier Testing**

The following physical tests may be used to demonstrate that the *sterile barrier system* maintained integrity:

1. Package Integrity
  - a. Seal Integrity
    1. Leak Testing per ASTM F2096, ASTM F2095, or ASTM D3078
    2. Dye Penetration Testing per ASTM F1929 or ASTM F3029
    3. Visual Inspection per ASTM F1886
  - b. Whole-Package Integrity
    1. Leak Testing per ASTM F2096, ASTM F2095, or ASTM D3078
2. Seal Strength
  - a. Tensile Strength Testing per ASTM F88
  - b. Burst Test per ASTM F1140 or F2054
3. Labeling
  - a. Application of labels must not damage the package or its contents.
  - b. The labeling, including the IFU, must remain intact and legible until point of use.

Note: If packages contain product immersed in a storage solution care should be taken that the presence of that solution does not impact test results.

#### **E. Tissue Protection Attributes**

The following testing shall be performed as appropriate to determine whether the package adequately protected the tissue:

- visual inspection of tissue for damage;
- functional testing, including ability to present the tissue aseptically, without potential for contamination; and
- verification that packaging material provided intended barrier properties (e.g., oxygen permeation, moisture vapor transmission, maintenance of temperature)

### **IX. SHIPPING/TRANSPORT PROCEDURE VALIDATION**

If the shipping/transport process cannot or will not be *fully verified* and documented, it must be *validated*. The shipping/transport of tissue shall be performed by responsible persons. Packaging

integrity and barrier requirements shall be defined to ensure tissue quality is not adversely affected during transport. Considerations shall include mode of transport, labeling, materials used, regional regulations and capabilities and, if applicable, required environmental conditions.

Thermal parameters and any special occurrence activities such as replenishment of a refrigerant during the course of transport must be considered in the validation.

Transport containers may be utilized to ship tissues following recovery/acquisition, during processing, or distribution of final packaged tissue (finished tissue). Transport containers shall be specified and validated to protect the tissue and ensure sterile barrier packaging integrity. If tissue is required to be transported under controlled temperature conditions, transport containers shall be validated to meet thermal requirements. Validation is recommended but not required if the tissue bank adequately monitors and documents every shipment. For example, for transport within a facility or between facilities, a temperature monitoring system (e.g., datalogger, temperature sensor dots, RFID) can be used to fully verify controlled temperature conditions were met. Documentation upon receipt must include, at minimum, visual inspection of the transport container and the tissue packaging integrity upon receipt.

Note: When transporting samples to testing laboratories, it may be appropriate to verify that transport containers meet expectations regarding sample quality that could affect testing.

If validation is performed by the container manufacturer or third-party laboratory, it is the responsibility of the tissue bank to ensure continued compliance to validation.

Validation conditions shall be representative of the expected environmental conditions and transport hazards that a container will sustain in transport such as climatic conditions, drops, vibration, and impact.

Validation conditions shall include simulated or actual tissue and packaging components. Conditions shall represent the worst-case shipping condition (e.g. minimum and maximum range of actual tissue load and refrigerant if applicable). Note: carrier restrictions (e.g., refrigerant type and weight) should be considered in the configuration.

If tissue is required to be transported under controlled temperature conditions, the validation must include evidence (i.e., data, scientific rationale) the specifications have been maintained during transport.

- Transport simulation per ASTM D3103, ISTA 7D or 7E is the preferred method for testing insulated transport containers to maintain required temperature control of the environment of the tissue and to evaluate the effects of external and internal packaging temperature exposures. Simulation shall be performed using standard test conditions described unless sufficient data has been obtained to establish actual conditions.

The transport validation testing can be performed using simulated or actual environments. Environments should be representative of the range of actual transport conditions. Note: If tissue is to be shipped internationally or domestically, both transport environments should be considered.

Transport simulation per ASTM D4169, ASTM D7386, or applicable ISTA procedure such as ISTA 2A or ISTA 3A are the preferred methods of assuring transport compatibility. Simulation shall be performed using standard test conditions described unless sufficient data has been obtained to establish actual transport conditions.

1. Environmental conditioning shall be included if the transport environment contains climatic conditions that have an effect on the performance characteristics of the tissue, packaging, transport container, or components such as cushioning (additional protective packaging).
2. When evaluating multiple climatic conditions, each condition should be carried out separately. Multiple test conditions can cause a false failure due to their compound effect.
3. It should be noted that different environmental conditions may exist between origin and destination points of a transport cycle and should be considered.
4. In some circumstances, special climatic conditions may need to be considered, such as those given in ASTM D4332, F2825, or D951.

For a list of commonly used transport containers a discussion of potentially applicable test conditions refer to ASTM 4169 and ISTA Test Procedures. A condensed listing is available in Annex G of this document.

## ***X. PACKAGE STABILITY TESTING***

Stability testing shall demonstrate that the *sterile barrier system* maintains integrity over time. For further details on *stability testing*, see ISO 11607-1, Section 6.4 with guidance given in ISO 16775, Annex M. *Stability testing* and performance testing (e.g. shipping, or environmental challenges) are separate entities.

*Stability testing* shall be performed using real-time aging. Accelerated aging shall be regarded as sufficient evidence for claimed expiry dates until data from real-time aging studies are available. Real-time and accelerated aging tests should begin simultaneously.

When expiry dates are based upon *tissue* performance, *stability testing* for *tissue* performance should be conducted along with package *stability testing*.

If accelerated aging tests are performed, a documented rationale for the accelerated aging conditions and test duration chosen shall be established. Care should be taken when defining worst-case temperature and humidity conditions. If there is a predefined temperature and humidity range for storage, the worst-case temperature should be used when calculating accelerated aging duration. For accelerated aging guidance, reference ASTM F1980.

- If including tissue in accelerated aging, it must be established that tissue will not be impacted by the temperatures of accelerated aging or create an effect that would not be present outside of those temperatures.

*Stability testing* will be conducted on the worst-case *sterile barrier system* produced at the established process limits of sealing and after exposure to all the specified sterilization processes.

When it is determined that the tissue does not interact with the specified *sterile barrier system* over time, previously documented data for stability testing shall be sufficient.



## **XI. PROCESS CHANGES AND REVALIDATION OR RE-VERIFICATION**

Documents concerning packaging and sealing, storage, or transport processes shall be covered by a change-control procedure for documenting, verifying, and authorizing change. This includes, but is not limited to, evaluation of the impact of the change on packaging processes or package performance and the rationale for authorizing the change.

Revalidation of packaging and sealing processes or re-verification of package performance shall be conducted if changes are made to the equipment, tissue, packaging materials or packaging process, which compromise the original validation and affect the sterility, safety, or quality of the finished tissue.

The need for revalidation or verification shall be evaluated and documented. Periodic reviews may indicate if revalidation or re-verification is needed. Multiple changes could cumulatively affect the package performance, stability, or validation status of the process. If the situation does not require that all aspects of the original validation be repeated, this revalidation does not have to be as extensive as the initial validation.

The following is a list of changes, which may be considered when reviewing the status of a validated process:

- a packaging materials change that would impact the process parameters;
- a new piece of equipment is installed;
- transfer of processes and/or equipment from one facility or location to another (including within the same facility);
- *sterilization* process changes; or
- negative trends in quality or process control indicators.

## **XII. REFERENCES**

FDA 21 CFR Part 1271 Regulations

FDA 21 CFR Part 820 Regulations

AATB *Standards for Tissue Banking* (current edition)

Commission Regulation (EU) No 722/2012 of 8 August 2012 concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilizing tissues of animal origin

NOTE: For specific requirements cited in Section II and XII see annex A – Applicable Regulatory Requirements

ISO 10993-1 Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process

ISO 11607<sup>1</sup>

ISO 11607-1 Packaging for Terminally Sterilized Devices Part 1: Requirements for materials, sterile barrier systems and packaging systems; and

ISO 11607-2 Packaging for Terminally Sterilized Devices Part 2: Validation requirements for forming, sealing and assembly processes

ISO 16775 Packaging for Terminally Sterilized Devices - Guidance on the application of 11607-1 and 11607-2

ANSI/ASQ Z1.4-2003 (R2013): Sampling Procedures and Tables for Inspection by Attributes

ANSI/ASQ Z1.9-2003 (R2013): Sampling Procedures and Tables for Inspection by Variables for Percent Nonconforming

ASTM F17 Standard Terminology Relating to Flexible Barrier Packaging.

ASTM D3078 Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission

ASTM D4332 Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing

ASTM D4169 Standard Practice for Performance Testing of Transport Containers and Systems

ASTM F1140 Standard Test Methods for Internal Pressurization Failure Resistance of Unrestrained Packages

ASTM F1886 Standard Test Method for Determining Integrity of Seals for Medical Packaging by Visual Inspection

ASTM F1929 Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration

ASTM F1980 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices

ASTM F88 Standard Method for Seal Strength of Flexible Barrier Materials

ASTM F2054 Standard Test Method for Burst Testing of Flexible Package Seals Using Internal Air Pressurization within Restraining Plates

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<sup>1</sup> ISO 11607-1 and ISO 11607-2 are recognized standards for sterile medical packaging while ISO 16775 is a broad guidance resource that contains helpful information not described in detail in ISO 11607-1 and ISO 11607-2.

ASTM F2095 Standard Test Methods for Pressure Decay Leak Test for Flexible Packages with and without Restraining Plates

ASTM F2096 Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization

ASTM F2097 Standard Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products

ASTM F3039 Standard Test Method for Detecting Leaks in Nonporous Packaging or Flexible Barrier Materials by Dye Penetration

ASTM F2638 Standard Test Method for Using Aerosol Filtration for Measuring the Performance of Porous Packaging Materials as a Surrogate Microbial Barrier

ASTM F2981 Standard Test Method for Verifying Nonporous Flexible Barrier Material Resistance to the Passage of Air

ASTM F2475 Standard Guide for Biocompatibility Evaluation of Medical Device Packaging Materials

ASTM F1608 Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method).

ASTM F1249 Standard Test Method for Water Vapor Transmission Rate Through Plastic Film and Sheeting Using a Modulated Infrared Sensor

ASTM D3985 Standard Test Method for Oxygen Gas Transmission Rate Through Plastic Film and Sheeting Using a Coulometric Sensor

ASTM F2203 Standard Test Method for Linear Measurement Using Precision Steel Rule

ASTM D5264 Standard Practice for Abrasion Resistance of Printed Materials by the Sutherland Rub Tester

ASTM F2250 Standard Practice for Evaluation of Chemical Resistance of Printed Inks and Coatings on Flexible Packaging Materials

ASTM D1709 Standard Test Methods for Impact Resistance of Plastic Film by the Free-Falling Dart Method

ASTM D3420 Standard Test Method for Pendulum Impact Resistance of Plastic Film

ASTM F1306 Standard Test Method for Slow Rate Penetration Resistance of Flexible Barrier Films and Laminates

ASTM D1922 Standard Test Method for Propagation Tear Resistance of Plastic Film and Thin Sheeting by Pendulum Method

ASTM D1938 Standard Test Method for Tear-Propagation Resistance (Trouser Tear) of Plastic Film and Thin Sheeting by a Single-Tear Method

ASTM F392/F392M Standard Practice for Conditioning Flexible Barrier Materials for Flex Durability

ASTM F2251 Standard Test Method for Thickness Measurement of Flexible Packaging Material

ASTM D882 Standard Test Method for Tensile Properties of Thin Plastic Sheeting

ASTM D4321 Standard Test Method for Package Yield of Plastic Film

ASTM D3776/D3776M Standard Test Methods for Mass Per Unit Area (Weight) of Fabric

ASTM F904 Standard Test Method for Comparison of Bond Strength or Ply Adhesion of Similar Laminates Made from Flexible Materials

ASTM F2029 Standard Practices for Making Heatseals for Determination of Heatsealability of Flexible Webs as Measured by Seal Strength

ASTM D3103 Standard Test Method for Thermal Insulation Performance of Distribution Packages

ASTM D4169 Standard Practice for Performance Testing of Shipping Containers and Systems

ASTM D7386 Standard Practice for Performance Testing of Packages for Single Parcel Delivery Systems

ASTM F2825 Standard Guide for Climatic Stressing of Packaging Systems for Single Parcel Delivery

ASTM D951 Standard Test Method for Water Resistance of Shipping Containers by Spray Method

ISTA Procedure 2A (2011) Partial Simulation Performance Test Procedure, Packaged-Products 150 lb. (68 kg) or Less

ISTA Procedure 3A: Packaged-Products for Parcel Delivery System Shipments 70kg (150 lb.) or Less (standard, small, flat or elongated)

ISTA Procedure 7D: Temperature Test for Transport Packaging

ISTA Standard 7E: Testing Standard for Thermal Transport Packaging Used in Parcel Delivery System Shipment

BS EN 868-5:2009 Packaging for terminally sterilized medical devices. Sealable pouches and reels of porous and plastic film construction. Requirements and test methods.

### **XIII. ANNEXES**

#### **Annex A**

#### **Regulatory Requirements for Packaging**

The requirements stated below are a sample of sections that directly apply to packaging and packaging validation. They are provided for convenience of reference and may not be the latest or fullest release. This does not represent a comprehensive list of requirements; for example, regulatory requirements for personnel and training apply but are not included here. For additional requirements, please consult the current and complete applicable regulations and standards.

1. **FDA Title 21 CFR Part 1271 -- HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS**

**Subpart D--Current Good Tissue Practice**

**§ 1271.265 Receipt, predistribution shipment, and distribution of an HCT/P.**

**§ 1271.265(d) Packaging and transport** - Packaging and transport containers must be designed and constructed to protect the HCT/P from contamination. For each type of HCT/P, you must establish appropriate transport conditions to be maintained during transit.

**§ 1271.265(e) Procedures** - You must establish and maintain procedures, including release criteria, for the activities in paragraphs (a) through (d) of this section. You must document these activities. Documentation must include:

- (1) Identification of the HCT/P and the establishment that supplied the HCT/P;
- (2) Activities performed and the results of each activity;
- (3) Date(s) of activity; identification of who performed activity
- (4) Quantity of HCT/P subject to the activity; and
- (5) Disposition of the HCT/P (e.g., identity of consignee).

2. **FDA Title 21 CFR Part 820 -- QUALITY SYSTEM REGULATION**

**Subpart K--Labeling and Packaging Controls**

**§ 820.130 Device packaging** - Each manufacturer shall ensure that device packaging and transport containers are designed and constructed to protect the device from alteration or damage during the customary conditions of processing, storage, handling, and distribution.

**Subpart G--Production and Process Controls**

**§ 820.75 (a) – Process Validation** - Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and where appropriate the major equipment validated, shall be documented.

3. European Directive [722/2012] where a CE-marked product's packaging that comes in contact with tissue must be free of animal derivatives

**Annex B**  
**Common Types of Tissue Packaging - Sterile barrier systems**

1. **Common Types of Trays** - typically sealed with foil or Tyvek® lid or used inside a *preformed sterile barrier system*
  - a. polyethylene terephthalate (PET) or Polyethylene terephthalate glycol-modified (PETG)
    - i. common type of resin biocompatible with tissue
    - ii. not capable in high heat sterilizations such as steam or autoclave
    - iii. can be used in ethylene oxide (with porous lid) and radiation sterilization methods
  - b. polyvinyl chloride (PVC)
    - i. contains chlorine, many medical companies moving away from its use
  - c. polypropylene
    - i. can be processed in high heat steam/autoclave sterilization
    - ii. can be damaged in radiation sterilization. Modified resin can be used for Gamma irradiation sterilization
  - d. polycarbonate
    - i. can be processed in high heat steam/autoclave sterilization
2. **Common types of pouches** (*preformed sterile barrier systems*)
  - a. spun bonded polyolefin (Tyvek®) to Film
    - i. Used for gamma irradiation or ethylene oxide (EtO) sterilization
    - ii. Tyvek® porosity allows sterilant gases to enter package
  - b. film to Film and foil to foil
    - i. Typically used for gamma irradiation
    - ii. Breathable vent can be added for EtO sterilization
    - iii. Consider if needed for barrier properties for moisture and oxygen
  - c. paper to paper and paper to Film
    - i. Gamma irradiation or EtO, steam sterilization
    - ii. Porous
3. **Common types of bags** (*preformed sterile barrier systems*)
  - a. vented or header bags
  - b. self sealing bags
4. **Common types of jars/vials**
  - a. types of vials
    - i. plastic
    - ii. glass
  - b. types of stoppers (e.g. rubber, silicone)
  - c. types of caps (e.g. twist, crimp)

**Annex C**  
**Discussion of Test Methods Typically Used in Selection and Evaluation of Packaging Materials and Packages (Sterile Barrier Systems)**

Test methods provide a means to measure characteristics of packaging and packaging materials that can assess suitability of use and as an indirect means of monitoring the manufacturing process. For a list of packaging test methods and information about their established precision and bias refer to ISO 11607-1 Annex B. This annex will provide a brief overview of the ones commonly used for tissue packaging material and package assessment.

*NOTE: Where the term package (or packaging) is used, it includes primary, primary and secondary or sterile barrier system depending on where used and the objective of use.*

**1. Safety Considerations**

- a. Many concerns about package material safety can be addressed through certifications from packaging suppliers. The exception is any interaction between sterile barrier system material and package contents, which is best determined only by the user of the package.
- b. Packaging materials should be nontoxic. Guidance can be found in ASTM F2475 and ISO 10993-1. Typically the packaging supplier can provide this information and address concerns regarding latex, materials of animal origin, heavy metals, etc.,. Complete traceability of a preformed sterile barrier system and its components is maintained by the packaging supplier.

**2. Barrier Requirements**

- a. All sterilizable medical packaging materials for sterile barrier systems must provide an effective microbial barrier. (ISO 11607-1 5.2) In nonporous materials this requirement is met by demonstrating that the material does not permit the passage of air, as detailed in Annex C of ISO 11607 as well as in ASTM F2981. In porous packaging materials, the microbial barrier can be assessed using ASTM F1608 or F2638 Aerosol Filtration Method.
- b. Packaged tissue that must retain or is sensitive to moisture, or which are affected by oxygen or other gases will require packaging materials that provide a specific barrier for the gas or vapor of interest. Water vapor transmission is covered by ASTM F372 and F1249, while oxygen transmission can be quantified by use of ASTM D3985.
- c. Quantification of light permeation can be accomplished spectroscopically, with foreknowledge of the wavelengths of light that are of interest. Manufacturers of medical packaging materials can provide information regarding the barrier characteristics of the material but performance evaluation and validation performed by the user of the package will assess whether a given material meets a specific tissue requirements.

**3. Durability Requirements**

- a. Packaging must permit sterilization as well as protect the tissue until such time as it is needed. The shape and mass of the tissue, the type of additional protective packaging (if applicable), and the transport and storage systems will all play a role in challenging durability. While the only definitive means of establishing the appropriateness is through actual challenge or use, a number of standard physical properties provide a means of judging potential materials for use in a given application. Few if any of these properties represent identically the manner in which a particular tissue will challenge a packaging system. Manufacturers of packaging materials will make available values for some of

these properties, but it is important to remember they serve as a screening tool, and are usually provided as typical values, rather than specification values where rigid tolerances are imposed.

- b. *Puncture Resistance*: the puncture resistance of a material may be important to consider if the tissue contains sharp edges or protrusions that may penetrate the packaging material, destroying its integrity. ASTM D1709, D3420, and F1306 provide guidance.
- c. *Abrasion Resistance*: abrasion resistance is the ability of a surface to withstand the effects of repeated rubbing, scuffing, and scratching. This can occur between the tissue and the sterile barrier system or the sterile barrier system and other layers of protective packaging during distribution. As no test currently exists that is predictive of these effects, packaging system performance testing of actual tissue is usually required.
- d. *Tear Resistance*: the ability of a material to resist tearing or for the material to continue to propagate an initiated tear may be important to the opening features of the sterile barrier system. For example, the materials for a peel open sterile barrier system should be resistant to tearing while the materials for a tear open sterile barrier system should readily propagate a tear. Test methods to assess tear resistance include ASTM D1922 and D1938.
- e. *Flexural Durability*: the ability of a material to withstand damage by repeated flexing or folding is described as its flexural durability. The tissue shape, the type of protective packaging used, and the transport system will determine the importance of this attribute. ASTM F392 provides guidance on testing flexural durability.
- f. *Thickness*: Generally, as the thickness of a material increases its relative durability increases. However, since increasing thickness also increases stiffness, a point may be reached where increased thickness creates a brittle material more prone to flex cracking (reduces flexural durability). Test methods to determine thickness include ASTM D645 and F2251.
- g. *Tensile Strength*: the tensile strength of a material is the maximum force (tension) required to break or fracture the material. It is often referred to as ultimate tensile strength and is expressed as force per unit area. Although the tensile strength will remain consistent, increasing the thickness of a material will increase the force required to break the material. Because the tensile strength measurement is taken at a point beyond the elastic limit or yield point (the amount of force required to permanently deform the material), its usefulness in predicting durability is limited. In fact, tensile strength is often inversely related to durability. ASTM D882 provides guidance on testing tensile strength.
- h. *Elongation*: the difference in length, expressed as a percentage of the original length, when a material is subjected to a tensile load. Typically, elongation at break is reported. Because elongation at break is beyond the elastic limit or yield point (the amount of force required to permanently deform the material), its usefulness in predicting durability is limited. ASTM D882 provides guidance on testing elongation.
- i. *Basis Weight*: the basis weight of a material is its mass per unit area. Test methods to determine basis weight include ASTM D4321 and D3776.



- j. *Bond Strength*: the bond strength is the amount of force needed to separate interlaminar plies of a material. ASTM F904 provides guidance on testing bond strength.

#### 4. Sterile Barrier System Integrity

- a. *Sterile barrier system* integrity is an essential element. The *sterile barrier system* provides confidence that the *tissue* remains in a *sterile* condition to the point of use, and facilitates the *aseptic delivery*. In most cases, loss of sterility is regarded as an event-related phenomenon, i.e., it occurs only in conjunction with a physical breach of the *sterile barrier system*. Hence, it is critical to ensure a packaging system provides an appropriate level of protection, and that an inspection of that packaging system, including the *sterile barrier system*, can reliably serve as a measure of sterility maintenance. Test methods associated with package integrity involve probing for physical breaches in the microbial barrier, due either to the failure of a package (*sterile barrier system*) seal or a failure of the material itself.
- b. *Visual Inspection*: employing ASTM F1886, channel defects in package (sterile barrier system) seals can be detected with good probability. While subject to some material limitations, and insufficient to definitively rule out pinholes and minute tears in sterile barrier system materials, visual inspection is nevertheless a valuable means of monitoring integrity.
- c. *Dye Penetration*: ASTM F-1929 involves the wicking of a dye solution through a channel defect in a porous package. ASTM F3039 is the standard test method for detecting leaks in nonporous packaging.
- d. *Bubble Testing*: ASTM D3078 and F2096 involve submersion of a package (sterile barrier system) in a fluid and the application of a pressure differential. An evolution of gas may indicate the presence of a leak. Best suited for gross leaks, it is commonly employed on packaged tissue that has been subjected to actual or simulated transport conditions to assess package (sterile barrier system) integrity.
- e. *Other Integrity Methods*: alternative techniques include employing CO<sub>2</sub> or helium as a tracer gas, pressure or vacuum-decay measurement, as well as, ultrasonic methods that can characterize leaks and other anomalies.
- f. *Whole package (sterile barrier system) Microbial Challenge Testing*: while there are no universally accepted test methods, they may be appropriate for evaluating the integrity of tortuous path closure sterile barrier system when properly validated.

#### 5. Seal Strength and Burst Strength

- a. *Seal Strength*: the primary means of characterizing package (sterile barrier system) seal strength is to measure the force required to separate two packaging components sealed together. Such a separation may be part of the packaging system design, in order to facilitate aseptic presentation, or it may represent the force required to rupture a permanent (or “weld”) seal. In either case package (sterile barrier system) seal strength measurements are key indicators of the package formation process.

Additionally, in many cases seal strength serves as a measurement to indicate that a process to form the seal is under control, and that confidence exists that the package (sterile barrier system) represents a structurally sound container for the medical device. It

is frequently used to evaluate pre- and post-sterilization seal strength. Seal strength measurements are also used to monitor manufacturing and to ensure a process is in control.

For peelable seals, EN 868-5 can be used as a starting point to determine the minimum seal strength for packaging, however, each tissue bank must establish internal acceptance criteria for the protection of tissue quality.

ASTM F88 is the definitive test method for characterizing seal strength. A tensile testing machine pulls apart two “legs” of a precision-cut seal section at a controlled rate of separation, measuring separation distance and tensile load during the process. Typically seals are tested at several points around the package perimeter. ASTM F88 provides information on the effect of differences in technique.

- b. *Burst Strength*: a means by which an entire package (sterile barrier system) is tested, burst testing involves internally pressurizing a package and noting the impact of that pressure on the package seals. The degradation of seals (creep), the time to package failure (creep to burst), and the ultimate burst strength are measurements obtained by ASTM 1140 (unrestrained) and ASTM 2054 (restrained) test methods.

While burst strength testing probes the entire package (sterile barrier system) at once, it does not apply the force equally to all parts of the package, and necessarily carries more variability in the observed results than peel testing. Burst testing is more typically used for in-process control. When used as a control, tensile seal strength and burst testing should be performed at the time of validation.

## **6. Material Processing Requirements**

- a. Many packaging system specifications and process characterizations are determined through dimensional measurements. Typical dimensional considerations related to device fit and functions are overall length and width, inside length and width, and seal width. Refer to ASTM F2203 for linear measurement guidance.
- b. Sterile barrier system formation and sterility maintenance are dependent on sealability. Packaging materials can seal at a variety of conditions. Therefore the characterization of a packaging material’s sealability may include the following: size of seal window, seal strength, seal evidence (if peelable), and the processability of temperature sensitive materials. It is a common practice to evaluate sealing on lab equipment. Due to the variation in the location of thermocouples, seal tool mass and other factors, sealing conditions may vary from one piece of equipment to another. See ASTM F2029 for further guidance.

## **7. Printing Requirements**

- a. New packaging materials to be printed may need an evaluation for printability. The printability of a material is related to its wettability or surface tension. Surface tension measurement, whether utilizing contact angle equipment, or dyne solutions, can be used to determine the level of surface treatment and/or the printable side of a substrate. Some treated surfaces can degrade, which can affect their printability over time.
- b. Poor ink or anchorage/adhesion to material can affect the appearance and legibility of print. Since the acceptability of the degree of anchorage is specific to each application, an

acceptability criterion needs to be agreed upon by user and producer of packaging material. Printing intended to convey information should have no missing print, smears, smudges, or offset that renders it incorrect or illegible. Printing in the seal area may affect the sealability of a material, as well as the sealing process may affect the ink and /or print legibility. Other considerations may include compatibility with the chosen sterilization process or storage conditions, where temperature and/or chemical resistance could affect printing. The evaluation of printed material often encompasses the use of one or more of the following methods to characterize the level of ink adhesion or other simulated effects on print readability.

- i. Abrasion of printed packaging material in the distribution environment can change the graphic appearance of a packaging system by scuffing, removing, or rendering print unreadable. In laboratory conditions, comparing abrasion resistance of surface printed materials against established standards can approximate the effects during transport and handling. See ASTM D5264 for further guidance.
- ii. The printed surface of packaging system materials may be exposed to chemicals during its life cycle. Chemicals can degrade, soften, smear, and remove printing, which affects its appearance and legibility. The relative resistance to known or expected chemicals needs to be evaluated. For further guidance see ASTM F2250.

## **8. Cleanliness and Particulates**

- a. Foreign material that is on the surface of the packaging system material and that can be brushed or rubbed off is considered loose particulate. Loose particulate should be minimized. The level of particulate inherently present will be dependent upon the packaging material chosen. Size of particulate is frequently estimated using a TAPPI Dirt Estimation Chart.
- b. Foreign material that is embedded between layers of a laminate or within a film, non-woven, or paper, should be minimized. Gels, small particles of resin with higher-than-average molecular weight and that appear as small, hard, glassy particles, are not foreign material and are inherent to many polymer based materials. Carbon particles are bits of parent material that have seen excessive heat in processing. Gels and carbon particles should be considered separately from embedded foreign material particulate.

**Annex D**  
**Recovery/Acquisition Considerations**

- 1. Identify package use**
  - a. Direct contact
    - i. Package/material pre-sterilized
    - ii. Enable aseptic delivery of tissue into processing or re-implantation
  - b. Secondary or additional protective packaging
    - i. Where processing aseptically, may be necessary to pre-sterilize
    - ii. Closure designed to prevent contamination and cross contamination
- 2. Address package handling at recovery/delivery site during aseptic setup**
  - a. Control sources of contamination
  - b. Select leak-proof packaging
  - c. Provide necessary protective packaging layers that withstand defined environmental conditions needed to maintain tissue quality during transit

Note: See Figure 1: Typical Tissue Packaging System: Recovery/Acquisition

**Annex E**  
**In-Process Controls for Packaging**

Processing/storage considerations for tissue not going directly from recovery/acquisition to final packaging/use.

**1. Identify processing steps and points of interaction with packaging**

- a. Aseptic Processing
  - i. Opening features of primary packaging must enable *aseptic presentation* of tissue to the sterile field
  - ii. Package/material is cleaned or pre-sterilized to prevent contamination of the tissue when used during or after processing
  - iii. Packaging must be selected for protection of the tissue
    - 1. Effectively contain moisture for hydrated tissue
    - 2. Effectively prevent moisture from entering package for sensitive dehydrated, freeze dried or lyophilized tissue
- b. Secondary or additional protective packaging
  - i. Where processing aseptically, may be necessary to pre-sterilize
  - ii. Closure designed to prevent cross contamination

**2. Address package handling**

- a. Control sources of packaging material degradation or tissue contamination
- b. Provide necessary protective packaging layers that withstand defined environmental conditions needed to maintain tissue quality during transit

**3. Address temperature and conditions for storage of tissue**

- a. Relative to maintaining tissue quality during storage

**Annex F**  
**Final Tissue Packaging Considerations**

1. Packaging must be selected for protection of the tissue during transport and handling and for the anticipated period of storage to expiration date
2. Effectively contain moisture when necessary to maintain tissue quality
3. Effectively control moisture from entering package when necessary to maintain tissue quality
4. Provide necessary protective packaging layers that withstand defined environmental conditions needed to maintain tissue quality during transit

Note: See Figure 2: Typical Tissue Packaging Systems: Inner Packaging Assembly

## Annex G

### Examples of Typical Transport Container Systems and Discussion of Simulated Test Conditions for Transport Validation

A typical transport container system for tissue may be disposable or reusable and may consist of an outer container, insulation (as applicable), refrigerant (as applicable), and a designated area for tissue.

Note: See Figure 3a: **Typical Transport Container with Refrigerant** and Figure 3b: **Typical Transport Container without Refrigerant**.

Refer to ASTM D4169, ASTM D7386, and ISTA Test Procedures for additional guidance and procedures for performance testing of transport containers and systems using simulated test conditions. This is accomplished by subjecting test units to a sequence of anticipated hazard elements encountered in various distribution cycles.

The following is a typical test cycle that simulates Air (intercity) and Motor Freight (local, single package up to 150 lb.) transportation:

- Hot Environmental Conditioning or Cold Environmental Conditioning (if applicable)
- Schedule A: Manual Handling
- Schedule C: Vehicle Stacking
- Schedule F: Loose-Load Vibration
- Schedule I: Low Pressure
- Schedule E: Vehicle Vibration
- Schedule J: Concentrated Impact
- Schedule A: Manual Handling

Discussion of Hazard Elements and Test Conditions:

1. *Environmental Conditioning* (Atmospheric Conditioning) – intended to determine the ability of a transport container to withstand the hazards of climatic conditions required to maintain internal temperatures of the tissue.
2. Common transport practices include manual handling: may include drop, impact, and stability tests. Intended to determine the ability of the transport unit to withstand the hazards occurring during manual handling, such as loading, unloading, stacking, sorting, or palletizing. The common hazards from these operations are the impacts caused by dropping or throwing. Size, weight, and shape of the transport unit will affect the intensity of these hazards. Several test method options are permitted, including free fall and simulated drop test using shock machines.
3. *Vehicle Stacking*: includes compression test. Intended to determine the ability of the transport unit to withstand the compressive loads that occur during vehicle transport. The required loading must consider the effects of length of time in storage, the alignment or stacking pattern of the container, variability in container strength, moisture content, temperature, previous handling and transportation, method of load support, and vibration.

4. *Loose-Load Vibration*: includes repetitive shock test. Intended to determine the ability of the transport unit and its contents to withstand the repetitive shocks occurring during transportation of bulk or loose loads. The test levels and test method account for amplitude, direction, and duration of the repetitive shocks.
5. *Low Pressure*: includes vacuum test. Intended to provide for the anticipated reduction in pressure when packaged products are transported via certain modes of transport, such as feeder aircraft or by ground over mountain passes. This differential pressure test should be included for products and packages that could be sensitive to a low/high pressure change environment, for example, sealed flexible non-porous packages, liquid filled containers, or porous packages that may be packed in such a manner as to be adversely affected by low/high pressure environments. This test may be deleted when transport containers include primary packages that have a porous material or subject to pressure changes.
6. *Vehicle Vibration*: includes vibration test. Intended to determine the ability of transport containers to withstand the vertical vibration environment during transport. The test levels and methods account for the magnitude, frequency range, duration, and direction of vibration. Two test method options are permitted, sine and random. The two methods are not equivalent; they will not necessarily produce the same results. The random test method results in a better simulation of actual transport vibration environments, and is the preferred method for qualification. The sine test method is often used in conjunction with the random method as a means of determining and observing system resonances.
7. *Concentrated Impact*: includes impact test. Intended to provide a simulation of anticipated low level concentrated impacts as received by packages during sorting operations and in transit. The test is only applicable to lightweight singlewall corrugated transport containers (under 275 Burst or 44 ECT) and plastic film wrapped packages and unitized loads. It may also be applicable to packages with weighted contents or having protruding corners or sharp edges that may puncture container materials.