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Packaging for terminally sterilized medical devices

Emballages pour dispositifs médicaux entièrement stérilisés

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Contents

International Organization for Standardization
Case postale 56 • CH-1211 Genève 20 • Switzerland
Internet central@iso.ch
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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

International Standard ISO 11607 was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products.*

Annex A forms an integral part of this International Standard. Annexes B, C and D are for information only.

Introduction

The process of designing and developing a package for terminally sterilized medical devices is a complicated and critical endeavour. The device components and the package system should combine to create a total product which performs efficiently, safely and effectively in the hands of the user.

The specific nature of the medical device; the intended sterilization method(s); and the intended use, shelf life, transport and storage all influence the package design and choice of packaging materials.

Clause 4 of this International Standard specifies the basic attributes required of materials intended for use in packaging for terminally sterilized medical devices while considering the wide range of potential materials, medical devices, packaging designs and sterilization methods that are available.

Based upon the complexities outlined above, determination that a material is appropriate for packaging of terminally sterilized medical devices should not be made without reference to all parts of this document. European standards providing specifications for particular materials are currently under development as the EN 868 series (see annex D).

The basic requirements described in this International Standard allow either the producer or the manufacturer to conduct a formal qualification to determine if a potential packaging material meets the performance requirements. Once a material has been determined to adequately meet the performance requirements, product specifications may be established by the producer, manufacturer or a regulatory body. From that point in time, compliance qualification of the material can be conducted to demonstrate that the material meets these stated specifications.

The development and validation of packaging operations are crucial to assure package integrity to the users of sterile medical devices. There should be a documented process validation programme demonstrating the efficacy and reproducibility of all sterilization and packaging processes. Along with the sterilization process, some of the packaging operations that can affect package integrity are forming, sealing, capping or other closure systems, cutting and process handling. Clause 5 provides manufacturers with a framework of activities to validate the process used to make and assemble the package.

The microbial barrier properties of packaging materials, together with suitable forming and sealing, are critical for assuring package integrity and product safety. As long as no validated final package challenge method is available or applicable, the barrier properties of materials should be evaluated separately from the effectiveness of forming and sealing.

Clause 6 is intended to assist in the selection of tests and to provide criteria that can be used to evaluate the performance of packages for terminally sterilized medical devices.

It is intended that historical data and supporting rationale are acceptable for use in the verification of requirements of this International Standard.

Packaging for terminally sterilized medical devices

1 Scope

1.1 Inclusions

1.1.1 This International Standard specifies the requirements for single-use materials and reusable containers used for packaging of terminally sterilized medical devices, whether produced industrially or in health care facilities (see clause 4).

1.1.2 This International Standard outlines principal requirements for packaging process development and validation for the manufacturer of terminally sterilized medical devices (see clause 5).

Forming and sealing are considered to be the most critical processes. It is recognized that there are other process operations that can affect the final package, and these are addressed also. Guidelines are provided for the most common practices and techniques.

NOTE — For the purposes of this International Standard, hospitals or other organizations that package medical devices are considered to be manufacturers.

1.1.3 This International Standard specifies requirements for essential criteria used to evaluate the performance of packages for sterile medical devices (see clause 6).

The intent of this International Standard is to provide designers and manufacturers of medical devices with a framework of laboratory tests and evaluations that can be used to qualify the overall performance of the package used to protect device components during handling, distribution and storage.

1.2 Exclusions

1.2.1 This International Standard does not necessarily apply to packaging for products manufactured aseptically; in such cases, additional requirements are necessary to ensure that the packaging and packaging process do not present a source of contamination of the product.

1.2.2 This International Standard does not define sampling plans or the number and duration of replicate runs.

NOTE — Such protocols should be developed by the producer and manufacturer based on the requirements for the particular medical device(s).

2 Normative references

The following standards contain provisions which, through reference in this text, constitute provisions of this International Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this International Standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of IEC and ISO maintain registers of currently valid International Standards.

ISO 186:1994, *Paper and board — Sampling to determine average quality.*

ISO 2859-1:[1], *Sampling procedures for inspection by attributes — Part 1: Sampling plans indexed by quality level (AQL) for lot-by-lot inspection.*

ISO 5636-5:1986, *Paper and board — Determination of air permeance (medium range) — Part 5: Gurley method.*

ISO 11140-1:1995, *Sterilization of health care products — Chemical indicators — Part 1: General requirements.*

3 Definitions

For the purposes of this International Standard, the following definitions apply:

3.1 closure: Means used to close a package where no seal is formed; for example, by repeated folding to construct a tortuous path.

3.2 closure integrity: Condition of the closure which ensures that the closure presents a microbial barrier to at least the same extent as the rest of the packaging.

3.3 compliance qualification: Documented evidence that packaging meets the requirements for packaging for terminally sterilized medical devices based on testing for conformity to an agreed material specification.

3.4 development: Process of refining a prototype design or process to meet established product criteria.

3.5 failure: Event in which a component of the package does not perform one or more of its required functions within the specified limits under specified conditions.

3.6 failure analysis: Logical, systematic examination of an item to identify and analyze the probability, causes and consequences of potential and real failures.

3.7 final package: Primary containment system in which the product is sterilized (excluding shelf cartons and shipping containers) that protects contents to the intended level over a specific period of time (i.e. a barrier to physical, microbial or chemical challenges).

3.8 manufacturer: Natural or legal person, individual or organization with the responsibility for packaging and/or sterilizing the medical device.

3.9 medical device: Any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purposes of

— diagnosis, prevention, monitoring, treatment or alleviation of disease;

— diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;

— investigation, replacement or modification of the anatomy or of a physiological process;

— control of conception;

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.

3.10 microbial barrier: Attribute of the packaging system that prevents the ingress of microorganisms under specified conditions.

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[1] To be published. (Revision of ISO 2859-1:1989)

3.11 labelling system: Assembly of the package label and any supplied information on usage that is included within or in contact with the final package.

3.12 packaging compatibility: Attribute of the packaging material and/or system to allow it to achieve the required performance without detrimental effect on the medical device.

3.13 package integrity: Unimpaired physical condition of a final package.

3.14 performance qualification: Documented evidence that packaging meets the appropriate requirements for sterile packaging based on testing of the particular packaging material for compliance with the applicable requirements of this International Standard.

3.15 producer: Natural or legal person, individual or organization with the responsibility for manufacturing the packaging material and/or system.

3.16 product: Combination of both the medical device and/or additional components with the final package.

3.17 qualification: Documented evidence that all specified design and performance requirements are met.

3.18 revalidation: Documented procedure to reconfirm an established validation.

3.19 seal: Result of joining of the layers, e.g. by use of adhesives or thermal fusion.

3.20 seal integrity: Condition of the seal which ensures that it presents a microbial barrier to at least the same extent as the rest of the packaging.

3.21 seal strength: Mechanical strength of the seal.

3.22 sterile fluid path packaging: System of protective port covers and/or packaging designed to ensure sterility of the portion of the medical device intended for contact with fluids.

3.23 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 final package.

3.24 user: Natural or legal person, individual or organization with the responsibility for making use of the product.

3.25 validation: Documented procedure for obtaining and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications.

NOTE — Validation is considered to be a total process that includes written protocol, evidence that the equipment as installed meets design criteria and specifications (equipment qualification), use of calibrated instruments to collect data, and evidence that the equipment can deliver the process within specified tolerances under established operating conditions and is reproducible as demonstrated by replicate runs and process challenges (process performance qualification).

4 Packaging materials

4.1 Requirements

4.1.1 Quality systems

The activities described within this and subsequent clauses of this International Standard shall be carried out within a formal quality system.

NOTE — ISO 9001 and ISO 9002 specify requirements for suitable quality systems (see annex D). It is not necessary to obtain third-party certification of the quality system to fulfil the requirements of this International Standard.

4.1.2 Sampling

The sampling plans used for selection and testing of packaging materials shall be chosen by agreement between the producer and manufacturer, e.g. acceptable quality level (AQL) in accordance with ISO 2859-1 or ISO 186, or statistical process control (SPC). For each plan chosen, a rationale shall be documented.

4.1.3 General requirements

4.1.3.1 The intention of packaging for terminally sterilized medical devices is to maintain the sterility of the product with respect to its intended use, shelf life, transport and storage conditions.

4.1.3.2 Raw materials used for the manufacture of packaging materials may be virgin or reclaimed materials provided that the source, history and traceability of all raw materials, especially recycled materials, are known and controlled to ensure that the finished product will consistently meet the requirements of this International Standard.

NOTE — With current commercial technologies, it is unlikely that reclaimed material other than manufacturing waste will be sufficiently controlled to allow its safe use for packaging for terminally sterilized medical devices.

4.1.3.3 The packaging design and processing requirements shall be reviewed and applied against the material chosen. This should include effects of the sterilization process. Clauses 5 and 6 of this International Standard provide relevant performance criteria.

4.1.3.4 All test methods used to show compliance with this International Standard shall be validated and documented.

4.1.3.5 The following material properties shall be evaluated with appropriate test methods agreed by the producer and manufacturer:

a) microbial barrier;

b) toxicological attribute;

c) physical and chemical properties;

d) compatibility with respect to sterilization processes with which the material is intended to be used;

e) compatibility with respect to forming and sealing processes (see clause 5);

f) any shelf-life limitations for presterilization and poststerilization storage of the packaging material.

4.1.3.6 Listed in 4.1.4 through 4.1.7 are some essential performance requirements that shall be considered for packaging for terminally sterilized medical devices. This list is not intended to be all-inclusive. The manufacturer shall decide the material characteristics that are necessary for each particular application. Materials which have characteristics not listed in clause 4 can be evaluated using the performance criteria given in clauses 5 and 6.

4.1.4 General performance requirements

General packaging materials, e.g. wrapping materials, paper, plastic film or nonwoven high density polyethylene (HDPE), shall meet the following requirements.

a) Materials shall be nonleaching, nontoxic and odourless to such an extent that neither performance nor safety is impaired and the medical devices with which they are in contact are not adversely affected.

b) Materials shall be free of holes, cracks, tears, creases or localized thickening and/or thinning sufficient to impair functioning.

c) Basis weight shall be consistent with the producer's stated value.

d) Materials shall exhibit an acceptable level of cleanliness;

e) Specific or minimum physical properties, such as tensile strength, thickness variation, tear resistance, air permeance and burst strength, shall be established to meet the requirements of the medical device, packaging or sterilization process or final package.

f) Specific chemical properties, such as pH value, chloride and sulfate content, shall be established to meet the requirements of the medical device, packaging or sterilization process.

4.1.5 Additional requirements for adhesive-coated materials

In addition to the requirements given in 4.1.4, adhesive-coated materials shall meet the requirements listed below.

a) Coating patterns shall be continuous without skips or breaks in the pattern sufficient to cause a discontinuity in the seal.

b) Coating mass shall be consistent with the producer's stated value.

c) Materials shall demonstrate a minimum specified seal strength.

4.1.6 Additional requirements for formed packages

4.1.6.1 Components, e.g. materials, adhesive coating, ink or chemical indicators, shall not react with, contaminate, transfer to or adversely affect the product before, during or after sterilization.

4.1.6.2 In addition to meeting the materials requirements given in 4.1.4 and, if appropriate, 4.1.5, formed packaging (e.g. paper bags, heat-sealable pouches and reels) shall comply with the requirements listed below.

a) Packages shall meet producer's and manufacturer's specifications for seal width, burst and/or seal strength.

b) Process indicators printed on packages shall comply with ISO 11140-1.

c) Packages that have peel-open characteristics shall have a peel that is continuous and homogeneous without delamination or tearing of the material which can affect aseptic presentation.

NOTE — Paper bags and heat-sealable pouches and reels have construction and package design requirements as well as performance requirements.

4.1.7 Additional requirements for reusable containers

In addition to the general materials requirements given in 4.1.4 and, if appropriate, 4.1.5, reusable containers shall meet the requirements given below.

a) Each container shall be fitted with a tamper-evident system to provide a clear indication when the closure integrity has been compromised.

b) The sterilant port shall provide a barrier to microorganisms during removal from the sterilizer, transport and storage (see 4.1.3).

c) Gaskets/seals shall provide a barrier to microorganisms as specified in 4.1.3.

d) The container shall be constructed to facilitate visual inspection of all essential parts. The producer shall specify the acceptance criteria to be used on visual inspection prior to each reuse.

e) The producer shall specify the service, cleaning procedures and the manner of inspection, maintenance and replacement of components.

4.1.8 Responsibilities for package validation and for compliance and performance qualification

4.1.8.1 It shall be the responsibility of the manufacturer to ensure that the final package is validated in accordance with this International Standard.

4.1.8.2 The responsibility for conducting compliance qualification tests on materials shall rest with the producer.

NOTE — This does not exclude voluntary assumption of this responsibility by the manufacturer.

4.1.8.3 The responsibility for conducting performance qualification tests shall rest with the manufacturer.

4.1.9 Records

All validation procedures and results shall be fully documented and retained in accordance with a formal quality system.

4.2 Validation requirements

4.2.1 Compatibility with the sterilization process

4.2.1.1 The sterilization compatibility of the material shall be determined for the sterilization processes to be used.

This shall include determination that the packaging is sufficiently permeable to all the physical and chemical agents which affect the efficacy of the particular sterilization process (e.g. for ethylene oxide sterilization this would include permeability to ethylene oxide gas, water vapour and air), and that the physical properties of the material are not adversely affected over time by the sterilization process.

NOTES

1 Different limits on material properties may be set for inner and outer layers of packaging where the product is enclosed by multiple wrappings.

2 Determination of suitability may be carried out concurrently with validation of the sterilization process(es) to be used.

4.2.1.2 In specific cases where multiple sterilization cycles are required, the performance of the packaging materials shall be evaluated to ensure that the material performance remains within specified limits. This shall be the responsibility of the manufacturer.

4.2.1.3 Determination of suitability for the intended purpose shall include consideration of material variations which will occur during normal routine supply.

NOTE — Testing of materials should assess the effect which the random variation of essential attributes can have on the performance of the material (e.g. thickness and/or pore size of porous materials).

4.2.1.4 Means shall be provided to ensure that all packaging used in routine production is within the limits determined to be suitable for the sterilization process.

4.2.2 Compatibility with the product to be packaged

4.2.2.1 The suitability of the packaging for use with the particular medical device shall be determined by the manufacturer.

This should include determination of the resistance to puncture and resistance to tear (both with and without prior initiation of a tear) and, if applicable, determination of the effects of heat, light, moisture, air, etc.

Historical evidence may be used for materials which have previously been used satisfactorily.

4.2.2.2 The determination of limiting values for physical and chemical characteristics shall include consideration of both the adverse interactions that can occur between the packaging and the medical device, and the stresses which will be imposed during sterilization and subsequent transport and storage.

Examples of such adverse physical interactions can include effects of the mass, the medical device or the presence of sharp edges, and chemical interactions which can include possible migration of plasticizers, either from packaging to medical device or vice versa.

4.2.2.3 The manufacturer shall be responsible for ensuring that the packaging materials in combination with the specified sterilization and packaging processes do not adversely affect the safety and efficacy of the medical device.

4.2.2.4 The suitability of the packaging for use in protecting the particular medical device shall be determined by the manufacturer.

This shall include consideration of particular protection required by the medical device (e.g. protection against static discharge for electronic components) as well as the stresses which will be imposed during sterilization and subsequent transport and storage.

4.2.2.5 The suitability of the packaging for use with the intended labelling system shall be determined by the manufacturer.

This shall include documented evidence that:

a) the labelling system is not adversely affected by the sterilization process and/or subsequent transport and storage;

b) the sterilization process and/or subsequent transport and storage is not adversely affected by the labelling system;

c) for printed labels, there is no strike-through, bleed or fading of ink which would adversely affect the medical device or product identification;

d) for adhesive labels, there is adequate adhesive retention.

4.2.3 Microbial barrier properties

4.2.3.1 General

The microbial barrier properties of packaging materials are critical for assuring package integrity and product safety. The methods used for evaluation of the microbial barrier properties are divided into two categories: those which are appropriate for impermeable materials and methods appropriate for porous materials.

4.2.3.2 Impermeable materials

The impermeability of a material shall be determined according to annex A. Demonstrating that the material is impermeable shall satisfy the microbial barrier requirement.

4.2.3.3 Porous materials

4.2.3.3.1 Porous materials shall provide an adequate microbial barrier to microorganisms in order to provide sterile package integrity and product safety.

NOTE — There is no universally applicable method of demonstrating microbial barrier properties. Evaluation of the microbial barrier properties of porous materials is typically conducted by challenging samples with an aerosol of bacterial spores or particulates under a set of test conditions which specify the flowrate through the material, microbial challenge to the sample, and duration of the test. The microbial barrier properties of the material under these specified test conditions are determined by comparing the extent of bacterial or particulate penetration through the material with the original challenge. These methods provide a relative ranking of materials and do not predict performance under conditions other than the specified test conditions.

4.2.3.3.2 The producer of the material shall determine if the microbial barrier properties are adequate for sterile packaging for the intended use.

4.2.3.3.3 The manufacturer shall determine if the microbial barrier properties of a given material meet the criteria required for a specific package design.

4.2.3.4 Microbial barrier test methods

The microbial challenge method used to determine the microbial barrier properties shall first be validated by establishing a protocol, demonstrating acceptable repeatability of the method and demonstrating the ability to differentiate among packaging materials, examples of which are described in national Pharmacopoeias and national standards.

NOTES

1 Test methods for determining the microbial barrier properties are available and in the course of preparation, but none has been accepted as a standardized procedure.

2 If a validated physical test method is found to correlate with a validated microbiological challenge method, the data from the physical test method would be acceptable for determining the microbial barrier properties.

3 As validated microbial challenge methods for materials and final packages (e.g. reusable containers) become available, they will be considered for inclusion in future editions of this International Standard.

4.3 Storage conditions of packaging materials before use

As packaging materials can deteriorate during storage, the manufacturer shall ensure that the performance characteristics of the packaging material remain within specified limits (see 4.1 and 4.2) by either:

a) demonstrating retention of these characteristics under the manufacturer's defined storage conditions, or

b) ensuring that storage conditions remain within specified limits. These limits and conditions shall be determined by the producer.

5 Package forming and sealing

5.1 Equipment qualification

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.

There shall be:

a) the ability to monitor key parameters;

b) written calibration specifications and schedules with certified calibration of all relevant instruments, sensors, displays, controllers, etc.;

c) documented inspection of forming/sealing or other closure systems, fixtures (tooling);

d) written preventive maintenance schedules and cleaning procedures;

e) software validation, if applicable; and

f) documented operator training.

5.2 Process development

5.2.1 General requirements

The manufacturer shall conduct a process assessment to establish appropriate and necessary upper and lower processing limits. The assumption is made that materials have been selected in accordance with the requirements of clause 4 of this International Standard and the package design qualified in accordance with clause 6 to include compatibility with the intended sterilization process.

5.2.2 Material compatibility

5.2.2.1 It is the responsibility of the manufacturer to ensure that all incoming packaging materials for forming and sealing meet predetermined requirements or specifications, including those of clause 4, and to select producers who have been assessed for their capability to produce materials which consistently meet design requirements.

5.2.2.2 Lot-to-lot variations will still exist in received lots of accepted materials which can influence the quality of the package produced. These variations shall be considered by the manufacturer during process development.

5.2.3 Process design

5.2.3.1 The material characteristics shall be evaluated to determine those which have an effect on the final package.

5.2.3.2 Essential processing parameters shall be evaluated. These may include, but are not limited to,

a) temperature;

b) pressure/vacuum, including rate of change;

c) dwell time (line speed);

d) energy levels/frequency (radio frequency/ultrasonic);

e) torque limits for lid/cap closure systems.

5.2.3.3 The selected essential parameters shall produce a process that is capable of yielding final packages that meet predetermined design specifications.

NOTE — It is recommended that a package failure analysis be conducted to establish process conditions that result in unacceptable packages. This analysis ensures that the upper and lower process limits are sufficiently removed from marginal and failure conditions.

5.2.4 Process verification

5.2.4.1 Process verification shall be performed to challenge the process limits.

5.2.4.2 Packages shall be produced at both the upper and lower parameter limits and shall exhibit the properties which the manufacturer has defined for the final package (see clause 6). The following quality properties shall be considered

a) for forming/assembling:
   — package completely formed/assembled;
   — product fits appropriately into package;
   — essential dimensions met.

b) for sealing:
   — total continuous seal width;
   — punctures or tears;
   — material delamination or separation;
   — channels or open seals.

c) for other closure systems:
   — continuous closure;
   — punctures or tears;
   — material delamination or separation.

5.2.4.3 Physical package performance testing (see 6.5) shall be performed with packages made at the upper and lower process limits or those made at worst-case conditions.

5.3 Process performance qualification

5.3.1 The process performance qualification shall include multiple production runs at specified operating conditions and shall demonstrate the effectiveness and reproducibility of the process.

NOTE — The results of the process development provide the supporting documentation for the process performance qualification.

5.3.2 Documented procedures and specifications for process control elements of packaging operations shall be established and incorporated into the process performance qualification. For machine systems these shall include:

a) machine set-up procedures;

b) sealing and forming process parameters such as temperature, pressure, torque and dwell time, including setting and tolerances;

c) valid test methods for package quality attributes such as seal width, continuity and integrity; and

d) process start-up procedures.

5.3.3 Documented protocols shall specify an adequate number of test samples and replicate process runs to demonstrate reproducibility and variability within and between different runs. Essential process variables shall be monitored and recorded.

5.4 Process control

5.4.1 Either during or after the process validation, the manufacturer shall establish procedures to ensure that the packaging process will be under control during routine operation.

5.4.2 The manufacturer shall demonstrate adequate methods of process control and documentation.

5.4.3 Packaging and sealing process documents, including selection of packaging materials, shall be covered by a procedure for documenting, verifying and authorizing change.

5.5 Process certification and revalidation

5.5.1 Process certification is a documented review and approval process carried out as a final step in the validation program. Supporting documentation shall be available in a technical summary. It may include:

a) a summary of the development and/or qualification work that has been done;

b) quantitative, qualitative and/or statistically significant results;

c) references to the location of background technical data;

d) discussion of major problems and corrective action taken to solve them.

5.5.2 Processes shall be revalidated if changes are made to the equipment, product, packaging materials or packaging process which compromise the original validation and affect the sterility, safety or efficacy of sterile medical devices.

6 Final (product) package

6.1 Test selection and sampling

6.1.1 The sampling plans used for selecting the test units shall be chosen by the medical device manufacturer based upon that manufacturer's requirements (e.g. AQL, SPC). For each method chosen, a rationale shall be documented.

6.1.2 Each test selection cannot be considered as a stand-alone procedure for final package acceptance. The tests shall be considered in their entirety to ensure a validated package system.

NOTE — Additional tests may be required for specific medical devices (e.g. antistatic properties for electronic components).

6.1.3 When test packages are not assembled on validated manufacturing lines, the packages shall be built using systems and processes that simulate anticipated manufacturing conditions as closely as possible.

6.2 Visual testing for sterile package integrity

6.2.1 General requirements for visual evaluation of package integrity

6.2.1.1 Any visual evaluation shall be performed by an inspector with normal visual acuity (corrected if necessary) under specified conditions of distance, illumination, illumination source, time and magnification (if required).

6.2.1.2 All assessed defects shall be assigned categories which define actions to be taken by the manufacturer in the event that such defects are detected during normal production runs.

6.2.2 Inspection method

6.2.2.1 The external surface of the final package shall be inspected for defects such as:

a) irregularities in or on the sterile barrier materials, such as tears, cracks, holes or fractures;

b) presence of foreign material;

c) dimensional accuracy;

d) seal integrity (open or incomplete seals); and

e) presence of humidity, moisture or staining.

6.2.2.2 Opened package samples shall be inspected for defects such as:

a) foreign material, particularly on the device components;

b) any irregularities on the inside surfaces of the sterile barrier material, including tears, cracks, holes and fractures;

c) seal attributes (irregular, nonhomogeneous or noncontinuous seals); and

d) the presence of unacceptable humidity, moisture or staining.

6.3 Seal/closure evaluation

6.3.1 General

The properties of the closure or seal of the package sample shall be evaluated in accordance with 6.3.2 to 6.3.5.

6.3.2 Seal integrity

It shall be sufficient to demonstrate that the seal is impermeable and continuous by using physical tests. This, together with microbial barrier property testing of materials (4.2.3), establishes sterile package integrity.

6.3.3 Seal strength

6.3.3.1 The seal strength shall be determined at the upper and lower limits of defined critical sealing process variables and shall be demonstrated to be suitable for the intended purpose.

NOTE — When evaluating whether the package sealing process is under control, it is helpful to look for variations in seal strength values.

6.3.3.2 In determining the required limits for the seal strength, consideration shall be given to the strength of the material and whether or not the seal is intended to be peeled apart during aseptic removal of the product.

Various methods can be used to determine seal strength, e.g. tensile strength testing and burst/creep pressure testing. Examples of such methods include the following.

a) **Tensile seal strength test** (ASTM F-88, D-903 or equivalent)
This test method measures the strength of the package seal by tensile testing a portion of that seal. It does not measure seam continuity or any other seal properties beyond the force required to tear (peel) apart the seal between two materials.

b) **Burst/creep pressure test** (ASTM F-1140 or equivalent)
A final package pressure test used to evaluate overall minimum seal strength of the package by pressurizing the entire package to a point of failure (burst) or to a known critical value for a period of time (creep).

NOTE — There is no general correlation between tensile strength and burst/creep testing. They are separate tests and the results obtained have entirely different implications regarding package/seal strength.

6.3.4 Closure integrity

6.3.4.1 If a package is not closed by sealing (such as, but not limited to, sterilization wraps, packaging for sterile fluid path products and reusable containers), the closure system shall be demonstrated to provide acceptable microbial barrier properties.

6.3.4.2 For any performance requirement for the closure given in this International Standard, it shall be sufficient for the user to demonstrate that the closure is formed in strict accordance with the manufacturer's operating instructions.

6.3.5 Peelable seals

The seal shall be demonstrated to be uniform and, on peeling, it shall be demonstrated that fibre shedding, and splitting or tearing of the package material is within limits specified by the manufacturer to ensure that the utility of the medical device is not impaired.

6.4 Physical testing for sterile package integrity

NOTE — When evaluating package integrity, it is assumed that the package design has met the requirements of 6.5, which documents the package's ability to protect the contents from damage and maintain sterile package integrity.

6.4.1 Package integrity testing

The manufacturer shall demonstrate the integrity of the sterile package by testing the package. This can be accomplished by physical tests.

Specific methods and test values shall be determined by the manufacturer to take into consideration the specific package materials, design and medical device.

Each test method shall have rationale statements, detailed test plans, step-by-step procedures and good data collection.

Some examples of such physical test methods are described below.

a) Internal pressure test: Increase the internal pressure of the sterile package while it is submerged in water and note any escaping air bubbles.

b) Dye penetration test: Fill the package with a liquid containing a penetrating dye and observe any paths in the seal area or holes in the packaging material.

c) Gas sensing test: Pressurize the sterile package with a traceable gas and use appropriate gas sensors or other measuring equipment to detect holes in the materials or open paths in the seals.

d) Vacuum leak test: Immerse sealed packages in a test solution and apply vacuum. When the vacuum is released, the difference in pressure will force the test solution through any openings in the package.

6.4.2 Sterilization compatibility testing

6.4.2.1 Final packages shall be tested for compatibility with the sterilization process.

This should include both demonstration of attainment of sterilizing conditions within the package and the integrity and performance of the package after the sterilization process.

6.4.2.2 In instances where more than one sterilization run is allowed, due to, for example, out-of-specification runs and/or correction of packaging defects, the manufacturer shall ensure that the final package remains suitable for use.

NOTE — Reprocessed packages may require further validation of residual sterilant levels. Reprocessed packages may also require enhanced levels of inspection for any detrimental effect of the medical device or sterilization process on the package, seal or closure.

6.4.3 Maintenance of package integrity

6.4.3.1 The ability of the final package to maintain its integrity over time can be evaluated using the same functional tests that are used to test the packaging material's microbial barrier properties (4.2.3), seal/closure integrity (6.3.2 and 6.3.4) and whole-package integrity (6.4.1).

NOTE — The loss of final-package integrity is usually regarded as event-related rather than time-related.

6.4.3.2 The manufacturer shall demonstrate that, under the rigours of distribution, storage, handling and ageing, the integrity of the final package is maintained at least for the claimed shelf life of the medical device under storage conditions specified by the manufacturer, as long as the package is undamaged or unopened.

6.4.3.3 Microbial barrier properties of the package shall be evaluated after exposure to the environmental stresses expected for a finished package.

This shall include demonstration of attainment of sterilizing conditions within the package and the integrity of the package after the sterilization process.

The environmental stresses should include consideration of forming the package, sterilization, handling and storage.

NOTE — Whole-package microbial barrier testing is often impracticable. Equivalent evidence may be obtained by a combination of data from testing component materials, seals, etc., of the package.

6.4.3.4 For medical devices with a defined shelf life, the manufacturer shall have documented evidence that the performance of the packaging is not adversely affected by storage under specified conditions for a period not less than the shelf life of the medical device.

This shall be demonstrated by real-time ageing tests. Accelerated ageing tests may be undertaken in addition to real-time ageing tests by storage under conditions of increased severity. If accelerated ageing tests are performed, a documented rationale for the accelerated ageing conditions and test duration chosen shall be established. Accelerated ageing may be regarded as sufficient evidence for claimed shelf life on the introduction of new products. This does not preclude the requirement to perform real-time ageing tests.

NOTE — These ageing tests may be carried out on final packages with or without including the medical device; it should be noted that the presence of a medical device can stress the package and cause changes in performance.

6.4.3.5 It shall be demonstrated that all the material properties given in 4.1 remain within the validated limits of the performance specification after exposure to the sterilization process and on storage under the manufacturer´s specified conditions after sterilization.

6.4.3.6 The storage conditions before or after the materials are formed into packages can affect the nature and rate of deterioration. The storage and distribution conditions for the sterilized product in its packaging shall be defined by the manufacturer.

The following conditions shall be considered for all packaging:

a) temperature range;

b) pressure range;

c) humidity range;

d) and, where applicable, the maximum rate of change of the above;

e) exposure to light.

NOTES

1 The flowrate of air through a permeable barrier packaging material is influenced by the porosity of the material, the rate of temperature and pressure changes, the ratio of porous surface area to package volume, and package flexibility. The filtration efficiency of a material can be markedly affected by air flowrate.

2 The storage conditions defined for the product by the manufacturer of the medical device could require tighter limits than are necessary for the packaging alone.

6.5 Physical testing of package performance

6.5.1 The performance of the package in providing adequate protection to the medical device through the handling, distribution and storage systems shall be evaluated.

6.5.2 The packaging system shall also ensure retention of the product in the correct orientation for aseptic removal.

6.5.3 The manufacturer shall define the limiting conditions for handling, distribution and storage.

6.5.4 The manufacturer shall select test methods which are appropriate to determine whether the performance of the packaging is adversely affected by the distribution, storage and handling system.

NOTE — For examples of tests that can be used to evaluate package performance in the handling, storage and distribution systems, see annex B.

6.6 Documentation of testing

6.6.1 Before any performance testing is started, a test protocol shall be documented. This test protocol shall include

a) the design configuration to be qualified;

b) the tests to be performed;

c) the test sequence; and

d) product information such as mass, fragility levels, transport methods that will be used, and definitions of the product unit of sale configuration(s) to be qualified (e.g. one sterile barrier package, multipack container, pallet load).

6.6.2 This protocol shall also include pass/fail criteria for each attribute evaluated.

The test protocol should also include anticipated storage conditions and information regarding manufacturing systems and methods.

Annex A
(normative)

Test method for resistance of impermeable materials to the passage of air

A.1 Impermeable packaging materials shall be tested for air permeance in accordance with ISO 5636-5.

Test requirements: After not less than 1 h there shall be no visible movement of the cylinder within the tolerance of ± 1 mm.

A.2 Other test methods may be used for routine monitoring and production testing. Those methods shall be validated against the reference test method for the material used. Examples of such methods are the method for dye penetration as described in annex C of this International Standard and the Schopper method for determination of air permeance in accordance with ISO 5636-2.

NOTE — Conversion factors for different types of apparatus used in various methods for determination of air permeance are given in ISO 5636-1.