Technical Information Report

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Guidance for ANSI/AAMI/ISO 11607, Packaging for terminally sterilized medical devices

AAMI
Association for the Advancement of Medical Instrumentation

Guidance for ANSI/AAMI/ISO 11607, *Packaging for terminally sterilized medical devices*

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Abstract: This AAMI Technical Information Report (TIR) provides interpretive guidance for the application of ANSI/AAMI/ISO 11607—1997, *Packaging for terminally sterilized medical devices.* Also provided, in a special annex of this TIR , is a general review of the process of packaging validation.

Keywords: forming, integrity, material, performance, process, qualification, sealing, validation

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This Technical Information Report (TIR) was developed by the Sterilization Packaging Working Group of the AAMI Sterilization Standards Committee. Committee approval of the TIR does not necessarily imply that all committee and working group members voted for its approval.

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NOTE — Participation by federal agency representatives in the development of this Technical Information Report does not constitute endorsement by the federal government or any of its agencies.

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ISO 11607—1997, Packaging for terminally sterilized medical devices, was adopted by AAMI (with ANSI approval) as an American National Standard in 1997 (ANSI/AAMI/ISO 11607—1997). During the review of ISO 11607—1997 for possible adoption, significant questions were raised concerning the wording, definitions and interpretation of the ISO document. It is hoped that this guidance document, as a supplement to the ANSI/AAMI/ISO standard, will answer many of those questions so that the standard can be a more effective document.

This guidance is applicable to ANSI/AAMI/ISO 11607—1997, which is identical to the International Standard, ISO 11607—1997. The guidance contained in this TIR, however, has not been reviewed or approved by ISO/TC 198, Sterilization of health care products, the international technical committee that authored the International Standard.

There are several important points to consider when reading or attempting to implement ANSI/AAMI/ISO 11607—1997, *Packaging for terminally sterilized medical devices*.

- The scope of 11607 is limited to terminally sterilized medical devices. Additional requirements beyond those given in 11607 may be necessary for aseptically processed medical devices.

- ISO 11607 is written in the "translatable" English used in International Standards and ANSI/AAMI/ISO 11607 is taken verbatim from ISO 11607. The words and phrases were selected to facilitate direct translation into the other languages in which ISO standards may be published. To the American reader, however, the text may not always flow easily and may, in some areas, seem cumbersome.

- ANSI/AAMI/ISO 11607 assumes that the user of the standard has a working knowledge of the subject. Further, not all aspects of the full packaging process are covered and it is intended that other supportive information should be utilized. Some of this information can be found in the bibliography (annex D of 11607). However, even for the skilled or experienced user, a review of this information is suggested, and, as will be noted, this bibliography provides only a portion of the available information.

- There are three primary substantive sections of 11607 [materials, forming and sealing, and final (product) package testing] and these sections are interrelated. Although the three sections were separately drafted (and could have been better integrated), the standard should be read and understood in its entirety before focusing on any one section.

- The notes are important. They aid in understanding the specific sections and also provide continuity across sections. They are not, however, requirements.

- The requirements given by 11607 were written to permit flexibility as no one specific requirement is applicable in all situations.

- ANSI/AAMI/ISO 11607 employs both the verb forms "shall" and "should." Specific restrictions on the use of the two verb forms are given in Annex E of the *ISO/IEC Directives — Part 3: Rules for the structure and drafting of International Standards*. In brief, the use of "shall" means the text expresses a mandatory "requirement" whereas the use of "should" indicates that the text expresses a recommendation but is not mandatory.

- References are made within 11607 to three annexes: A, B, and C. Annex A is "normative," meaning it shall be complied with; annexes B and C are "informative," meaning they are provided for information or support but do not contain requirements.

GUIDANCE FOR ANSI/AAMI/ISO 11607—1997, *PACKAGING FOR TERMINALLY STERILIZED MEDICAL DEVICES*

NOTE—The clauses and subclauses of ANSI/AAMI/ISO 11607—1997 that are not referenced in this guidance document were determined to be sufficiently clear and needed no further clarification.

1 Scope

The guidance in this Technical Information Report **(**TIR) applies to ANSI/AAMI/ISO 11607—1997, *Packaging for terminally sterilized medical devices*.

Subsequent clause and subclause numbering in this TIR correspond to the relevant clause and subclause numbering in 11607. Thus, for example, subclause 6.3.2 (seal integrity) of this TIR provides guidance for subclause 6.3.2 (seal integrity) of 11607.

Also provided, as a special annex, is a general review of the process of packaging validation.

2 Normative references

No guidance is provided for this clause of 11607.

3 Definitions

Attention is brought to the definitions of **manufacturer** and **producer** given in 11607. These terms are often used interchangeably in practice, but have specific restricted definitions for the purposes of the American National/International Standard. As defined in 11607, the "manufacturer" is responsible for "packaging and/or sterilizing the device," and the "producer" has the "responsibility for manufacturing the packaging material and/or system."

Sterile package is not explicitly defined in ANSI/AAMI/ISO 11607, but is a packaging system of such construction that it is capable of protecting and maintaining the sterility of the enclosed medical device.

4 Packaging materials

Selection of appropriate packaging materials is a critical step in developing a suitable sterile package for terminally sterilized devices. The material selection process should not be conducted independently of the package design and processing requirements. The importance of evaluating materials within the framework of a total quality system is critical, as is utilization of validated test methodologies and protocols.

A key point in section 4 is the development of sampling plans. The sampling plan should be developed using statistical tools and appropriate rationales.

Throughout section 4, a variety of requirements have been outlined without reference to particular test methods. This was intended by ISO/TC 198 as the standard test methods used can vary among differing

regions of the world. For instance, Gurley porosity is commonly used in the United States while Bendsten is commonly used in Europe. To aid the user, Table 1 of this TIR contains a list of test methods commonly used in the U.S. for determining the specific attributes outlined in section 4 of 11607. This list is not intended to be restrictive as other methods may also be appropriate.

Table 1—Standardized test methods commonly used in the U.S. for satisfying ANSI/AAM/ISO 11607 requirements.

	ASTM	TAPPI	ISO 11607 Reference
Microbial Barrier	F-1608$^{\epsilon 1}$		4.2.3.3
Accelerated Aging	D-756-93		4.3(a)
Gas Transmission	D-1434-82 (1992)		4.1.4(e)
Oxygen Transmission	D-3985-95		4.1.4(e)
Stretch, Tensile Strength	D-638-95 (there is also D638(m)-93)		4.1.4(e)
Tear Resistance	D-1922-94a		4.1.4(e)
Water Vapor Transmission	F-372-94		4.1.4(e)
Basis Weight	D-726-94	T410 om-93	4.1.4(c)
Odor	F-34-92	T483 cm-82	4.1.4(a)
PH		T509 om-96 T435 om-96	4.1.4(f)
Chloride		T256 cm-85	4.1.4(f)
Sulfate		T255 cm-97	4.1.4(f)
Wet Strength (Paper)	D-829-95	Withdrawn	
Thickness	D-645(m)-96	T411 om-89	4.1.4(e)
Porosity (Air Resistance)	D-726-94	T460 om-97	4.1.4(e)
Extraction Resistance	F-34-92		4.1.4(a)
Seal Strength	F-88-94		4.1.5(c), 4.1.6.2(a)
Burst Strength	F-1140-96		4.1.6.2(a)
NOTES ON ASTM—If the designation shows a date with another date in parentheses, as in 82 (1992), this indicates that the standard was reaffirmed without any changes. If the designation shows a lower case letter, as in 94a, this indicates that the standard was current in 1994 and has also undergone one update during that year. If the designation includes an "m," as in D638(m), this indicates that a metric version is available.			
NOTES ON TAPPI—om = official test method; cm = classical test method			

These ASTM standards are the most current versions available at the time this guidance was printed. The user should always determine whether later versions are available that supersede those listed above.

Sections 4.1.4 through 4.1.6 outline a variety of performance requirements that should be considered in the material selection process. Not all of these requirements are appropriate for every device nor is every requirement listed for every conceivable device. The user must apply skill in determining the critical attributes of a material to be used. In addition, many of these attributes should be evaluated after sterilization processing. For instance, gamma irradiation can have a significant effect on mechanical properties of some materials. The material may perform perfectly in a presterilized condition, but poststerilization effects may make it an inappropriate choice for packaging a particular device.

4.1.6.2 (b) Process indicators

Process indicators printed on packages must comply with ISO 11140-1. It is important to note that process indicator standards are not harmonized. The U.S. standard (ANSI/AAMI ST60—1996) contains national deviations to ISO 11140-1 and also provides additional explanations for the requirements.

4.1.7 Reusable containers

Reusable sterilization containers typically used by hospitals or manufacturers for sterilization of instruments and devices are designed for reuse.

4.1.8 Compliance and performance qualification

This section can be confusing without reference to the relevant definitions given in section 3. To put it simply, not every "good material" will result in a "good package." Compliance qualification is documented evidence that the material is appropriate for use in the packaging of terminally sterilized devices as evidenced by the material's conformity with specifications, and is the responsibility of the material producer. Performance qualification is the documented evidence that the packaging meets the requirements for a particular medical device, and is the responsibility of the manufacturer.

4.2.1 Compatibility with the sterilization process, and
4.2.2 Compatibility with the product to be packaged

These sections stress the need to evaluate interactions between the device, the packaging, and the sterilization process. No additional guidance is offered as these sections are sufficiently clear.

4.2.3 Sterile barriers

This section addresses the ability of a material to function as a sterile barrier. The basic assumption is that microorganisms are incapable of transversing an impermeable material, such as a film or rigid tray. The difficulty exists with defining "impermeable" as most materials will allow gasses to pass through them slowly. An impermeable material is identified by meeting the criteria described in annex A. It is important for the reader to understand that manufacturing defects, such as pinholes, may allow microorganisms to pass through otherwise impermeable materials, however, current techniques of microbial barrier testing may not detect such defects. Some research has found that such defects are better detected via physical tests. For further guidance, see Hansen, J., L. Jones, H. Anderson, C. Larsen, H. Miller, M. Scholla, J. Spitzley, and A. Baldwin, "In quest of sterile packaging: Part 1; Approaches to package testing" (*Med. Dev. & Diag. Ind.* 17 [8]: 56-61, 1995) and Jones, L., J.H. Hansen, Anderson, C. Larsen, H. Miller, M. Scholla, J. Spitzley, and A. Baldwin "In quest of sterile packaging: Part 2; Approaches to package testing" (*Med. Dev. & Diag. Ind.* 17 [9]: 72-79, 1995).

If the material is not impermeable, the microbial barrier properties should be assessed. In the U.S., ASTM 1608 is one option for this assessment, but other validated methods are acceptable as well.

5 Package forming and sealing*

ANSI/AAMI/ISO 11607 progresses from material qualification to process qualification. As indicated in 5.2.1, General requirements, the assumption is made that the package design has been qualified prior to process qualification. Thus, the order of ANSI/AAMI/ISO 11607 need not be rigorously followed.

The approach of section 5, Package forming and sealing, is prospective validation. It is grouped into five subsections: equipment qualification, process development, process performance qualification, process control, and process certification and revalidation. It should be noted that the terms "qualification" and "validation" are used interchangeably in this section. Each section of the standard should be viewed as a qualification. The combination of applicable qualifications and the objective evidence that these processes consistently produce results or products meeting their predetermined specifications constitute validation. For further guidance to section 5, refer to the U.S. Food and Drug Administration (FDA) documents entitled "Guidance on General Principles of Process Validation," May 1987, Quality System Regulation (21 CFR 820), and "Medical Device Quality Systems Manual: A Small Entity Compliance Guide," December 1996.

5.1 Equipment qualification

Section 5.1 states that "before starting final process development, it shall be demonstrated that the process equipment and ancillary systems are capable of consistently operating within established design and operating limits and tolerances." The assurances of meeting these equipment qualification requirements are typically achieved through installation and operation qualification. Installation qualification is utilized to establish the confidence that the process equipment and ancillary systems meet the established design requirements or equipment claims. Upon completion of the installation qualification, the equipment can be released for operational and process qualification.

Operational qualification is the dynamic test of a piece of equipment. It (a) verifies that the equipment will perform as intended and includes a full functional test of the equipment and verification of its operating ranges, and (b) defines operating ranges and the development of monitoring and control standard operating procedures. Operational qualification also begins to identify the equipment elements that affect the package, establish environmental control and procedures, and the range of operation.

Separate equipment installation and operation plans are recommended utilizing the six elements (a through f) identified in this section of the standard.

5.2 Process development

5.2.2 Material compatibility, and
5.2.3 Process design

Material variation going into the qualification process should be reduced or eliminated. Material variation can significantly complicate the output of the validation process. Close communication with producers will aid in identifying and understanding the inherent variation. The elements within 5.2.3, Process design, and 5.2.4, Process verification, historically have been included within process (performance) qualification. A separate focus on each is helpful in understanding and ultimately controlling the qualification process.

* Additional guidance on packaging validation can be found in the special annex to this TIR.

Process design requires an assessment identifying and evaluating key parameters along with their operating range, settings and tolerances. Process parameters include those that are controlled during production and those that may not be equipment- or procedure-controlled, such as the environment. To aid in identifying the parameters that have the greatest effect on the process output and the potential interaction of these parameters, the following tools may be useful:

- experiment design;
- process capability studies;
- cause and effect diagrams;
- multi-variant analysis;
- fault tree analysis;
- failure mode and effects analysis; and, most importantly,
- historical information (if available).

Process design challenges the process limits. Upper and lower operating limits shall be established for all key parameters. In establishing these limits, operational conditions that have the highest chance of causing the product or process to fail (worst case) shall be identified. Such conditions do not necessarily induce product failure. They are typically the highest or lowest value of a given control parameter actually evaluated in a validation plan. These conditions are used to establish process limits sufficiently removed from failure or marginal conditions. Product produced at the identified upper and lower operating limits shall be evaluated to the final package requirements. The limits for each parameter need not be singularly evaluated but can be a combination of the worst case conditions.

Several key parameters are identified in 5.2.3.2. In evaluating these parameters, it is recommended that their worst case combinations also be considered. An example of a worst case sealing condition can include running the process at the low process conditions for dwell, temperature, and pressure concurrently.

5.2.4 Process verification

This section evaluates the output of the package validation through examination and test evidence that specified requirements have been fulfilled. Several key properties for evaluation are described in 5.2.4.2.

5.3 Process performance qualification

Use of (a) the process parameters along with their range of acceptable values established in 5.2.3, and (b) the package assessment plan developed in 5.2.4, demonstrates the effectiveness, reproducibility, and reliability of the process to the product specifications and other requirements.

For statistical reliability of the output, 5.3.1 requires “multiple production runs.” Typically, a minimum of three consecutive production runs, including setups, is made. The setups of each run should be distinct and not a continuation of the previous setup. The three runs should be at the same process settings, without making adjustments, to evaluate the process stability. If adjustments are made, they should be justified and evaluated as to the stability of the process.

Section 5.3.2 requires draft procedures and specifications to be developed prior to process performance qualification—key procedure considerations are described in this section. Process performance qualification should be a test of these procedures and specifications in a full manufacturing environment to ensure that the production packaging process will be under control.

5.4 Process control

The process parameters established in 5.2.3 and verified during process performance qualification (5.3), using the measures identified in 5.2.4, form the basis for process control. This information is utilized to establish procedures for process control ensuring conformance to requirements. Control charting of key process parameters (identified in 5.2.3.2) in correlation to the key package attributes (identified in 5.2.4.2) is typically utilized as a measure of process control. Further, to demonstrate process reproducibility, process capability calculated from process control data can be utilized.

All process and product documents must be managed under a change control procedure requiring analysis, verification or revalidation, and change approval.

5.5 Process certification and revalidation

A final step of the validation is the certification of the equipment, process, and product through a documented review and approval process. All documentation supporting certification must be included within a validation report. Section 5.5.1 identifies some of the supporting documentation to be included. Analysis of the data will establish the variability of the process and the adequacy of the equipment and process controls. The validation report should undergo a final review and approval before its acceptance.

Any changes to equipment, product specifications, components, materials, or process that can compromise the original validation and/or affect the ability of the package to maintain sterility, package safety, or efficacy should be validated. Changes also include:

- process revisions;
- unexpected deviations, i.e., increased rejects, stability failure;
- changes to specifications;
- changes identified in process monitoring;
- complaints traceable to the process;
- increased returns, scrap, rework;
- change in supplier (revalidation may not be required if the materials or components from new supplier are absolutely identical to those from old supplier);
- moving of equipment (no need to validate if verification shows no change in operation — good records are required);
- change in equipment (if new model is identical to the original, revalidation may not be required; however, verification is required);
- change in order of operations (no need to revalidate if the process change shows no effect on device performance, conformance to requirements, and process control); and/or
- change in process control software (no need to revalidate process if change in software is prevalidated and software change does not change process).

If root cause of problems can be isolated, revalidation may not be necessary. In several cases, the entire process may not require revalidation for a specific change; however, the impact of the change should be assessed relative to the full process and the product.

It is recommended that revalidation be considered on a periodic basis. However, appropriate monitoring is more important in that, if problems develop or changes are made, there is an immediate review to determine the need for revalidation.

6 Final (product) package

This section outlines the test protocols and methods used (a) to determine the ability of the sterile package (materials and seal closures) to maintain integrity, and (b) to evaluate the ability of the entire package (sterile package along with any outer protective shipping package) to protect the device during distribution, handling, and storage.

Seal and package integrity can be established by any validated visual and/or physical test that demonstrates that the seal and package are impermeable and continuous. These tests, along with microbial barrier testing of porous packaging materials, can be used to establish the capability of a package to maintain package integrity. Some examples of these physical tests that are used for seal integrity, as well as the integrity of the entire package, are outlined in 6.4.

In most cases, these packaging materials are selected for stability testing at a point when the specific device to be packaged has not been determined or the materials are planned for use with a wide variety of devices of varying dimensions, weights, and configurations. At this point, it would not be required to include devices in packages intended for shelf life testing of the packaging materials. In the worst case, information regarding the mass, configuration, and fragility of the device may not be available or the design of the device may not be completed and documented. In situations where a single device or family of devices is planned for a specific sterile package configuration with no anticipated changes in device dimensions, mass, or materials, sterile package integrity maintenance (shelf life) and physical package performance testing (6.5) can be conducted in parallel.

Shelf life testing for sterile packaging materials can be conducted before any specific package designs are developed and documented. Once a particular material combination along with the seal/closure method has been tested and approved for long-term stability and integrity maintenance, these materials can then be configured into a specific design that accommodates the device components to be packaged.

Sterile package integrity maintenance testing (shelf life) and package performance testing are two separate entities. Shelf life testing is normally designed to evaluate the stability of the sterile package materials and seal/closures. These studies should demonstrate that the materials and seals remain stable and maintain integrity over time. Package performance testing evaluates the interaction between the entire package and the device components in response to the stresses imposed by the manufacturing and sterilization processes and the distribution, handling, and storage environment.

6.1 Test selection and sampling

6.1.1 Sampling plans used in establishing test populations can be based on the manufacturer's requirements provided appropriate rationale and documentation are present. Sampling plans for qualification and validation may be different than for routine processing.

6.1.2 No single test detailed in this document is sufficient to evaluate an entire package system. A combination of several tests will likely be required to adequately evaluate the integrity maintenance and performance aspects of the package.

6.1.3 If it is not possible to assemble test packages on a validated line, the packages should be built using processes and equipment that simulate the anticipated manufacturing line as closely as possible. When a

validated assembly line becomes available, it should be used to assemble test packages for a final evaluation or to demonstrate equivalency to the original test packages. Equivalency can be demonstrated by statistically comparing the packages produced by both lines in terms of key evaluations, such as burst or peel strength. It is important that the same assessment method should be used on both lines. This situation often occurs when the design, development, and qualification of a new package design are completed before the actual production equipment is purchased, installed, and validated.

6.2 Visual testing for sterile package integrity

6.2.1 General requirements for visual evaluation of package integrity

A visual evaluation of the sterile package can be a good test for package integrity provided that the test is documented and has been validated. There should be clear requirements for the evaluation, assigned categories for the defects detected, and a course of action if a defect is observed. It is not recommended that visual testing be used by itself for process validation studies.

6.2.2 Inspection method

If the package to be inspected is in its intact condition, it should be inspected for irregularities, such as holes, cracks, or fractures in the barrier materials, loss of seal integrity (open or incomplete seals), dimensional accuracy, and other anomalies, such as foreign material or the presence of moisture or staining.

If the barrier materials are opaque or don't allow a visual examination of the package interior or seals, the package may be opened and examined for the same defects as listed above. Examples of these types of packages are foil pouches, paper-to-paper pouches, or thermoformed blister packages utilizing opaque tray and lidding materials, such as styrene and paper. Care must be exercised in opening and examining the seals so that the act of separating the package materials does not create defects or anomalies that are not present in the intact condition.

6.3 Seal/closure evaluation

6.3.1 General

Medical device package seals are generally evaluated for two critical properties: (a) seal/closure integrity, and (b) seal strength. These are two different attributes, and acceptable results in one do not guarantee success in the other.

6.3.2 Seal integrity

Seal integrity can be established by any validated test that demonstrates that the seal is impermeable and continuous. These tests can be used to establish the capability of a package to maintain package integrity. Some examples of the physical tests used for assessing seal integrity, as well as the integrity of the entire package, are outlined in 6.4.

6.3.3 Seal strength

Seal strength shall be determined at the upper and lower limits of the sealing process. Seal strength testing can also be utilized as a process control tool by observing variations in seal strength values. When

establishing seal strength limits, consideration should be given as to whether the seal is intended to be opened (peelable) upon use or if it is considered a final closure and not meant to be opened by the end user.

6.4 Physical testing for sterile package integrity

6.4.1 Package integrity testing

Physical test methods are an essential part of the evaluation of the integrity of sterile medical device packages. The selection of these test methods should take into consideration the package materials, the package design, and the attributes of the medical device. Examples of four types of physical tests for sterile package integrity are:

a) Internal pressure test—This test increases the internal pressure of the sterile package while submerged in water. Any escaping air bubbles are noted. Allowances should be made when the barrier materials are porous as air escaping through these substrates may not be a defect.

b) Dye penetration test—A penetrating dye solution is injected into the package. Any channels, paths, or voids in the seal area can be observed. Holes, breaches, cracks, and other material defects will also be indicated. Packages may also be submerged or dipped into the dye solution for the detection of the same defects. There are several formulations used for the penetrating solution, usually approximately 99% distilled water with the remainder of the solution consisting of varying degrees of surfactant and a contrasting dye. The more surfactant used, the more sensitive the solution. If the packages being tested have a fibrous barrier material as part of their structure, wicking may occur. Wicking is a phenomenon whereby the capillary action of the dye-penetrating solution allows the liquid to travel along the fibers of the material from one side of the sheet to the other and does not indicate a defect or a potential loss of integrity. Care must be taken to distinguish wicking from the normal detection of defects using dye penetrants.

c) Gas sensing test—The sterile package is pressurized with a traceable gas. Appropriate gas sensors or other measuring equipment is used to detect holes in the materials or paths/voids in the seal. If the packages being tested have a porous material as part of their structure, that portion of the package must be isolated from the test because the trace gases will readily pass through these materials, indicating a false leak. This can be accomplished by the use of masking or gasket materials. When using these techniques, it is important to make sure that any seal defects present are not filled or compressed, which could inhibit detection. An additional consideration for testing using a trace gas sensing system is the high level of sensitivity inherent in this type of system. Inappropriate levels of sensitivity could reject packages for anomalies that do not necessarily indicate a potential loss of integrity.

d) Vacuum leak test—Packages are immersed into a test solution that is contained in a vacuum chamber. A vacuum is applied, and the difference in pressure will force air through any defects in the package structure. Conversely, a vacuum is created within the package after immersion into the test solution. The pressure differential will force the test solution into the package through any defects in the material or seals. In the case of porous materials, it is critical to establish the bubble point or the vacuum level just below the point where the difference in pressure overcomes the forces restricting the flow of the solution through the material. If the bubble point is exceeded, bubbles form or liquid penetrates the pores of the material; this could erroneously indicate a leak.

6.4.2 Sterilization compatibility testing

Sterile packages should also be tested for compatibility with the sterilization process to be used during manufacturing. This includes evaluating the ability of the package to allow the attainment of the proper sterilization conditions within the package and the performance of the package after sterilization. If multiple sterilization runs are allowed, the manufacturer shall ensure that the package has been tested with the maximum number of runs allowed to evaluate the effect on its performance. Examples of some of the potential effects of the sterilization process on the package are partial or complete delamination of the seal (creep), material degradation as the result of heat, moisture, radiation or sterilization chemicals, and the distortion of plastic materials from exposure to the elevated temperatures seen during sterilization and aeration.

6.4.3 Maintenance of package integrity

When packaging materials are selected and combined into a configuration designed to provide a sterile barrier for a medical device, the first characteristic that must be determined is the ability of the packaging materials and seal or closure employed to maintain the sterility of the device over time. The time interval may be determined by the claimed shelf life of the medical device, or, if the device shelf life is indefinite, by the event-related integrity maintenance properties of the package. It should be noted that the loss of sterile package integrity is usually regarded as event-related rather than time-related. Once this time interval has been established, the packaging professional has to establish whether or not the materials and seals/closures remain stable over the expected shelf life of the packaged product. This can be demonstrated by exposing the packages to real-time aging and testing the materials and seals to ascertain if they have deteriorated in terms of strength, structure, visual characteristics, microbial barrier properties, and integrity by exposing the packages and seals to tests for strength and integrity as outlined in 6.2, 6.3, and 6.4.

Accelerated aging tests may be used to simulate real-time testing provided that they are done in parallel with real-time tests and that they are documented along with appropriate rationale. Accelerated aging testing is often used to obtain stability data on packaging materials and seals to allow commercial distribution on a more timely basis. There are several accelerated aging protocols utilized within the medical device industry. An excellent guideline that can be used to develop an aging protocol for medical packaging materials is the AAMI Technical Information Report, *Radiation sterilization— Material qualification* (AAMI TIR 17).

Packaging, constructed from a particular combination of material(s) and seals, should be qualified and tested to demonstrate stability over time. The ability of this combination to protect product and maintain integrity under the conditions of transit and storage should be tested as detailed in 6.4.3.6 of 11607. The package may be evaluated during package design qualification and performance testing as described in 6.5.

6.5 Physical package performance testing

Once the ability of the sterile package to maintain its sterility over time has been established and documented, the materials can be configured for specific devices and components taking into account the mass and dimensions of each device. Outer protective packaging is then added as necessary to provide additional protection during handling and storage and to provide for any literature or product inserts required.

When designing a test program to evaluate the performance of the package in the distribution environment, the manufacturer should select tests that take into account the conditions that can be expected. While these

tests can be conducted using simulated devices, perform at least one test program using packages containing actual functioning devices to assure the package protects the device. Annex B of 11607 details several package performance test methods that allow the engineer flexibility in developing a regimen which reasonably simulates the distribution environment of the manufacturer. Test methods have been developed by the American Society for Testing and Materials (ASTM) and the International Safe Transit Association (ISTA) and are based on several years of testing and data collection for the various types of distribution environments and storage conditions.

Annex A through Annex D

No additional guidance is provided for these annexes of 11607.

Special annex to Technical Information Report 22

Guidance on packaging validation

ANSI/AAMI/ISO 11607—1997 can be used to develop methodologies for packaging validation and, as such, should be viewed as a total process involving (a) the identification of materials and processing variables that affect the ability of the packaged device to meet its acceptance requirements, and (b) the determination of optimal processing criteria for each variable. A key motivation to validate is, of course, to achieve confidence in meeting the requirements and produce a safe and effective medical package. Also important is that validation may reduce inspection, increase output, and result in fewer complaints and less scrap and rework.

Validation—The general elements of validation are the (a) requirements, (b) assumptions, and (c) capability assessment (materials, equipment, and process) supported by a quality system and documented procedure. Validation examines the variation within a package, the variation from package to package, and the variation from lot to lot, as well as the effect of the interactions of all aspects of the entire system—materials, device, design, equipment, process, sterilization, human, environment, and distribution. Validation must be performed by one or more individuals with the necessary education, background, training, experience, and qualifications for the particular functions to be validated. At its onset and upon its completion, the validation program should be documented and approved. An efficient way to achieve these requirements is through design reviews. These reviews also provide a broad input to the process and aid in revisions and further analysis, as required. Additional information can be found in ISO 9001 and the Quality System Regulation (21 CFR 820), effective 1 June 1997.

In current terminology, there are three possible methods to validation: prospective validation, concurrent validation, and retrospective validation.

Prospective validation is performed before the packaged device is commercially distributed. Concurrent validation is also performed before the device is commercially distributed but with the intent to distribute devices produced during validation. As can be noted, these two types of validation significantly overlap in that packaged devices produced during prospective validation are also typically used for sale at commercial release of product. A better definition for concurrent validation would be validation that is performed on product produced for limited commercial applicability, i.e., produced only one or a few times a year. Both prospective and concurrent validation are utilized for new or significant changes to existing products, or when there is a manufacturing process and/or equipment change that may affect the product characteristics and/or quality.

Retrospective validation is performed after the packaged device has been commercially distributed. It is based on the review of historical production, testing, and control data collected and maintained during production. Retrospective validation is difficult to justify because the data may be incomplete or defective in that the right data may not have been collected or the data may not have been collected in a way that allows adequate analysis. Typically, this requires appropriate and accurate product data generated by qualified test methods with the corresponding manufacturing records, procedures, and continuous monitoring of key parameters (controllable and uncontrollable). For these data to be valid, the process must be in control as evidenced by few rejections and complaints. Thus, the general utility for retrospective validation is to review historical results to confirm the validity of an already validated process.

Verification/qualification/validation—There is much confusion over the terminologies of verification, qualification, and validation. To clarify these terms, the following usage is suggested:

The combined test and inspection results for a requirement provide a verification that specific requirements have been met at a point in time.

The combination of verifications for a capability assessment of how well equipment, a process, or a product can perform at a point in time provides a qualification. Specific examples of packaging qualification are:

- materials qualification;
- design qualification;
- installation qualification;
- operational qualification;
- process (performance) qualification;
- product (performance) qualification.

The combination of the appropriate qualifications and the objective evidence that these processes consistently produce a result or product meeting its predetermined specifications constitutes validation. Validation goes beyond verification by establishing that processes produce results or products that consistently meet specifications.

Validation plan or protocol—Although mentioned in several places within the standard but not explicitly described, a validation plan or protocol is recommended. General recommendations for this plan are:

a) clear and concise objectives with criteria for success and the identification of all assumptions including shifts, operators, equipment, components;
b) references to be utilized;
c) a description of the package design configuration to be qualified. This description should include the final product information, such as mass and fragility levels and sale configuration(s);
d) a description of all variation going into the process, such as the inherent variability of the primary package materials, additives, and manufacturing materials;
e) a description of the equipment and process parameters to be monitored and controlled including the methods of monitoring;
f) identification of operators and required operator qualifications;
g) a description of the range of environmental conditions and rationales stating why certain conditions do not require control;
h) identification of the package requirements/characteristics to be monitored and methods for monitoring;
i) the validation process to be utilized identifying its elements of qualifications and verifications;
j) the test method(s) to be utilized supported by rationale for each test along with the means for accurate, complete data collection. Consideration shall be given to the appropriateness, accuracy, reliability, precision, and bias of the test methods and procedures, and the ability to measure the output. All preparations, samples, tests and test sequences to be performed, and acceptance criteria with measurable pass/fail end-points for each evaluation shall be included, as well as statistically sound sample size and sampling plan to achieve reliable data. Testing shall be conducted under conditions that simulate actual product use;
k) the manufacturing and distribution methods, systems and environments, and storage environments;

l) the full data analysis required for each phase of validation and its integration for the full validation assessment;
m) the approval and documentation of the results.

Amendment 1 to AAMI TIR22:1998, *Guidance for ANSI/AAMI/ISO 11607, Packaging for terminally sterilized medical devices*

Note that the title of AAMI TIR22 has been changed to: AAMI TIR22:1998, *Guidance for ANSI/AAMI/ISO 11607, Packaging for terminally sterilized medical devices*. This change was necessary to remove the date of the first edition of ANSI/AAMI/ISO 11607 (1997), since TIR22 as amended applies to the second edition of ANSI/AAMI/ISO 11607 (2000).

General requirements (quality systems, sampling, test methods, responsibilities, and documentation) that were dispersed throughout the first edition of the standard have been compiled and now constitute section 4 in the second edition. Consequently, all sections in this TIR22 that refer to sections 4 and above actually refer to section 5 and above in the second edition, with the exception of 4.1.8 (see table below). A table for cross-referencing specific sections on page 3 of the TIR22 is below:

TIR22 Page Number	1st edition citation	2nd edition equivalent
3	4.1.6.2(b) Process indicators	5.1.8 b) 2)
3	4.1.7	5.1.9
3	4.1.8	4.4
3	4.2.1 and 4.2.2	5.2.1 and 5.2.2
3	4.2.3	5.2.4

All citations on pages 4–11 of the TIR align if one is added to the initial digit (e.g., 6.4.2 in the 1st edition = 7.4.2 in the second edition).

Background of amendment

AAMI TIR22:1998, *Guidance for ANSI/AAMI/ISO 11607, Packaging for terminally sterilized medical devices* was developed to serve as a supplement to the ANSI/AAMI/ISO standard. With the publication of a second edition of the standard (ANSI/AAMI/ISO 11607:2000), a question about revision of this guidance document arose. The Sterilization Packaging Working Group of the AAMI Sterilization Standards Committee recommended that a complete revision of this TIR was not necessary at this time. The guidance is still applicable, although reference to specifically numbered clauses may be different in the second edition.

The goal of the second edition of the standard was to harmonize the materials sections of ISO 11607 and EN 868-1 as much as practicable. These changes were primarily organizational and editorial in nature. Consequently, there are many new notes in the second edition that outline the requirements that would have to be met if compliance with EN 868-1 is desired. While it was the committee's desire that these notes be self explanatory, additional information can be obtained by referring to EN 868-1. Sections on Package Forming and Sealing, and Final (Product) Package did not change.

Approved 24 September 2001
Association for the Advancement of Medical Instrumentation