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Packaging for terminally sterilized medical devices — Guidance on the application of ISO 11607-1 and ISO 11607-2

Emballages des dispositifs médicaux stérilisés au stade terminal — Lignes directrices relatives à l'application de l'ISO 11607-1 et l'ISO 11607-2

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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.

The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2. www.iso.org/directives

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For an explanation on the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the WTO principles in the Technical Barriers to Trade (TBT) see the following URL: Foreword - Supplementary information

The committee responsible for this document is ISO/TC 198, *Sterilization of health care products*.

Introduction

Sterile barrier systems need to ensure the sterility of their contents until opened for use and ensure aseptic presentation.

The sterile barrier system, depending on conditions of handling, distribution or storage, may provide adequate protection for the sterile medical device. In circumstances where the packaged and sterilized device undergoes repeated handling, additional protective packaging may need to be combined with the sterile barrier system to create a packaging system.

Each establishment should evaluate the performance of each sterile barrier system or packaging system before selection and implementation to ensure conditions for sterilization, storage, and handling can be met. Each establishment that manages sterile items should have a documented plan of education on how to store, handle and transport sterile items.

Regional differences in quality management systems and other requirements exist and these might involve different approaches to human resource management. In any case however a sound education process is a key element and facilities should ensure that its personnel are aware of the relevance and importance of their packaging and sterilization activities for the safety of the patient.

ISO 11607-1 specifies the requirements for materials, sterile barrier systems, and packaging systems, including the qualification of the packaging system design and evaluation of that design, ISO 11607-2 specifies the requirements for packaging process validation. Both of these documents provide standards to ensure medical device protection, the ability to sterilize, maintenance of sterile package integrity and aseptic presentation. The scope of each of these standards applies to health care facilities and wherever medical devices are packaged and sterilized. It is recognized that the circumstances of the application of these standards will be different when they are used in a health care facility from when they are used by a medical device manufacturer or reprocessor.

The conditions of use of this guidance may vary widely around the world. ISO 11607-1 and ISO 11607-2 and this guidance document provide a guideline for use, subject to interpretation by circumstance and regulatory environments. In some regions of the world health care facility compliance to the series ISO 11607 is a national or regional regulatory requirement, in some regions the series ISO 11607 is considered guidance for health care facilities. For instance, it is recognized that in certain regions or regulatory applications conformance to ISO 11607-1 may be demonstrated but not conformance to ISO 11607-2, which requires process validation by the user. In other regions, where compliance to both ISO 11607-1 and ISO 11607-2 is a national regulatory requirement, this document will also provide guidance on performing validation. Clause 3 of this guidance document is applicable to health care facilities and Clause 4 is applicable to industry. Further guidance is given in Annexes A to S that may be applicable to health care facilities and/or industry, as indicated.

In Europe ISO 11607-1 assists the conformity assessment procedure for manufacturers and is designed and used as a tool for demonstrating compliance with the relevant essential requirements of the Medical Device Directive. Compliance with the standard is always voluntary.

At the time of publication of this document, Amendments to ISO 11607-1 and ISO 11607-2 are in the ballot process. This guidance document already considers the revised versions with the understanding that specific references to numbering may have changed. Annex B of ISO 11607-1 on test methods has been extensively revised and should be considered when available.

Packaging for terminally sterilized medical devices — Guidance on the application of ISO 11607-1 and ISO 11607-2

1 Scope

This Technical Specification provides guidance for the application of the requirements contained in ISO 11607-1 and ISO 11607-2. It does not add to, or otherwise change, the requirements of ISO 11607-1 and/or ISO 11607-2. This is an informative document, not normative. It does not include requirements to be used as basis of regulatory inspection or certification assessment activities.

The guidance can be used to better understand the requirements of ISO 11607-1 and/or ISO 11607-2 and illustrates some of the variety of methods and approaches available for meeting the requirements of those International Standards. It is not required that this document be used to demonstrate compliance with them.

Guidelines are given for evaluation, selection and use of packaging materials, preformed sterile barrier systems, sterile barrier systems and packaging systems. Guidance on validation requirements for forming, sealing and assembly processes is also given.

This Technical Specification provides information for health care facilities (see Clause 3) and for the medical devices industry (see Clause 4).

It does not provide guidance for applications of packaging materials and systems after their opening. In the use of packaging for other purposes such as a "sterile field" or transport of contaminated items, other regulatory standards will apply.

2 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11607-1 and ISO 11607-2 and the following apply.

2.1
packaging system
combination of the sterile barrier system and protective packaging

[SOURCE: ISO/TS 11139:2006, 2.28]

Note 1 to entry: The packaging system includes the sterile barrier system and the protective packaging. However, if the sterile barrier system protects the medical device, facilitates aseptic presentation, and is resilient enough not to require additional protective packaging, the sterile barrier system would also fulfil the requirements of a packaging system. Protective packaging is not always necessary however aseptic opening/presentation has to be ensured in all cases.

2.2
protective packaging
configuration of materials designed to prevent damage to the sterile barrier system and its contents assembly until the point of use

[SOURCE: ISO/TS 11139:2006, 2.37]

Note 1 to entry: National or regional regulations may require that protective packaging is used to avoid the potential contamination of the surgical environment. These regulations may also require that the protective packaging is removed prior to introduction of the sterile barrier system into the surgical environment.

Note 2 to entry: Protective packaging protects the sterile barrier and the contents. Examples would include a dust cover, a box, transport tray.

2.3
sterile barrier system
SBS
minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use

[SOURCE: ISO/TS 11139:2006, 2.44]

2.4
preformed sterile barrier system
sterile barrier system that is supplied partially assembled for filling and final closure or sealing

EXAMPLE Pouches, bags, and open reusable container.

[SOURCE: ISO/TS 11139:2006, 2.31]

Note 1 to entry: Preformed sterile barrier systems exist in a wide range of forms. The examples listed above are not intended to be all inclusive.

3 Guidance for health care facilities

IMPORTANT — Written instructions for use should be obtained from the packaging material and/or medical device manufacturer concerning their recommendations for sterilization and the subsequent maintenance of sterility of a sterile barrier system.

3.1 Test methods

For guidance on the requirements for test methods contained in ISO 11607-1 and ISO 11607-2, see the health care annexes of this document.

3.2 Guidance for conformance to ISO 11607-1

3.2.1 General guidance for materials, preformed sterile barrier systems and sterile barrier systems

3.2.1.1 Preformed sterile barrier systems should be evaluated before purchase and use. Therefore, the supplier should consider providing a statement of compliance to the applicable sections of ISO 11607-1 for the materials and/or preformed sterile barrier systems to be purchased. Before introducing associated components (e. g. labels, tapes, tray liners) into production, users should confirm that they will be suitable for use in their specific applications and conditions of use.

3.2.1.2 The key concepts that apply to all packaging materials and components are as follows:

a) they should be made of known and traceable materials with processes capable of meeting the requirements of ISO 11607-1 (see requirements in ISO 11607-1:2006, 5.1.3, 5.1.4 and 5.1.5);

b) they should be non-toxic, for guidance see A.3.3 (see requirement in ISO 11607-1:2006, 5.1.6);

NOTE 1 If the sterile barrier system or associated components contain natural rubber latex, the sterile barrier system should be labelled indicating natural rubber latex is present.

c) there should be documented evidence that the ingress of microorganisms can be prevented when demonstrated under test conditions which consider sterilization process, handling, distribution, transport and storage (see requirement in ISO 11607-1:2006, 5.1.6 and 5.2);

d) they should have a demonstrated ability to meet the required physical properties for materials and closures (such as weight or grade, seal width and seal strength), resist tearing or puncture, be capable of opening or peeling in a continuous and homogenous manner, without delamination tearing (see requirements in ISO 11607-1:2006, 5.1.7 and 5.1.9);

e) they should be compatible with the intended sterilization process and parameters capable of producing a sterile medical device (see requirement in ISO 11607-1:2006, 5.3);

f) they should be compatible with the labelling system; if present, have colour fast printing inks that do not degrade, fade or become illegible after exposure to the intended sterilization process (see requirement in ISO 11607-1:2006, 5.4);

g) they should be protected from the effects of environmental conditions (e.g. relative humidity, direct sunlight or fluorescent light, temperature) during storage (see requirement in ISO 11607-1:2006, 5.5 and Clause 7);

NOTE 2 Suggested storage conditions and shelf life should be provided by the material or preformed sterile barrier system manufacturer. If anticipated or actual storage is outside these conditions the manufacturer should be consulted.

h) they should allow aseptic presentation.

NOTE 3 Instructions for aseptic presentation should be provided by the manufacturer of the medical device and/or packaging system.

NOTE 4 The internet is a useful tool for finding information on materials, see Annex N.

3.2.2 Design and development guidance for packaging systems (ISO 11607-1:2006, 6.1 and 6.2)

3.2.2.1 Selection criteria

When a health care facility determines which packaging system to use, the design and development guidance for those packaging systems should be considered (see requirements in ISO 11607-1:2006, 6.1 and 6.2). When a health care facility uses a contract packager or sterilizer additional considerations are necessary (see Annex P).

The materials and systems chosen should:

a) be intended for use in medical packaging applications, as stated by the manufacturer;

b) be supported by technical information from the manufacturer confirming that it meets the requirements of ISO 11607-1 that relate to materials;

c) provide adequate protection for the medical device(s) during specified intended storage and transportation conditions to the point of use;

d) allow for and be compatible with the intended sterilization process, and have the ability to withstand conditions of the chosen process;

NOTE Not all materials are appropriate for all sterilization processes. Information on compatibility with a given sterilization process is typically provided by the manufacturer of the medical device and/or packaging system. For further explanation of challenges of common sterilization processes see Annex B.

e) maintain sterile barrier integrity until its time of use;

f) ensure aseptic presentation at the point of use;

g) allow a method of closure that is tamper evident;

h) allow for ease of identification of contents.

The user of the packaging materials should ensure that the sterile barrier system or packaging system complies with ISO 11607-1, that requirements concerning product compatibility are met and that processes for packaging, sterilization, storage and distribution are validated and controlled.

3.2.2.2 Selection considerations

The selection process at the health care facility should include an evaluation of the ability of both the sterile barrier system and protective packaging (if required) utilized to maintain the integrity of that sterile barrier system until its time of use and permit aseptic presentation at the point of use.

The choice of packaging components will be dependent on the risk associated with the medical device, its conditions of use, the storage and transport requirements and health care procedures practiced at the facility. These risks should be analysed by the health care facility and procedures put in place to mitigate/control those risks (see Annex K).

To choose the most appropriate material for the sterile barrier system and/or packaging system, the following should be considered:

a) Duration and conditions of storage may affect the type of sterile barrier system or packaging system needed. Some items may be stored for some time before use and may require a more durable sterile barrier system and/or the addition of protective packaging. The more the sterile barrier system or packaging system is handled the greater the probability that cracks, lid deformation, gasket damage, tears, holes or material separation may occur.

b) Size, weight and shape of the item to be sterilized should be considered. Some items will require more durable or more flexible sterile barrier systems than others.

c) If multiple types of packaging components are to be used it is important to verify that components are compatible with each other as well as the product contained inside and the intended sterilization process.

d) The means and conditions of transport should be considered. While in some cases routes are exclusively inside the facility, they can also be between different facilities. Exposure of the packaging systems to the uncontrolled environment may significantly increase the risk of loss of integrity of the package, compromise aseptic opening or contaminate the contents.

3.2.2.3 Assembly considerations

The following aspects should be considered:

a) Medical devices should be oriented to facilitate aseptic presentation.

b) Sharp items should be shielded so that the user is protected from injury and the sterile barrier system and medical device is protected from damage.

c) Associated components can be used inside the sterile barrier system in order to ease or facilitate the organization, drying or aseptic presentation (e. g. inner wrap, instrument organizer tray, tray liners or a containment device around the medical device).

d) The protection devices or associated components should:

   1) be non-toxic, be intended for use in medical packaging applications, as stated by the manufacturer;

   2) provide protection of the medical device(s) during storage and transportation to the point of use;

   3) allow for and be compatible with the intended sterilization process, and have the ability to withstand conditions of chosen process;

NOTE 1 Not all materials are appropriate for all sterilization processes. Information on compatibility with a given sterilization process is typically provided by the manufacturer. For further explanation of challenges of common sterilization processes see Annex B.

4) not undergo chemical or physical change to such an extent that the performance or safety is impaired or the medical device that they contact is adversely affected;

5) not compromise aseptic presentation;

6) allow for easy identification of contents;

7) be stored in a controlled environment to maintain cleanliness and fitness for use.

e) The weight of the packaging system and its contents should not exceed national regulations for manual handling.

NOTE 2 Current national regulations range from about 5 kg to 11,4 kg.

3.2.2.4 Labelling considerations

Part of the selection process should include consideration of how labelling is to be accomplished. The facility's labelling procedure for the sterile barrier system or packaging system should include the following:

a) When identification is performed in a health care facility:

— for pouches and reels the label should be placed on the film if applied before sterilization or on either side if after, the label should not conceal the device;

— for pouches and reels printing or writing should be placed outside the area enclosed by the outside dimensions of the seals;

— care should be taken when applying labels to filled sterile barrier systems so as not to damage packaging materials or contents.

b) Writing on wrapped packages should be on the closure tape, not directly on wrappers.

c) Special labels intended for a specific sterilization process may be written on. If these labels are used they should not impede the sterilization process (i.e. should not block the breathable area of the package).

d) Labelling should remain securely adhered to the sterile barrier system through the sterilization process and storage until the point of use.

e) Labels or closure tapes used as labels, and their adhesive systems should be non-toxic.

f) Only non-toxic ink that is suitable for use with the chosen sterilization process should be used.

g) Ballpoint pens or any writing instrument with the potential for creating a hole or puncture in the sterile barrier system should not be used.

3.2.2.5 Regulatory considerations

Specific national or regional regulatory requirements may apply. These requirements should be considered during the selection process for a sterile barrier system and/or for a packaging system.

3.2.2.6 Common choices for sterile barrier systems

3.2.2.6.1 General

Sterile barrier systems can be manufactured using mainly, but not limited to, the following concepts:

— sealable pouches and reels; and/or

— sterilization wrap; and/or

— reusable container.

Aspects to be considered in using these systems follow.

3.2.2.6.2 Sealable pouches and reels (preformed sterile barrier systems)

Sealable pouches and reels are typically purchased in two forms:

— The continuous roll or reel type is sealed along both edges. The roll is unwound and cut to the desired length. The medical device is placed between the two layers and both ends are sealed.

— The pouch is pre-cut to a specific size and sealed on three sides. The medical device is placed inside the pouch and the fourth side is sealed.

The following aspects should be considered:

a) The size of the pouch and the strength of the packaging materials should be based on the medical device which is going to be packaged. Items either too large for a package or with sharp edges will put extra pressure on the seals and the materials. This may cause rupture. There should be enough space to make seal closure possible. Too many small items in the sterile barrier system may cause the items to move around, rupture the seal, penetrate or abrade the package materials. Thin or fragile materials can be damaged during handling, transport, and distribution.

b) If not specified otherwise by the manufacturer the preformed sterile barrier system should be filled up to a maximum of 75 % of the inner surface area of the porous side. Care should also be taken to ensure that the distance from the seals is increased for products of greater height.

c) When two pouches are used, the inner pouch should be able to move within the outer pouch. This allows penetration of the sterilant and prevents the pouches from sticking together during the sterilization process. Folding of the inner pouch in order to fit into the outer pouch or folding of the outer pouches should be avoided in order to prevent stressing or damage to the sterile barrier system. For combining two pouches made from film and porous material it is important that film meets film and porous material meets porous material for identification of content and permeation of sterilant.

d) All pouch seals, including closure seal, should be smooth, i.e. without folds, bubbles, or wrinkles.

e) Self-seal pouches and those closed with tape may provide less security than heat sealed pouches. Sealing procedure should dictate that folds and closures should not be skewed, and care should be taken to ensure that both corners are well sealed, in order to ensure a complete closure across the entire end. Correct tape placement is critical to provide complete closure and thus sterile barrier system integrity. Special attention should be paid to proper method of closure to ensure package integrity.

f) Sealing devices should be able to control and monitor critical process parameters (e.g. temperature, pressure, sealing time/speed) in accordance with their validation criteria (e.g. alarms, warning system or machine stop in the event of any critical process parameter deviation). Operators should not modify critical process parameters unless they have been suitably trained, fully comply with appropriate operating procedures and stay within the validation process. The sealer should be capable of attaining the sealing conditions suggested by the preformed sterile barrier system

manufacturer. Sealing devices manufactured and intended for preformed sterile barrier systems should be used.

g) Closing accessories that compress the package or medical device should not be used (e.g. ropes, string, elastic bands, paperclips, staples or similar items).

h) The pouch should be loaded so that the enclosed medical device will be presented aseptically. For instance, the grip of the medical device should be placed toward the opening end. It should be noted that the seal areas are considered non-sterile when opened.[108]

i) The pouch should be opened according to the manufacturer instructions, if there is a specific orientation needed to prevent fibres delamination when opening that orientation should be followed. The formed package should show by design which direction the packaging has to be opened (e.g. arrow sign, shape of seal).

j) Reels (rolls) are used for the packaging of medical devices of diverse dimensions that do not easily fit standard preformed pouch sizes. Due to the fact that the packaging is sealed on two sides the pointed seal (chevron) is missing. In the absence of the chevron, the peel direction for reels should be provided by the manufacturer. Additionally, it is advisable to have more space above the seal that is intended to be opened according to the manufacturer's information.

NOTE In most areas of the world, certain sterile barrier systems, which are not peelable and require cutting to gain access to the product inside, are used in lieu of peelable preformed sterile barrier systems. For example, some of the sterile barrier systems formed using either sterilization bags, header bags, or pouches produced using reel material constructed from one layer of porous material and one layer of plastics film, sealed together along the parallel sides. In these applications, there is a greater risk of the product coming into contact with the non-sterile outer surface of the sterile barrier system and extra care should be taken to ensure aseptic presentation. This is achieved by cutting the top off and then inverting to allow the medical device to drop out onto a suitable surface without touching the outsides.

3.2.2.6.3 Sterilization wrap

Sterilization wrap comes in many sizes and grades to accommodate a wide range of applications. It is also available in single use or reusable fabric forms. Careful consideration should be given to the item to be wrapped and the technique to be used. Sterilization wrap can be used for wrapping of individual medical devices or medical devices in instrument cases, cassettes or instrument organizing trays.

The following aspects should be considered:

a) The grade of the sterilization wrap should be chosen according to the size, shape and weight of the medical devices to be wrapped or based on guidelines within the health care facility and wrap manufacturer's recommendations for use.

b) The size of the sterilization wrap should be selected to achieve adequate coverage of the item being packaged. It is essential to wrap the item securely to prevent gaps, billowing and air pockets from forming. The item should not be wrapped too tightly as this could create holes or tears in the wrap. It is also necessary that the sterilization wrap be large enough to accommodate movement of the wrap during the sterilization cycle without ripping or tearing. When choosing sheets of sterilization wrap the wrapper should be large enough to cover the medical device, but it should not be so big that it has to be wrapped several times around the medical device, as this may impede sterilant penetration.

c) Proper wrapping technique is essential to provide a tortuous pathway to impede microbial migration into the sterile barrier system. A wrapping technique can be used if the manufacturer has demonstrated the efficacy of this technique and recommends it for this application (see 3.2.2.1). The wrapping method chosen should allow aseptic presentation of the medical device. The health care facility should verify or validate the application in its own facilities per national or regional regulations. National standards or professional guidelines for wrapping techniques may be available. Examples are given in Annex C.

d) The sterilization wrapping technique should be designed in a manner that the opened wrapper should drape away from the sterile field.

e) The assembly surface area for wrapping should be flat, smooth, of adequate size, well lit and clean.

f) The wrapped package should be designed in a manner so that all edges are secured and do not interfere with aseptic presentation into the sterile field.

g) Closure systems should provide evidence of tampering.

h) Indicator tape is the most common closure for wrapped packages and there are different kinds of tape based on the method of sterilization. There are different tapes designed for use on woven or nonwoven wrappers. Closures that compress the package or medical device should not be used (e.g. ropes, strings, elastic bands, paperclips, staples or similar items).

i) When reusable fabrics are used as sterilization wrap there are additional requirements to ensure the suitability of the wrap prior to each use (see requirements in ISO 11607-1:2006, 5.1.11 and 5.1.12).

3.2.2.6.4 Reusable containers

A rigid reusable container is designed to hold medical devices and accessories and is sterilized without exterior wrapping. This container typically consists of a bottom or base with carrying handles and a lid that is secured to the base by a latching mechanism. It may contain a basket or tray to hold medical devices. The container incorporates a means for air evacuation and sterilant penetration. In regional or other standards it may be referred to as a “rigid container” or a “reusable container”.

Instrument cases, cassettes or organizing trays are containment devices but not sterile barrier systems. They should be contained in a sterile barrier system.

When using rigid containers the following should be considered (see requirements in ISO 11607-1:2006, 5.1.10):

a) Only filters which are proven to be compatible with the specific container, particular sterilization process and capable of maintaining sterility should be used. Filter manufacturer should give documented evidence that demonstrates these capabilities.

b) Containers should be inspected and prepared in accordance with the manufacturer’s instructions.

c) Tamper evident devices appropriate for the sterilization process should be secured in accordance with the container manufacturer’s instructions and indicate that the sterile barrier system has not been opened intentionally or accidentally and therefore the contents exposed to potential contamination before intended use.

d) Each container should have a visible identification label and/or information card unless the container is designed for emergency-use sterilization and used for that purpose. ID label and card should be appropriate for the sterilization process.

e) The sealing surfaces of the base and lid should be inspected for damage at each time of use to ensure the proper closure of the container.

f) The instrument organizing tray dimensions should be suitable for use with the specific container and sterilization method.

g) Procedures should be in place for the cleaning, disinfecting and maintenance processes for containers after each use. These processes should be validated. Containers should not be used beyond the manufacturer’s stated usable life (see requirements in ISO 11607-1:2006, 5.1.12). Procedures should be in place to ensure that the manufacturer’s stated usable life is not exceeded (see requirements in ISO 11607-1:2006, 5.1.12).

h) As with all sterile barrier systems, to ensure aseptic presentation the outside of the container and the joint between top and bottom should not come in contact with sterilized contents.

3.2.2.7 Protective packaging

Protective packaging may be used to protect or prolong the shelf life of properly packaged and sterilized items that could be subjected to environmental challenges or multiple handling. Transportation or movement of the sterile barrier system in particular may require protective packaging to be applied to ensure that transportation and handling does not affect the sterile barrier system. Sterilized packages should be handled as little as possible. Loss of sterile barrier system integrity is regarded as event related rather than time related, this is why it is so crucial to guard against damage to the sterile barrier system.

When protective packaging is used, the sterile barrier system should be clearly identifiable. Protective packaging is designed to provide additional protection against damage and outside elements. If any protective packaging is to be applied after steam sterilization, it should be applied once the items are thoroughly cool and dry.

National or regional regulations may require that protective packaging is used to avoid the potential contamination of the surgical environment. These regulations may also require that the protective packaging is removed prior to introduction of the sterile barrier system into the surgical environment.

3.2.3 Packaging system performance testing (ISO 11607-1:2006, 5.3, 5.4, 5.5, 6.3)

Before any packaging system is used in a facility for the first time, its performance should be tested. Performance testing should allow verification on how well the sterile barrier system or packaging system holds up to the rigors of anticipated conditions of handling, distribution and transportation, before and after sterilization. The sterile barrier system needs to maintain its integrity without any holes, tears or seal/closure rupture that may be caused by the imposed stresses.

Performance testing should:

a) be evaluated through all the intended processes of sterilization, handling, distribution and storage, up to the point of use;

b) be evaluated for expected worst-case scenarios. In determining these, a number of factors should be considered. These include but are not limited to:

   1) Assembly of sterile barrier systems which contain the medical device configuration which presents the greatest challenge to the sterile barrier system (e.g. biggest, heaviest, most dense, sharpest items see ISO 11607-1:2006, 6.3.4).

   2) Samples for verification testing should be prepared to allow monitoring of the efficacy of the sterilization process depending on national or regional requirements for the monitoring of sterilization efficacy. Examples include but are not limited to biological, chemical indicators or process challenge device (PCD) by measuring and recording of physical parameters using thermocouples or data loggers. Determination of suitability may be carried out concurrently with validation of the sterilization process(es) to be used. Medical devices should be packaged and sterilized in accordance with the instructions of the manufacturer of the medical device and preformed sterile barrier system.

   3) Sterilization of the sterile barrier system in the intended sterilization process, considering mixed loads or fully loaded sterilizer chambers.

   4) Distribution / handling / storage / opening of the sterile barrier system.

Consideration should be given to the environment and other conditions in which the sterile barrier system or packaging system will be stored. Product pressed tightly into bins and storage locations increases the chance of shear action between two sets of packaged medical devices and can be detrimental causing pinholes and tears.

It is particularly important to consider all conditions of storage and distribution, as many sterilization sites are not adjacent to the point of use.

After performance testing, health care facilities should visually inspect the sample sterile barrier systems for package integrity (no holes or tears) and seal integrity, then verify that sterilization parameters have been achieved.

If more thorough testing is desired, alternative test methods may be found in ISO 11607-1:2006, Annex B.

If a sterile barrier system is designed to be reusable and a degradation of performance characteristics is predicted by the manufacturer (see ISO 11607-1:2006, 5.1.11 and 5.1.12) the monitoring or inspection system used should clearly identify when the end of the useful life has been reached as defined by the manufacturer.

3.2.4 Sterile barrier system stability evaluation (shelf life) (ISO 11607-1:2006, 6.4)

Evaluation on the ability of the sterile barrier system materials or preformed sterile barrier systems to maintain their performance characteristics and seal integrity over time is normally performed by the manufacturer of the preformed sterile barrier system (see also requirements in ISO 11607-1:2006, 6.4.7).

However, even though the materials have been shown to be an acceptable microbial barrier, the health care facility should demonstrate that the assembled sterile barrier system or packaging system can maintain integrity under the anticipated environmental conditions until the time of use.

Loss of sterile barrier system integrity is regarded as event related rather than time related and is dependent on the performance of the sterile barrier system or packaging system, as well as the possible interaction between the medical device and the selected sterile barrier system, the storage conditions, the conditions during transport and the amount of handling. Appropriate storage environment includes a wide variety of considerations, i.e. preventing any damage, maintaining temperature and humidity stability, limit exposure to dust and sunlight, keep protective packaging in place, minimizing handling, physical separation of clean and contaminated items etc.

Maximizing maintenance of package integrity by limiting the risk of damage to the sterile barrier system can be greatly influenced by adequate inventory control and management systems.

NOTE National or regional guidance may give further information on storage requirements, such as distance from floor and ceiling, stock rotation, cleaning of storage area, more specific limits on temperature and humidity, type of shelving non-porous, enclosed and dedicated room, ventilation air exchanges and air quality, air borne particles.

3.2.5 Documentation

The health care facility should follow a plan or criteria for evaluating the choice of sterile barrier systems. Results of testing should be compared to the acceptance criteria. The results of the evaluation should be documented.

Validation documents and gathered data should be maintained in accordance with the facility's policy. In ISO 11607-1:2006, 7.1 requires that documented information shall include the type, size or grade and batch number identification of the materials tested, the sterilization processes, any known expiry dates or suggested storage conditions, any known restrictions on handling or use, and for reusable materials, the frequency allowed and nature of maintenance.

3.3 Guidance on conformance to ISO 11607-2, *Validation requirements for forming, sealing and assembly processes*

3.3.1 General

ISO 11607-2 addresses the validation requirements for all packaging processes. This includes the assembly or filling and the following processes:

— sealing process: pouch, reel, or bag forming and sealing;

— wrapping process: sterilization wrap folding and closing of sterilization wraps;

— container process: closing of reusable containers.

Validation of processes may rely on data from previous installation qualification (IQ) and operational qualification (OQ). That data can be used for determination of the tolerances for critical parameters.

The packaging process activities should be executed in the frame of a formal quality management system. While there are regional differences between health care quality systems, key elements include, (but are not limited to) an efficient system of document control, a formal education process, process control/monitoring, and a corrective/preventive action system to maintain (and continuously improve) the effectiveness of the packaging processes.

The definitions for IQ, OQ and Performance Qualification (PQ) in ISO 11607-2 all refer to equipment used in the sealing or closing process. However all forming, sealing and assembly processes require manual operations. Consequently the functions performed by persons should be included as part of the validation.

Typically an IQ is only performed when there is equipment to be installed. Alternatively, for a process that involves only people and their execution of tasks, the development of the Standard Operating Procedures (SOP) and the training on them may be considered by some facilities to be an IQ. The training of the specific operators employed for the OQ and PQ should be documented in those reports.

3.3.2 Method of validation

3.3.2.1 General

Fundamentally, a documented method of validation or a standard procedure for validation should exist.

This documented method or procedure consists of:

a) drafting of a validation plan (see 3.3.2.2);

b) implementation of validation (see 3.3.2.3) consisting of:

   1) IQ (see ISO 11607-2:2006, 5.2);

   2) OQ (see ISO 11607-2:2006, 5.3);

   3) PQ (see ISO 11607-2:2006, 5.4);

c) procedure for addressing failure and corrective action to be taken;

d) validation approval (see 3.3.2.4);

e) process control and routine monitoring (see 3.3.2.5);

f) process/packaging changes and revalidation (see 3.3.2.6).

3.3.2.2 Drafting of validation plan

At a minimum, the validation plan should include the following information:

a) responsibilities (i.e. facility, location, name of person responsible for validation and operator);

b) description of the sealing and closure procedures/SOP's (e.g. heat sealing of pouches, wrapping and closing of sterile barrier system, loading and closure of container);

c) description of the sterile barrier systems used and if relevant, of optional protective packaging (e.g. manufacturer's description);

d) description of sterile barrier system contents utilized. Sterile barrier systems should be assembled as for normal use, see 3.2.2.3, 3.2.2.4, 3.2.2.6 and 3.2.2.7;

e) description of the sterilization process (e.g. moist heat sterilization at 134 °C and 121 °C, Ethylene oxide (EO), Gas plasma, low temperature steam formaldehyde (LTSF)), including the process parameters and loading configuration used;

f) description of transport, distribution and storage of the respective sterile barrier systems;

g) qualification steps (IQ, OQ and PQ), (see ISO 11607-2:2006, 5.2, 5.3 and 5.4) for further explanations for each process see 3.3.2.7., 3.3.2.8, 3.3.2.9;

h) sample size taking into consideration that the number of units to be tested should be based upon a statistically valid rationale (see Annex L);

NOTE It is important to understand that the sample size greatly influences the confidence level and the reliability. Tools for determining sample size can easily be found by searching the internet using the keywords “sample, size, calculator”.

i) acceptance criteria taking into consideration that the user should determine which attributes(s) will be evaluated, the method of evaluation and the results that will be considered acceptable;

j) validation approval.

The validation plan checklist in D.2 to D.4 can be used. A separate validation plan should be used for each different combination of sterilization procedure and sterile barrier system and/or packaging system (manufacturer, type, etc.), the Table D.1 shown in Annex D can be used for organizational purposes.

3.3.2.3 Implementation of validation

After drafting the validation plan, the validation activities will commence according to the validation plan. For guidance specific to each of the three processes described in 3.3.1 above please refer to the following sections: sealing process (3.3.2.7), wrapping process (3.3.2.8), and container process (3.3.2.9).

3.3.2.4 Validation approval

The documented and evaluated validation report should allow traceability and should be approved by the responsible person as defined in the approved validation plan (see D.2 to D.4).

Deviations should be resolved and approved prior to approval of the validation report. The impact of the deviation on the validation study should be assessed to establish if the study should be repeated.

The IQ report should be approved prior to the execution of the OQ. Also, the OQ report should be approved prior to the execution of the PQ.

After each step, failures or deviations should be investigated to determine the root cause and implement corrective action before starting the next validation step. The need for completely or partially repeating the previous validation step should be evaluated. Corrective or preventive actions should be managed using a formal system and the effectiveness of the actions should be evaluated and documented.

3.3.2.5 Process control and routine monitoring

Procedures should be established to ensure that the packaging process is under control and within the established parameters during routine operation.

Critical process parameters should be routinely monitored and documented.

3.3.2.6 Process/packaging changes and revalidation

3.3.2.6.1 Processes should be revalidated if changes are made to the equipment, product, packaging materials or packaging process, which could potentially compromise the original validation and affect the sterility, safety or efficacy of sterile medical devices however, a documented rationale should be developed to support this conclusion.

NOTE The following is a list of changes that could affect the status of a validated process and necessitate the need for revalidation:

— sterile barrier system material changes;

— new equipment;

— transfer of processes and/or equipment from one facility or location to another;

— sterilization process changes;

— review of end user complaints or non-conforming product, negative trends in quality or process control indicators;

— change in sterile barrier system contents that are outside the parameters of the worst-case originally evaluated;

— change of transport route or means (e.g. from within the building only to transport between buildings which may involve significantly changed challenges to the package).

3.3.2.6.2 The need for revalidation should be evaluated and documented. If the change does not require that all aspects of the original validation be repeated, this revalidation does not have to be as extensive as the initial validation, however a documented rationale should be developed to support.

3.3.2.6.3 A documented rationale should be written for the acceptance of changes that are judged to not need revalidation activities (e.g. change of material or material supplier if the supplier provides evidence that the materials are essentially equivalent).

3.3.2.6.4 Periodic revalidation activities, verifications or reviews should be considered since multiple minor changes could cumulatively affect the validation status of the process.

Revalidations can also be used to show that the operation staff still has the required knowledge and competence to carry out the processes in an efficient way and they can also be used to retrain personnel and to realign practices.

3.3.2.7 Validation of the sealing process (pouch, reel or bag forming and sealing) of preformed sterile barrier systems

NOTE Information on the validation of the sealing process of the preformed seals should be available from the preformed sterile barrier system manufacturer, this process validation pertains to the closure seal(s) made at the health care facility's site.

3.3.2.7.1 Installation Qualification

This means that the sealing device should be appropriate and correctly installed. The sealing equipment should come pre-calibrated from the factory with a calibration certificate and the facility should have an ongoing calibration program in place to ensure the correct sealing parameters at the sealing interface. In addition the user should be trained on how to correctly operate the sealing device.

The following IQ aspects should be considered: environmental conditions such as cleanliness, temperature, humidity; documented/operated training; operating manual or procedure.

The following questions should be addressed:

a) Are the critical process parameters defined (e.g. the critical process parameters are at least temperature, contact pressure and sealing/dwell time)?

NOTE 1 If using rotary sealing equipment the dwell time is typically expressed as a sealing speed (i.e. metres per minute). If using a bar sealer, the dwell time is the amount of time the heated bars are in contact with the packaging materials.

b) Is the sealing temperature based on the preformed sterile barrier system manufacturer's recommendations?

c) Is the sealing device equipped with systems to control and monitor the critical process parameters?

d) Is the sealing device equipped with an alarm, warning system or machine stop in the event that the critical process parameters exceed the limits?

e) Are the specifications for seals to be created known and understood (i.e. specific seal width if regulated by national standards)?

f) Are documented plans for preventative maintenance and cleaning available to the users?

g) Have all users been trained how to operate the sealing device and has this been documented?

For the implementation of the IQ the use of a checklist is recommended.

NOTE 2 The IQ checklist in E.1 can be used for documentation purposes.

3.3.2.7.2 Operational Qualification

The sealing temperature range to be used in a health care facility should be determined by that facility using information provided by the preformed sterile barrier system manufacturer and the sealing equipment manufacturer.

The preformed sterile barrier system manufacturer typically provides upper and lower temperature limits, at a defined pressure and dwell time.

The sealing equipment manufacturer typically provides information on how the sealing device monitors critical parameters.

Contact pressure and seal/dwell time are generally present to a certain range by the sealing equipment manufacturer and it is important to ensure that the equipment is capable of obtaining the limits recommended by the preformed sterile barrier system manufacturer. In conditions of use different sterile barrier systems may require different sealing temperatures.

Using the information provided the user should seal sterile barrier systems at the upper and lower limits and evaluate the quality of the seals produced. The sealing equipment should be checked before use that it has been calibrated.

Operators should be trained and assessed for competency in heat sealing process.

Packages should be assembled in accordance with a documented procedure. In assembling these packages the worst-case configuration should be included (see Annex H).

Samples should be sealed and evaluated at each upper and lower variable parameter limit. For a limit to be considered successfully established, all samples should pass the acceptance criteria. The acceptance criteria for sealed sterile barrier systems should include:

a) intact seal for a specified seal width;

b) no channels or open seals;

c) no punctures or tears;

d) no wrinkles or creases that traverse the seal width;

e) after the intended sterilization process, no material delamination or fibre tear upon peel opening that would interfere with the aseptic presentation.

When destructive tests are used for the evaluation of seals multiple sets of packaged products per sealing parameter have to be prepared.

In order to achieve the above acceptance criteria after sterilization a minimum seal strength may be necessary (e.g. EN 868-5 indicates a minimum reference value of 1,5 N per 15 mm for moist heat sterilization processes and 1,2 N per 15 mm for other sterilization processes). If the measurement of seal strength is not performed during OQ, there may be a higher risk of not meeting the acceptance criteria during PQ, which would require performing the OQ again.

These quality properties should be checked with an appropriate system (e.g. commercially available dye penetration test kits or other seal integrity indicator, see Annex A.7.3). The results should be documented.

NOTE 1 Seal integrity indicator should consist of the same material as the porous material of the pouch or reel (e.g. EN 868–3). If the quality properties are achieved at both the upper and lower limits, the set point is typically the average of these two values (e.g. lower limit = 170° C and upper limit = 190° C; sealing temperature = 180° C).

NOTE 2 The OQ checklist in F.1 can be used to define the sealing temperature.

3.3.2.7.3 Performance Qualification

The PQ demonstrates that the process, including both the equipment and the operator, will consistently produce acceptable sterile barrier systems under specified operating conditions.

The following should be considered:

a) Evaluation of the sterile barrier system should be performed after the sterile barrier system has been sealed and sterilized.

b) The batch documentation for batches used during the validation studies should form part of the validation records. The batch identification should include, but is not limited to:

   1) operator;

   2) time and date;

   3) sterilization process, parameters and cycle number ;

   4) sterile barrier system materials used;

   5) contents of sterile barrier system;

   6) heat sealing equipment used.

c) The calibration of the test equipment and sealing equipment should be checked using the procedure recommended by the manufacturer. This should be carried out before sealing takes place.

d) Samples should be sealed and evaluated. All samples should pass the acceptance criteria. For guidance on sample size see 3.3.2.2 h).

   In order to achieve the acceptance criteria after sterilization a minimum seal strength may be necessary, (e.g. EN 868-5 indicates a minimum reference value of 1,5 N per 15 mm for steam sterilization processes and 1,2 N per 15 mm for other sterilization processes).

   When destructive tests are used for the evaluation of seals multiple sets of packaged product per sealing parameter have to be prepared.

e) Three batches or sets of sealed sterile barrier systems should be made; these batches should encompass the potential significant sources of variation such as operator, time of day, material (size,

source, lot), sterile barrier system contents. Package contents that present the greatest challenge (worst-case) should be included.

f) Test samples of the sterile barrier system should be sterilized using the sterilization process(es) previously identified as being appropriate to demonstrate suitability of the sterile barrier system. Three batches of test samples should be exposed to the same sterilization process in three separate cycles to demonstrate reproducibility.

g) The sterile barrier systems should be evaluated after exposure to the sterilization process and after the expected worst-case handling, distribution, and storage conditions until the point of use, using acceptance criteria from OQ. Results should be documented. See also 3.2.3 and ISO 11607-1:2006, 6.3.

NOTE The checklist for the PQ in G.1 can be used for documentation purposes.

3.3.2.7.4 Self-sealing or taped pouches

While the use of self-sealing or taped pouches is discouraged when heat sealing equipment and pouches are available, the assembly and closure of these should be validated if they are used (see requirements in ISO 11607-2:2006, 5.1.1). All appropriate elements and steps of validation detailed in ISO 11607-2:2006, Clause 5 should be addressed.

3.3.2.8 Validation of the wrapping process (folding and closing of sterilization wraps)

3.3.2.8.1 Installation Qualification

Although a wrapping process is typically a manual process, the following IQ aspects should be considered: environmental conditions such as cleanliness, temperature, humidity; documented/operated training; operating manual or procedure.

3.3.2.8.2 Operational Qualification

There should be a documented procedure for assembly of packages. This method should consider 3.2.2.3 and 3.2.2.6.3. Guidance on the assembly and closure of wrapped packages can be obtained from the wrap manufacturer.

Operators should be trained and assessed for competency. The folding methods should constitute a tortuous pathway to impede passage of microorganisms (see Annex C).

Packages should be assembled in accordance with a documented procedure. In assembling these packages the worst-case configuration should be included, see Annex H. Samples should be closed/sealed and evaluated. All samples should pass the acceptance criteria. For guidance on sample size see 3.3.2.2 h) and Annex L.

Depending upon the test methods used for the evaluation of the closure(s) multiple sets per batch should be prepared.

Sterile barrier systems are evaluated for sterile barrier system integrity and proper closure. Acceptance criteria should include, but are not limited to:

a) closure continuity and integrity;

b) absence of channels, openings or gaps;

c) absence of punctures or tears;

d) absence of material delamination or separation upon opening;

e) unwrapping or opening should demonstrate that the sterile barrier system is capable of enabling aseptic presentation of the contents.

f) sterilization parameters are achieved

g) drying parameters are achieved.

In addition to the evaluation of the closed sterile barrier systems the package should be opened and assessed for conformance to the documented assembly procedure.

NOTE The OQ checklist in F.2 can be used.

3.3.2.8.3 Performance Qualification

The PQ demonstrates that the wrapping process will consistently produce acceptable sterile barrier systems under specified operating conditions:

a) Evaluation of the sterile barrier system should be performed after the sterile barrier system has been closed and sterilized.

b) The batch documentation for batches used during the validation studies should form part of the validation records. The batch identification should include, but is not limited to:

   1) operator;

   2) time and date;

   3) sterilization process, parameters and cycle number;

   4) sterile barrier system materials used;

   5) closure tape used;

   6) contents of sterile barrier system;

c) Three batches of test samples should be exposed to the same sterilization process in three separate cycles to demonstrate reproducibility.

d) Three batches or sets of closed sterile barrier systems should be assembled in accordance with the facility's documented procedures. These three batches should encompass the potential significant sources of variation such as operator, time of day, material (size, source, lot), sterile barrier system contents. The contents that present the greatest challenge (worst-case) should be included. If a reusable sterile barrier system is exposed to multiple and/or different sterilization processes to achieve terminal sterilization the validation should cover all processes in the order performed. The reuse of sterile barrier systems intended for single use is bad practice and should not be permitted.

e) Samples should be sealed/closed and evaluated. All samples should pass the acceptance criteria. For guidance on sample size see 3.3.2.2 h).

f) Depending upon the test methods used for the evaluation of the closure(s) multiple sets per batch should be prepared.

g) The sterile barrier systems should be evaluated after exposure to the sterilization process and after the expected worst-case handling, distribution, and storage conditions until the point of use, using acceptance criteria from OQ. Results should be documented.

   NOTE The checklist for the wrapping process PQ in G.2 can be used for documentation purposes.

3.3.2.9 Validation of the container process (filling and closing of re-usable containers)

ISO 11607-2 and this guidance address filling and closing of re-usable containers; however, they do not address cleaning or decontamination of these containers prior to their reuse. In real hospital application, reusable containers should however be subjected to a validated cleaning/decontamination process prior to filling and closing.

When performing process validations using reusable containers, it is important to make sure that all the manufacturer's instructions are met and documented for each container used in the validation (e.g. condition of gasket, container, etc.).

3.3.2.9.1 Installation Qualification

Although filling and closing of containers is typically a manual process, the following IQ aspects should be considered: environmental conditions such as cleanliness, temperature, humidity; documented/operated training; operating manual or procedure. If equipment is used, then IQ should be performed in accordance with ISO 11607-2:2006, 5.2.

3.3.2.9.2 Operational Qualification

There should be documented procedures for assessment for damage, filling and closing of the containers. These procedures should consider 3.2.2.3 and 3.2.2.6.4. Details should be obtained from the manufacturer.

Operators should be trained and assessed for competency. The SOP has to be written and approved prior to beginning the process qualification.

Containers should be cleaned and inspected, loaded and closed with a tamper evident system in accordance with the manufacturer's instructions and facility's documented procedure. In determining or choosing the contents of these containers the worst-case configuration of content should be included, (e.g. container loading with respect to weight, volume, and material). Sterile barrier systems where typical adjustments such as filter changes have been made by the operator should also be included. All samples should pass the acceptance criteria. For guidance on sample size see 3.3.2.2 h). For this qualification the samples may be assembled at one time or over time using the same container(s), depending on the conditions of use. Depending upon the test methods used for the evaluation of the closure(s) multiple sets per batch should be prepared.

Assembled sterile barrier systems should be evaluated for sterile barrier system integrity and proper closure. Acceptance criteria should include, but are not limited to checking:

a) the sealing, mating surfaces, and edges of the container system and lid to ensure that they are not dented or chipped;

b) that filter retention mechanisms and fasteners, such as screws and rivets, are secure and not distorted or burred;

c) that securing mechanisms are functioning properly;

d) that the integrity of the filter media is not compromised;

e) that gaskets are pliable, securely fastened, and without breaks or cuts;

f) that valves work freely;

g) closure continuity and integrity;

h) no damage of filters, mechanical valve elements, or sterilant port;

i) ability to open container without damage to contents;

j) the container should allow for aseptic presentation of the contents;

k) tamper evident mechanism is effective and intact;

l) sterilization parameters are achieved;

m) drying parameters are achieved.

In addition to the evaluation of the closed sterile barrier systems the containers should be opened and assessed for conformance to the documented cleaning, inspection and loading portion of the assembly procedure.

NOTE The OQ checklist in F.3 can be used.

3.3.2.9.3 Performance Qualification

The manufacturer of the container should provide evidence to demonstrate the suitability of the container with a specified sterilization process and of the ability of the sterilized container to maintain sterility of its contents. The PQ demonstrates that the process of loading, filling and closing will consistently produce acceptable sterile barrier systems under specified operating conditions.

Evaluation of the sterile barrier system should be performed after the sterile barrier system has been closed and sterilized. The following points need to be considered:

a) The batch documentation for batches used during the validation studies should form part of the validation records. The batch identification should include, but is not limited to:

   1) operator identification;

   2) time and date;

   3) sterilization process, parameters and cycle number;

   4) sterile barrier system materials used;

   5) any tamper evident closure used;

   6) contents of sterile barrier system;

b) Three batches or sets of closed sterile barrier system(s) should be assembled in accordance with the facility's documented procedures. These three batches should encompass the potential significant sources of variation such as operator, time of day, material (size, source, lot), sterile barrier system contents. The contents that present the greatest challenge (worst-case) should be included. If the same sterile barrier system is intended to be used in several different sterilization processes each should be validated.

c) All samples should pass the acceptance criteria. For guidance on sample size see 3.3.2.2 h).

d) The sterile barrier systems should be evaluated after exposure to the sterilization process and after the expected worst-case handling, distribution, and storage conditions until the point of use, using acceptance criteria from OQ. In addition to the OQ acceptance criteria contents should be assessed after sterilization to ensure that sufficient drying has occurred in moist heat sterilization process.

e) Three batches of test samples should be exposed to the same sterilization process in three separate cycles to demonstrate reproducibility.

f) All evaluation results should be documented.

   NOTE The checklist for the PQ in G.3 can be used for documentation purposes.

g) If packaging failures are found, investigation should be made to identify a root cause, see Annex R.

3.4 Quality system

ISO 11607-1:2006, 4.2 and ISO 11607-2:2006, 4.2 require a formal quality system and no further guidance is given.

4 Guidance for industry

4.1 General guidance

4.1.1 Quality systems

4.1.1.1 The application of ISO 11607-1 should be performed within a formal quality system (ISO 11607-1:2006, 4.2).

4.1.1.2 A critical element of this quality system is design control. Design control procedures are intended to ensure that the design of the packaging system and any modifications or revisions meet the specified design requirements ISO 11607-1:2006, 6.2.1.

For further information on developing the specified design requirements see 4.3 and Annex J on design inputs.

4.1.1.3 The design history file typically provides documentation of the packaging system development process and any later modifications or revisions (ISO 11607-1:2006, 4.5 and 6.2.5).

4.1.1.4 A fundamental requirement of many quality systems is risk management. A formal risk analysis should be conducted to anticipate the possible failures that can occur in the packaging process and their effects on the safety and efficacy of the medical device. The key requirement is to design the packaging system to minimize the safety hazard to the patient and user under the intended specified conditions of use (see ISO 11607-1:2006, 6.1.1). ISO 14971 describes the requirements and applicability of risk assessment within the scope of medical devices. Tools for conducting risk analysis are described in Annex K.

4.1.1.5 For references on regulatory frameworks, design controls and other quality system aspects see Annex N.

4.1.2 Test methods

ISO 11607-1 and ISO 11607-2 require that all test methods used to show compliance with this standard are validated (see Annex O). For guidance on the requirements on test methods in ISO 11607-1 and ISO 11607-2, see Annex A of this document.

Test methods that have been subjected to systematic inter-laboratory studies are preferred since the repeatability, reproducibility, and in some cases the sensitivity have been determined. When incorporating these methods into a specific laboratory it is important to demonstrate the accuracy and repeatability of the method are at least as good as the reproducibility from inter-laboratory studies.

Test methods developed independently or from the scientific literature can be used. However it is important to determine if the test method meets the required sensitivity and that the accuracy and repeatability meet predetermined criteria.

4.1.3 Sampling

Sampling plans should be applicable to packaging systems, reflective of risk tolerance, and be based on statistically valid rationale (ISO 11607-1:2006, 4.3). See 4.8.2 and I.4 for further information.

4.2 Design inputs

Prior to considering materials and/or packaging system design, a set of design inputs should be developed (ISO 11607-1:2006, 6.2.2 and 6.2.3). These will be used in assessing the materials and/or design.

The design inputs will reflect user needs. This information will come from users engineering, manufacturing, marketing, regulatory, etc. Some examples of design inputs are medical device attributes,

medical device protection requirements, sales unit configuration, sterilization process, distribution, handling, and use environment (ISO 11607-1:2006, 6.1 and 6.2).

NOTE For guidance on developing these design inputs see Annex J.

4.3 Selection and evaluation of materials

NOTE Information on these topics may be found in Annex A.

4.3.1 Guidance on sterilization requirements (ISO 11607-1:2006, 5.1.6 e) and 5.3)

When assessing the material characteristics important to the medical device, process, and end use, it is critical to keep in mind that the material possesses characteristics appropriate for the sterilization process (e.g. porosity for gaseous sterilization) as well as be able to withstand the rigors of the sterilization process. There are further details on sterilization in Annex B.

4.3.2 Guidance on safety requirements (ISO 11607-1:2006, 5.1.5 and 5.1.6)

When choosing a material for a sterile barrier system there are basic safety requirements that should be met. The source, history and traceability of materials should be known and controlled. Chemical properties should be evaluated. This will typically include toxicity and an evaluation of possible chemical interactions between material and medical device. Testing for the presence of toxic heavy metals is often included. Further details are provided in Annex A.

4.3.3 Guidance on barrier requirements (ISO 11607-1:2006, 5.1.4 and 5.1.6)

The barrier requirements of the medical device and the chosen sterilization method will help define the appropriate sterile barrier and packaging system materials. Various methods can be used to assess the material characteristics and evaluate the barrier or barrier levels required to protect the medical device. Some of the areas to consider include porosity, microbial barrier, air (oxygen), moisture, temperature and light transmission. These are detailed in the section on barrier in Annex A.

4.3.4 Guidance on visibility and appearance requirements

Visibility and appearance requirements, if applicable, will be determined by the desired aesthetics (for example a sterile barrier system with high gloss versus one with a matte finish), labelling approach (for example, a label insert may require a sterile barrier system with good clarity), and the desire to see (or mask) the device. Areas to consider are haze, gloss, opacity, and clarity; further information is in Annex A.

4.3.5 Guidance on physical property requirements (ISO 11607-1:2006, 5.1.6 c), 5.1.7 e), and 6.3.2)

The sterile barrier system should be capable of protecting the medical device's sterility, efficacy, and/or functionality until time of use. The sterile barrier system or preformed sterile barrier system physical property requirements will depend on the mass and profile of the contents, the type of protective packaging (if applicable), storage conditions and the distribution system. There are several factors that impact material performance. Examples include resistance to puncture, abrasion, and tear, flexural durability, thickness, and basis weight. These factors are detailed further in Annex A. Test methods to assess physical properties will characterize the material, but are not directly predictive of completed sterile barrier system performance and further evaluation, such as laboratory simulated packaging system performance tests, frequently need to be performed to assess material performance of the sterile barrier system for a specific medical device.

4.3.6 Guidance on heat sealability requirements [ISO 11607-1:2006, 5.1.6 d) and 5.1.8 c)]

Seals should be tested for tensile peel strength and reviewed to determine if the results meet the desired seal strength for the sterile barrier system. Other criteria include peelability, seal visual attributes, and

failure of material(s) during opening. A tensile test of the seal is typically used as a screening tool for selection of material combinations and can be used to evaluate heat seals pre and post sterilization. A number of different test methods for seal strength can be used. See Annex B of ISO 11607-1. ASTM F88 contains details of some of these methods and also includes information on the effect of differences in technique.

4.3.7 Guidance on processing requirements (ISO 11607-1:2006, 5.1.2 to 5.1.9)

As packaging materials are evaluated for compatibility with equipment and processing conditions, consideration needs to be given to predetermined requirements which ensure consistent and reliable production of sterile barrier systems. Common methods used to assess process requirements and conditions are dimensional measurements, coefficient of friction (COF), sealability, and coat weight: these are discussed in more detail in Annex A.

4.3.8 Guidance on printing requirements (ISO 11607-1:2006, 5.4)

It is important to keep in mind the attributes of the packaging materials when designing the print. Font sizes or styles may be inappropriate for specific substrates, print colour(s), artwork placement and copy should also be considered. Evaluations of new substrates need to consider the ability to be printed. Printed ink properties need to ensure physical and chemical resistance to degradation, and printed process indicators function for the intended exposure or sterilization process(es). Thought should be given to printing before and/or after forming to guarantee that the graphical appearance is not significantly altered and the information to be conveyed is not rendered illegible. For further information on evaluating materials for specific printing requirements see Annex A.

4.3.9 Guidance on cleanliness and particulate requirements [ISO 11607-1:2006, 5.1.7d)]

Typical cleanliness expectation is that packaging materials should be adequately free of dirt, dust, grease, and other forms of contamination. Particulates may be embedded or loose, foreign or bits of parent material. For further information on particulates see Annex A. The level of particulate inherently present will be dependent upon the packaging material chosen. Size of particulate is frequently estimated using a TAPPI Dirt Estimation Chart.

4.3.10 Device-packaging system interaction

Material stiffness, sticking, discoloration or other attributes could interact with the medical device use.

Sterile barrier system components could migrate into the medical device (leachables) and interact with its contents, which could lead to adverse effects. In the same way, medical device materials could migrate into the packaging system materials resulting in adverse effects. The risk needs to be assessed and compatibility studies should be performed as appropriate.

4.4 Sterile barrier system and protective packaging design (packaging system development)

4.4.1 Key elements in the design

Use documented procedures for the design and the development of the sterile barrier system and protective packaging (ISO 11607-1:2006, 6.2.1).

A key component of the packaging system design process is gathering and assessing the design inputs (ISO 11607-1:2006, 6.2.2 and 6.2.3), these have been previously covered in 4.3 and Annex J.

The package development function should be included in the design control system or process. The process of designing a packaging system for a terminally sterilized medical device should begin very early in the overall development cycle for the medical device. It is important to be engaged in the medical device development process and have a keen understanding of all of the attributes of the medical device, including all relevant medical device, sterilization and manufacturing specifications.

Sterile barrier system and protective packaging (i.e. packaging system) design may be performed in conjunction with a contract packager. Guidance on the use of contract packagers may be found in Annex P.

4.4.2 Steps in packaging system design

4.4.2.1 Design the sterile barrier system

4.4.2.1.1 The goal of the package design process is a sterile barrier system which allows the medical device to be sterilized, maintains sterility to the point of use or expiry date and allows the medical device to be presented in an aseptic manner at the point of use (ISO 11607-1:2006, 6.1 and 6.2).

4.4.2.1.2 Select the type of sterile barrier system and the materials of construction based on the information (design inputs) gathered through participation in the medical device development process. Some common preformed sterile barrier system types and sterile barrier system types are:

a) preformed tray and lid (ISO 11607-1:2006, A.3.2):

b) preformed pouch (ISO 11607-1:2006, A.3.3);

c) preformed sterilization bag (ISO 11607-1:2006, A.3.4);

d) preformed header bag (ISO 11607-1:2006, A.3.5);

e) reusable containers (ISO 11607-1:2006, A.3.12);

f) self-contained products with tortuous path closures (ISO 11607-1:2006, A.3.11);

g) those requiring fabricating of sterile barrier system and making all seals – form/fill/seal and four-side-sealing (ISO 11607-1:2006, A.3.6 and A.3.7).

4.4.2.1.3 Specify and document the materials, dimensions, tolerances, geometry and physical characteristics of the sterile barrier system, in accordance with the procedures outlined in the quality system.

NOTE Assure tolerances are reasonable for the supplier capabilities and the equipment being used.

4.4.2.2 Design the protective packaging

The protective packaging provides physical protection to the sterile barrier system and its contents.

Specify and document the materials, dimensions, geometry, and physical characteristics of the protective packaging, in accordance with the procedures outlined in the quality system.

4.4.2.3 Prototype the packaging system

a) If assessment is successful, proceed to feasibility testing;

b) If the prototype packaging system is unacceptable, return to the design phase;

NOTE Guidance for packaging system design feasibility testing may be found in S.2.

4.4.2.4 Labelling considerations for the packaging system design

NOTE The design and printing of labelling is a critical and time-consuming activity in the medical device industry. The responsibility for specifying the labelling content is not generally the sole responsibility of the packaging area or group. Assuring that this specified labelling is incorporated into the packaging system is usually the responsibility of the packaging area or group.

4.4.2.4.1 The completed labelling system should remain intact and legible at the point of use, be compatible with all materials and processes, and not transfer to the medical device or react with the packaging system in a way that impairs the utility of the packaging system.

4.4.2.4.2 Determine if labelling will be accomplished by printing directly on the packaging materials or by affixing labels to the packaging system.

4.4.2.4.3 If labels are used, specify the dimensions of die cut label stock, materials, coatings, and adhesives.

4.4.2.4.4 If labels are used, determine whether they will be pre-printed or printed on the manufacturing floor.

4.4.2.4.5 Specify the type of printing to be used. Printing types include but are not limited to laser, ink jet, and thermal transfer.

4.4.2.4.6 If necessary, specify system of printing variable medical device information on the labels. Variable information includes but is not limited to lot or serial number, manufacturing date, and expiry date.

4.4.2.4.7 Incorporate instructions for use (IFU) and any included medical device literature into the packaging system design.

4.5 Packaging process feasibility evaluation

NOTE Feasibility is not a requirement of ISO 11607-1 or ISO 11607-2. This section is used to assess the feasibility of the packaging system.

4.5.1 Sterile barrier system manufacturing process

Define the manufacturing process for the chosen sterile barrier system. Establish a process map or flow chart for the manufacturing process. Show each stage of the fabricating, loading, sealing, and packing process. For each step, analyse potential risks for failure of the sterile barrier system or packaging system as well as sources of variation that could lead to quality issues. Evaluate risks, decide on ways to control and redesign the packaging process accordingly (for guidance see Annex K). Indicate packaging system material and medical device movement. For guidance on detailed analysis see Annex S. For guidance on determining process parameters, see Annex Q.

4.5.2 Equipment Installation Qualification guidance

Determine equipment IQ requirements for each stage/piece of equipment defined in the process map or flowchart. See ISO 11607-2:2006, 5.2 for discussion of IQ as well as 4.8.

a) If using existing equipment, determine whether new or current tooling will be used and assess IQ accordingly.

b) If using new equipment, perform IQ.

4.5.3 Prototype or trial runs

Producing prototype packaging for initial performance testing is recommended as it reduces the risk for failure during validation of the packaging process.

Prototype sterile barrier systems should be produced using process parameters that are to be used for sterile barrier system performance testing.

4.6 Sterile barrier system design feasibility evaluation

4.6.1 General considerations

4.6.1.1 This is an engineering evaluation in which the sterile barrier system (possibly only a prototype at this point) is subjected to testing. Results of this testing determine if the design is worth pursuing.

4.6.1.2 This testing typically assesses:

a) Whether the sterile barrier system contained the medical device and protected it from being physically damaged.

b) Possible interactions between sterile barrier system and contents.

4.6.1.3 While this step is frequently not a full-scale validation, useful guidance may be found in Annex I, generating a final packaging system validation protocol.

4.6.2 Sterile barrier system test method

4.6.2.1 Use a documented test plan employing validated test methods (ISO 11607-1:2006, 6.3.2). See Annex A for further information on test methods.

4.6.2.2 This test plan should include pass-fail criteria.

4.6.2.3 Sterile barrier system tests should be conducted on samples that have been constructed considering the worst-case elements identified in 4.6.3 (ISO 11607-1:2006, 6.3.4).

4.6.2.4 Samples should be exposed to dynamic testing which simulates the expected distribution environment (ISO 11607-1:2006, 6.3.5).

4.6.3 Worst-case feasibility condition

NOTE Further guidance on addressing worst-case may be found in Annex H.

To properly determine feasibility, determine worst-case conditions, or what at this point in the process are believed to be worst-case, for a number of factors related to the packaging system. These include but are not limited to:

a) sterile barrier system manufacturing (sealing parameters, etc.);

b) sterilization process (parameters, number of cycles, etc.): it may not be necessary for the samples to be sterilized for initial feasibility testing;

c) shipping configuration: this requires an understanding of how the medical device will be shipped to the customer;

d) distribution environment: this requires an understanding of how the medical device will be shipped to the customer;

e) shelf life testing is usually not required at this point; however accelerated aging may be used. Accelerated aging testing allows the simulation of the effects of time on a packaging system by subjecting the fully processed protective packaging system to elevated temperatures in a controlled environment. Real time is generally estimated by assuming the degradation of packaging materials follows the kinetics described by the Arrhenius reaction rate function. For further guidance see ISO 11607-1:2006, Annex B.

4.6.4 Pass/fail status of packaging system

4.6.4.1 On completion of testing determine whether the packaging system met the acceptance criteria for the feasibility tests.

4.6.4.2 The packaging system passes the feasibility testing if the packaging system met all criteria set forth in the test plan. This establishes confidence that the design will work. Begin preparing for packaging system validation, typically performed on a validated manufacturing process as in 4.7.

4.6.4.3 If the packaging system failed to meet all of the criteria set forth in the test plan, the failure modes should be determined and investigated. Corrective action(s) for the failures should be put in place. This may include redesigning the concept and repeating feasibility. Guidance on determining failure mode and appropriate corrective action may be found in Annex R.

4.7 Validation of sterile barrier system manufacturing process

Validation of the sterile barrier system often means the involvement of additional functional elements of the medical device manufacturer, and/or contract packagers and packaging suppliers. For preformed sterile barrier system, the medical device packager's process is often limited to the filling and application of a sterile barrier system closure seal. In the event a form-fill-seal method is employed, the medical device packager typically performs the validation of the sterile barrier system formation and the closure following insertion of the medical device. It is recommended to review this guidance along with ISO 11607-2.

4.7.1 Development of written process validation protocol

4.7.1.1 Validation protocols may be written for sterile barrier system families. The rationale for determining the sterile barrier system families to evaluate should be documented.

4.7.1.2 Often historical data exists for specific material combinations. This information should be evaluated to determine if it is appropriate for use. Document the rationale.

4.7.1.3 IQ activities need to be planned and documented. If an IQ has been previously performed on the equipment of interest, this work should be assessed to determine if it meets the needs of the current validation activities.

4.7.1.4 OQ activities need to be planned and documented. The acceptance criteria need to be detailed. These predefined requirements generally include dimension, seal strength, seal integrity, opening features, and material integrity.

4.7.1.5 PQ activities need to be planned and documented. The acceptance criteria need to be detailed. These predefined requirements generally include dimension, seal strength, seal integrity, opening features, and material integrity.

4.7.1.6 The process validation protocol needs to be reviewed and approved by appropriate personnel.

4.7.2 Performance of validation activities detailed in protocol

4.7.2.1 Installation Qualification (if not satisfied from previous IQ work) (ISO 11607-2:2006, 5.2)

IQ activities may include:

a) establishing an installation checklist:
   - equipment design features;
   - installation conditions;
   - safety features;
   - supplier documentation, prints, drawings, and manuals;
   - spare parts list;

b) verifying that the equipment operates within design parameters;

c) performing software validation;

d) establishing environmental conditions;

e) establishing approved SOP's for equipment operation and documenting operator training;

f) verifying that critical process parameters are controlled and monitored, such as
   - temperature;
   - pressure or gauge pressure;
   - dwell;

g) establishing calibration procedures and schedules;

h) establishing preventive maintenance cleaning procedures and schedules.

4.7.2.2 Operation Qualification (ISO 11607-2:2006, 5.3)

4.7.2.2.1 Perform engineering studies to establish a worst-case operating window. Typically, this is the extremes of the operating window (e.g. lowest and highest temperature, lowest and highest pressure, and shortest and longest dwell.) This window should be assessed to verify that it is appropriate given the capability of the process. The conclusions drawn should be documented.

4.7.2.2.2 Samples produced under worst-case conditions need to be included in the performance testing protocol, which will make sure that the entire process window is validated (see ISO 11607-1:2006, 6.3.4 and Annex H). Samples for performance qualification can be built during the OQ if manufactured under conditions confirmed under PQ.

NOTE Further guidance on addressing worst-case conditions can be found in Annex H.

4.7.2.2.3 Verify that all control measures defined in the risk management process are in place and operate effectively.

4.7.2.2.4 Verify that the sterile barrier system produced at operating extremes will reliably meet the acceptance criteria defined in the protocol.

4.7.2.3 Performance Qualification (ISO 11607-2:2006, 5.4)

Three successful production runs are typically evaluated. These runs are produced at normal operating conditions and the runs can be interrupted by other manufacturing processes on the equipment. However, all three production runs for PQ need to be successful without a failed run in between. Considerations should be given to sufficient run time, and the effects of changeovers, breaks, and multiple shifts. Verify that the sterile barrier system produced meets the acceptance criteria defined in the protocol.

4.7.3 Assessment of validation results

Assess validation results (ISO 11607-2:2006, 5.4.7). Assess the activities performed in 4.7.2 to verify that they meet the acceptance criteria detailed in 4.7.1.4 and 4.7.1.5. Any deviations from the protocol need to be documented, and reviewed and assessed to determine if the intent of the validation protocol has been met.

4.7.4 Approval of process validation

The process validation needs to be reviewed and approved by appropriate personnel (ISO 11607-2:2006, 5.5).

4.7.5 Establishment of documented ongoing process control and monitoring

Establish documented ongoing process control and monitoring (ISO 11607-2:2006, 5.6). This typically includes:

a) monitoring and recording critical process parameters, and

b) in process testing of sterile barrier systems in accordance to the quality system.

NOTE Selected monitors must be suitable for monitoring the process. Use data and process knowledge to choose monitor(s) suitable for the process as reflected in the Quality System.

4.8 Packaging system design validation

4.8.1 General

The packaging system design validation (ISO 11607-1:2006, 6.3, 6.4) includes:

a) developing a validation protocol, which is the plan by which the packaging system will be tested,

b) performing the conditioning and testing defined in the protocol,

c) assessing whether the test results obtained meet the acceptance criteria detailed in the protocol, and

d) obtaining formal approval of the validation.

4.8.2 Validation protocol

The validation protocol should include detailed information on the following subjects:

a) Establish the plan objectives, which may include physical testing to see if the sterile barrier system has maintained its integrity after life cycle events such as sterilization, packaging system simulated distribution testing, and stability testing. Alternatively, stability testing may be performed during the feasibility portion of the design activities and should be conducted separately.

   NOTE Microbial testing methods may be necessary for tortuous path closures.

b) Establish the packaging system details and specification, for both the sterile barrier system and any additional layers of protective packaging. Ensure specifications are controlled prior to finalization test protocol.

If using the same packaging system for multiple medical devices or a family of medical devices, then a rationale should be developed indicating that the other included medical devices provide a less severe challenge than the specific configuration to be validated.

c) Establish the sampling plan to be used: sample sizes need to be large enough to provide for statistically significant analysis to provide a high degree of reliability, and will be dependent on corporate risk policy, economics, and regulatory requirements. For further guidance see I.4.

Prepare the packaging system as follows:

— the sterile barrier system used in the packaging system to be tested should be manufactured in a validated process or a process that will be validated. Samples for testing should be production or production equivalent to those made in the validated process;

— the sterile barrier system or packaging system should be sterilized in the anticipated medical device/ packaging configuration and in a validated sterilization process. If specified, the sterilization process may be performed multiple times to simulate worst-case conditions;

— packaging systems to be tested should contain the sterile barrier system with medical devices or a medical device surrogate inside, labelling, IFU's, and all additional packaging layers.

d) Define the accelerated aging to be performed, for a discussion of accelerated aging see I.8 and A.12 and for stability testing see Annex M.

e) Define the handling, distribution, and storage testing to be performed; for a discussion of these see I.7 and A.12.

f) Select appropriate test methods for the packaging systems to be tested, for guidance on test methods see Annex A.

g) Establish the acceptance criteria based on risk policy and a measured result such as maintenance of sterile barrier system/packaging system integrity and/or medical device functionality.

h) Review and approve all documentation by the appropriate personnel.

For further guidance on these subjects, see Annex I, generating a packaging system validation protocol.

4.8.3 Performing testing

Tests should be performed according to the protocol. Any deviations to the protocol should be documented and a rationale provided.

4.8.4 Documenting validation results

Results of testing should be compared to the acceptance criteria defined in the protocol and this assessment of passing or failing the protocol should be documented.

Validation reports and gathered data should be maintained in accordance with the quality system requirements. The last step is the formal approval of the final report.

4.9 Revalidation

4.9.1 Revalidation is required when changes have been made to the medical device, packaging system, process, or equipment that will affect the original validation. Some examples are changes in physical characteristics of medical device contained in the sterile barrier system, process locations,

methods of formulation or type of equipment, component manufacturer, and analytical techniques used (ISO 11607-2:2006, 5.7).

4.9.2 Revalidation concerns are frequently addressed in the quality system procedures or in the original validation protocol.

4.9.3 Revalidation is often affiliated with design control and the associated change control procedure, the extent of the revalidation chosen will depend on the nature of the change and how it affects the process or medical device. For further references on design control see Annex N.

4.9.4 Review of the process, medical device, packaging system should be considered periodically to ensure that multiple minor changes, which did not require revalidation, have not affected the packaging system (ISO 11607-2:2006, 5.7.4).

Annex A
(informative)

Selection, evaluation and testing of packaging materials and sterile barrier systems — Guidance for industry and health care facilities

A.1 General

Choosing an appropriate packaging material for a sterilizable medical device requires careful consideration, and should not be made in haste (ISO 11607-1:2006, 5.1, Clause 6). Aspects of the sterile barrier system to be considered include compatibility with sterilization, robustness with respect to shipping and handling, barrier properties, and a number of considerations regarding end use of the medical device. It is most desirable to include packaging system material selection early in the design process of the medical device. Leaving this important consideration until the end of the design process can result in delays in a medical device being introduced into the marketplace, or impose limitations on shelf life or other end use considerations. Manufacturers of medical packaging can be a significant asset in determining suitable options.

Test methods exist to provide measures of sterile barrier systems and/or packaging systems and packaging materials, both to assess suitability for use and as a means of monitoring the manufacturing process. Test methods that have statements of precision and bias are preferred, see ISO 11607-1:2006, Annex B. Not all test methods are appropriate all of the time. The choice of which test method to employ is driven by the requirements of the medical device through its life cycle, and should be chosen such that the parameters probed are closely related to medical device sterile barrier system and/or packaging system attributes. Additionally, some test methods are most appropriate for research and development and others for compliance monitoring. Annex A is not intended to serve as a compendium of available test methods, but rather to serve as a brief overview of the more common ones and the rationale behind their applicability. For a guide to available tests see EN 868 series or ASTM F2097, a publication of the Sterilization Packaging Manufacturers Council (SPMC) of the Flexible Packaging Association (FPA).

A.2 Compatibility with the sterilization process

A.2.1 The ability of packaging materials to withstand the sterilization process and to maintain their structural integrity are critically important requirements for a sterile barrier system and/or packaging system (ISO 11607-1:2006, 5.3, 6.1.3). As a result, the method(s) of sterilization should be identified early.

A.2.2 Gaseous sterilization processes such as EO, and moist heat sterilization processes and others, require the removal of air and penetration of the sterilizing agent though the sterile barrier system and/or packaging system. They also require elevated temperature and humidity conditions, with which the materials chosen need to be compatible. The introduction and evacuation of these sterilant gases also challenges the sterile barrier system with pressure changes, so overall sterile barrier system and/or packaging system robustness and an adequate unhindered porous region of the sterile barrier system and/or packaging system are required, as is suitable room in all additional layers of packaging to accommodate sterile barrier system expansion.

A.2.3 While material changes due to EO are often negligible, other methods, such as radiation or gas plasma, can effect significant changes in material properties, see AAMI TIR 17.

A.2.4 It is imperative that the type and number of anticipated sterilization cycles are evaluated, preferably on the final sterile barrier system, including the medical device, as part of the selection process. Annex B offers a more detailed review of sterilization methods to assist with material selection.

A.3 Safety considerations

A.3.1 Most aspects of packaging material safety can be addressed systematically through standard tests and certifications obtained from packaging suppliers. The exception is any interaction between sterile barrier system material and the medical device, which is best determined only by the medical device manufacturer.

A.3.2 Complete traceability of sterile barrier system and/or packaging systems and its components is typically maintained by the manufacturer of medical packaging, primarily as an aid in determining the root cause of any non-conformances.

A.3.3 Packaging materials should be non-toxic. Guidance to assess biocompatibility can be found in ISO 10993-1 and ASTM F2475.

Although not required by medical packaging regulations, food packaging regulations are commonly used as the first point of reference when evaluating the toxicological properties of packaging materials e.g. FDA Code 21 CFR 170 –189, BFR 36 XXXVI and the European Commission Regulation No 10/2011 on plastic materials and articles intended to come into contact with food. Biocompatibility testing is subsequently carried out depending on the specific application.

An additional safety concern that may be relevant is the possibility of extractables that may leach out of packaging materials over time, potentially contaminating the medical device or the environment. ASTM D4754 deals with extractables testing.

A.4 Barrier guidance

A.4.1 All sterilizable medical packaging materials for sterile barrier systems need to provide an effective microbial barrier (ISO 11607-1:2006, 5.2). In non-porous materials this requirement is met by demonstrating that the material does not permit the passage of air, as detailed in ISO 11607-1:2006, Annex C. In porous packaging materials, the microbial barrier can be assessed using test methods as listed in ISO 11607-1:2006, Annex B.

A.4.2 In addition to microbial protection, a sterile barrier system may need to provide a barrier to the passage of gases or light. Note that in this context gas transmission is a separate topic from porosity, and refers to the much slower migration of gas molecules through a solid material. Medical devices that need to retain or are sensitive to moisture or which are affected by oxygen or other gases will require packaging materials that provide a specific barrier for the gas or vapour of interest. Water vapour transmission is covered by ASTM F372 and ASTM F1249 while oxygen transmission can be quantified by use of ASTM D3985.

A.4.3 Quantification of light permeation can be accomplished spectroscopically with foreknowledge of the wavelengths of light that are of interest. Manufacturers of medical packaging materials can provide information regarding the barrier characteristics of the material but the medical device manufacturer's sterile barrier system and/or packaging system validation will assess whether a given material meets a specific medical device's requirement.

A.4.4 Contamination can be both airborne and waterborne. The wet bacterial barrier performance is governed by the ability of the packaging material to be as much water resistant as possible.

A.5 Visibility and appearance of the medical device

Several standard test methods exist which can be used to compare packaging materials to each other or to gauge the ability of a material to meet medical device visibility or appearance goals. Haze, which describes the scattering of light as it passes through a material, can be measured using guidance from ASTM D1003. Gloss, which is the reflectance or surface sheen of a substrate, can be determined with ASTM D2457. Opacity is the ability of a material to stop the transmission of light, more information on which can be found in ASTM D589.

A.6 Material physical property

A.6.1 Some of the physical properties that may be considered are listed in A.6.2 to A.6.11. Examples of standard test methods are mentioned in the text, but other examples of test methods are listed in ISO 11607-1:2006, Table B.1.

In addition to withstanding the sterilization process, sterile barrier system and/or packaging systems for medical devices need to also protect the medical device's sterility and efficacy until such time as it is needed. The shape and mass of the medical device, the type of protective packaging (if applicable), and the transport and storage systems will all play a role in challenging this attribute of the sterile barrier system and/or packaging system. While the only definitive means of establishing the appropriateness is through actual use with the medical device, a number of standard physical properties provide a means of judging potential materials for use in a given application. Few if any of these properties represent identically the manner in which a particular medical device will challenge a sterile barrier system and/or packaging system. Manufacturers of packaging materials will make available values for some of these properties, but it is important to remember they serve as a screening tool, and are usually provided as typical values, rather than specification values where rigid tolerances are imposed.

A.6.2 *Puncture resistance:* The puncture resistance of a material may be important to consider if the medical device contains sharp edges or protrusions that may penetrate the packaging material, destroying its integrity. ASTM D1709, ASTM D3420 and ASTM F1306 provide guidance.

A.6.3 *Abrasion resistance:* Abrasion resistance is the ability of a surface to withstand the effects of repeated rubbing, scuffing, and scratching. This can occur between:

— the medical device and the sterile barrier system,

— the sterile barrier system and sterile barrier system, or

— the sterile barrier system and the protective packaging

during distribution. As no test currently exists that is predictive of these effects, sterile barrier system and/or packaging system performance testing of actual medical device is usually required.

A.6.4 *Tear resistance*: The ability of a material to resist tearing and for the material to continue to propagate an initiated tear may be important to the opening features of the sterile barrier system. For example, the materials for a peel open sterile barrier system should be resistant to tearing in the peel open area, while the materials for a tear open sterile barrier system should readily propagate a tear. Test methods to assess tear resistance include ASTM D1922 and ASTM D1938.

A.6.5 *Flexural durability*: The ability of a material to withstand damage by repeated flexing or folding is described as its flexural durability. The medical device shape, the type of protective packaging used, and the transport system will determine the importance of this attribute. ASTM F392 provides guidance on testing flexural durability.

A.6.6 *Thickness*: Generally, as the thickness of a specific material increases its durability increases. However, since increasing thickness also increases stiffness, a point may be reached where increased

thickness creates a brittle material more prone to flex cracking (reduces flexural durability). Test methods to determine thickness include ISO 534 and ASTM F2251.

A.6.7 *Tensile strength:* The tensile strength of a material is the maximum force (tension) required to break or fracture the material. It is often referred to as ultimate tensile strength and is expressed as force per unit area. Although the tensile strength will remain consistent, increasing the thickness of a specific material will increase the force required to break the material. Because the tensile strength measurement is taken at a point beyond the elastic limit or yield point (the amount of force required to permanently deform the material), its usefulness in predicting durability is limited. In fact, tensile strength is often inversely related to durability. ISO 1924-2 and ASTM D882 provide guidance on testing tensile strength.

A.6.8 *Elongation*: The difference in length, expressed as a percentage of the original length, when a material is subjected to a tensile load. Typically, elongation at break is reported. Because elongation at break is beyond the elastic limit or yield point (the amount of force required to permanently deform the material), its usefulness in predicting durability is limited. ASTM D882 provides guidance on testing elongation.

A.6.9 *Basis weight*: The basis weight of a material is its mass per unit area. Test methods to determine basis weight include ASTM D4321 and ASTM D3776.

A.6.10 *Bond strength*: The bond strength is the amount of force needed to separate interlaminate plies of a material. ASTM F904 provides guidance on testing bond strength.

A.6.11 *Wet strength.* The wet strength may be important to consider if the packaging is sterilised in wet conditions as moist heat and EO.

A.7 Sterile barrier system integrity

A.7.1 Sterile barrier system integrity is an essential element for a medical device that is supplied in the sterile state. The sterile barrier system provides confidence that the medical device remains in a sterile condition to the point of use, and facilitates the aseptic delivery of that medical device. Loss of sterility is regarded as an event related phenomenon i.e. occurs in conjunction with a physical breach of the sterile barrier system. Exposures to excessive and frequent temperature and pressure variations during storage and transport or wetting of packages are also considered as events. They are not easy to detect and increase the probability of contamination. Hence, it is critical to ensure a sterile barrier system and/or packaging system provides an appropriate level of medical device protection, and that an inspection of that sterile barrier system and/or packaging system, including the sterile barrier system can reliably serve as a measure of sterility maintenance. Test methods associated with package integrity involve probing for physical breaches in the microbial barrier, due either to the failure of a package (sterile barrier system) seal or a failure of the material itself.

A.7.2 *Visual inspection***:** Employing ASTM F1886 channel defects in package (sterile barrier system) seals can be detected with good probability. While subject to some material limitations, and insufficient to definitively rule out pinholes and minute tears in sterile barrier system materials, visual inspection is nevertheless a valuable means of monitoring seal integrity. Other tools that have also been useful include polarized light and black light. These are generally not employed as the sole methods by which sterile barrier systems are evaluated during initial sterile barrier system and/or packaging system, but frequently serve as an in-process check during regular sterile barrier system and/or packaging system production.

A.7.3 *Dye penetration*: ASTM F1929 involves the wicking of a dye solution through a channel defect. This is a common test for seal validation if seal quality has not yet been correlated with visual inspection. This test is more difficult to perform on cellulosic materials.

Dye tests can be affected by the materials used, and operator training and experience. As such, careful interpretation of test results is necessary. It is important that these tests are performed by operators who have been assessed as competent to perform the tests. Once the correct interpretation of these tests is understood they provide a reliable and sensitive means for detecting channels, holes etc.

A.7.4 *Bubble testing:* ASTM D3078 and ATSM F2096 involve submersion of a package (sterile barrier system) in a fluid and the application of a pressure differential. An evolution of gas may indicate the presence of a leak. Best suited for gross leaks, it is commonly employed on packaged medical device that has been subjected to actual or simulated shipping conditions to assess package (sterile barrier system) integrity.

A.7.5 *Other integrity methods*: Alternative techniques include employing CO_2 or helium as a tracer gas, pressure or vacuum-decay measurement, as well as ultrasonic methods that can characterize leaks and other anomalies.

A.7.6 *Whole package (sterile barrier system) microbial challenge testing:* The sterile barrier system is placed into a chamber and exposed to an aerosol challenge of a known concentration of a known microorganism. The outside of the system is then decontaminated, aseptically opened, and a sterility test is performed on the medical device. This is an alternative to physical integrity testing, but these methods are not particularly reliable and are technically challenging to execute. While there are no universally accepted test methods, these methods may be appropriate for evaluating the integrity of tortuous path closure sterile barrier system when properly validated. ISO 11607-1:2006, Annex B.

A.8 Seal strength and burst strength

A.8.1 *Seal strength*: The primary means of characterizing package (sterile barrier system) seal strength is to measure the force required to separate two packaging components. Such a separation may be part of the sterile barrier system and/or packaging system design, in order to facilitate aseptic presentation, or it may represent the force required to rupture a permanent (or "weld") seal. In either case package (sterile barrier system) seal strength measurements are key indicators of the package formation process.

The strength of the peelable seals of preformed sterile barrier systems is a function of the materials and the manufacturing process of the supplier. The anticipated range of seal strength values is best specified by the manufacturer. This is also true for suppliers of materials for sterile barrier systems.

A.8.2 Additionally, in many cases seal strength serves as a measurement to indicate that a process to form the seal is under control, and that confidence exists that the package (sterile barrier system) represents a structurally sound container for the medical device. The sealability of the material combinations under evaluation should be tested in the laboratory using a range of conditions designed to demonstrate extremes in seal strength and quality. These seals should be tested for tensile peel strength and reviewed to determine if the results meet the desired seal strength for the sterile barrier system and/or packaging system. This process is typically used as a screening tool for selection of material combinations and can be used to evaluate pre- and post-sterilization seal strength. Thereafter, seal strength measurements may be used to monitor manufacturing and to ensure a process is in control as long as seal strength data has been demonstrated to be a suitable monitor of the process.

A.8.3 ASTM F88 is the definitive test method for characterizing seal strength. A tensile testing machine pulls apart two "legs" of a precision-cut seal section at a controlled rate of separation, measuring separation distance and tensile load during the process. Typically seals are tested at several points around the package perimeter. ASTM F88 provides information on the effect of differences in technique. Guidance in seal strength characteristics are also given in EN 868-5.

A.8.4 *Burst strength:* A means by which an entire package (sterile barrier system) is tested, burst testing involves internally pressurizing a package and noting the impact of that pressure on the package seals. The degradation of seals (creep), the time to package failure (creep to burst), and the ultimate burst strength are measurements obtained by ASTM F1140 (unrestrained) and ASTM F2054 (restrained) test methods. While burst strength testing probes the entire package (sterile barrier system) at once, it does not apply the force equally to all parts of the package, and necessarily carries more variability in the observed results than peel testing. Burst testing is more typically used for in-process control. When it will be used as such a control then concurrent tensile and burst testing should be performed at the time of validation.

A.9 Material processing guidance

A.9.1 Many sterile barrier system and/or packaging system specifications and process characterizations are determined through dimensional measurements. Typical dimensional considerations related to medical device fit and functions are overall length and width, inside length and width, and seal width. Other dimensions should be determined based on individual application and process performance requirements. Refer to ASTM F2203 for linear measurement guidance.

A.9.2 Friction can affect the processing of packaging materials when moving over metal surfaces, other substrates, or themselves. For example, in stacking and auto-loading operations, materials can feed incorrectly due to high levels of friction. Categorization of the static and kinetic coefficients of friction of materials can help the dependability of sterile barrier system and/or packaging system processing. See ASTM D1894 for further guidance.

A.9.3 Sterile barrier system formation and sterility maintenance are dependent on sealability. Packaging materials can seal at a variety of conditions. Therefore the characterization of a packaging material's sealability may include the following: size of seal window, seal strength, seal evidence (if peelable), and the processability of temperature sensitive materials. It is a common practice to evaluate sealing on lab equipment, and due to the variation in the location of thermocouples, seal tool mass and other factors, sealing conditions may vary from one piece of equipment to another. See ASTM F2029.

A.9.4 The coat weight of an adhesive coated substrate can affect its sealability, seal strength, and transfer. Depending on the adhesive and substrate, coat weight can influence the cohesive or adhesive failure modes of the seal during peeling, which affect the consistency of seal strength and coating transfer appearance between two substrates. For consistent results in sealing and peeling the coat weight needs to fall within the agreed range. See ASTM F2217.

A.10 Printing guidance

A.10.1 New packaging materials to be printed may need an evaluation for printability. The printability of a material is related to its wetability or surface tension. Surface tension measurement, whether utilizing contact angle equipment, or dyne solutions, can be used to determine the level of surface treatment and/or the printable side of a substrate. Some treated surfaces can degrade, which can affect their printability over time.

A.10.2 Poor ink or anchorage/adhesion to material can affect the appearance and legibility of print or the functionality of coatings on packaging materials. Since the acceptability of the degree of anchorage is specific to each application, an acceptability criterion needs to be agreed upon by user and producer of packaging material. See ASTM F2252.

a) Printing intended to convey information should have no missing print, smears, smudges, or offset that renders it incorrect or illegible (ISO 11607-1:2006, 5.4). Printing in the seal area may affect the sealability of a material, as well as the sealing process may affect the ink and/or print legibility. Other considerations may include compatibility with the chosen sterilization process, where temperature and/or chemical resistance could affect printing.

b) Abrasion of printed packaging material in the distribution environment can change the graphic appearance of a sterile barrier system and/or packaging system by scuffing, removing, or rendering print unreadable. In laboratory conditions, comparing abrasion resistance of surface printed materials against established standards can approximate the effects during shipping and handling. For further guidance see ASTM D5264.

c) The printed surface of sterile barrier system and/or packaging system materials may be exposed to chemicals during its life cycle. Chemicals can degrade, soften, smear, and remove printing, which affects its appearance and legibility. The relative resistance to known or expected chemicals needs to be evaluated. For further guidance see ASTM F2250.

A.11 Cleanliness and particulates

A.11.1 Foreign material that is on the surface of the sterile barrier system and/or packaging system material and that can be brushed or rubbed off is considered loose particulate. Loose particulate should be minimized. The level of particulate inherently present will be dependent upon the packaging material chosen. Size of particulate is frequently estimated using a TAPPI Dirt Estimation Chart.

A.11.2 Foreign material that is embedded between layers of a laminate or within a film, non-woven, or paper, should be minimized. Gels, small particles of resin with higher-than-average molecular weight and that appear as small, hard, glassy particles, are not foreign material and are inherent to many polymer based materials. Carbon particles are bits of parent material that have seen excessive heat in processing. Gels and carbon particles should be considered separately from embedded foreign material particulate. See e.g. IEST-STD-CC1246D that provides a basis and a uniform method for specifying product cleanliness levels and contamination control program requirements.

A.12 Accelerated aging and environmental challenging

A.12.1 The following definitions have been incorporated into ASTM F17*:*

a) **accelerated aging** — a technique to simulate the effects of time on a package by subjecting the product/package system to elevated temperatures in a controlled environment representative of controlled environment storage conditions. The equivalent time is generally estimated by assuming the degradation of packaging materials follows the kinetics described by the Arrhenius reaction rate function, more discussion of which is available in ASTM F1980.

b) **environmental challenging** — the process of subjecting a package to extremes of temperature and/or humidity and/or other environmental conditions, with the goal of determining sensitivities of the package to environmental stresses. In contrast to accelerated aging, environmental challenging often includes conditions, or transitions, or both, of temperature and humidity that equal or exceed those that can be encountered in a package life cycle. For further guidance see ASTM F2825.

For examples of real time aging temperature selection and accelerated aging duration calculations, see ASTM F1980.

A.12.2 In accelerated aging, the temperature and humidity levels are chosen to ensure the materials do not reach the physical transition points. When performing environmental challenging, the aim is either to assess sterile barrier system and/or packaging system performance at the extreme conditions possible in a package life cycle, or to stress the material near or past its failure point.

This delineation is centred upon the fact that different materials have varying sensitivities to temperature and moisture, and conclusions regarding a given material's suitability as a sterile barrier system and/or packaging system component may not be valid. For example, paper is particularly sensitive to relative humidity. Excessive drying negatively impacts strength properties, and excessive humidity can lead to mould growth. Some laminates may fail under extreme conditions, although real time or controlled aging rarely or never demonstrates such a result.

A.12.3 The medical device industry is a dynamic environment, so requiring real time aging prior to marketing and selling a medical device is often impractical. Using accelerated aging to test sterile barrier system or packaging system shelf life is generally accepted as valid for new medical device introductions, provided real time aging is in place to confirm accelerated aging test results. Typically, a series of tests are carried out to probe package integrity, opening features (if applicable), and the general properties of the packaging materials themselves. Generating both pre-sterile and post-sterile attribute values are important in order to capture the effects of the sterilization process prior to beginning the aging process on the sterile barrier system materials and seals. Aging studies can be performed on empty sterile barrier systems (see ISO 11607-1:2006, 6.3) as long as they have been exposed to the maximum sterilization cycles expected. If aging sample does not include contents a rationale should be documented that supports the sample configuration used. Other approaches involve a shipping study performed at time zero. Material property testing then follows as a measure of the influence of time simulated by accelerated aging.

Use of the Arrhenius equation is generally recognized as an approach for defining the effect of elevated temperature on a homogeneous first order reaction rate. Phrased more simply, the easier $Q_{10} = 2$ calculation developed from this equation assumes that the aging process is approximately doubled for each 10 °C rise in temperature. For example, 45 days at 55 °C is equivalent to one year at 25 °C. (Further discussion is available in AAMI TIR17 and ASTM F1980.)

The temperature should be chosen carefully so that materials are not damaged because of conditions that would not be expected to occur in real world or are outside of the recommended range of use for that material. See ASTM F1980 for guidance on the effects of the humidity during accelerated aging.

When choosing the temperature to conduct the accelerated aging care should be taken to select temperatures, which do not cause any material transitions or sterile barrier system and/or packaging system distortion, or induced nonlinear changes such as crystallinity, generation of free radicals, and peroxide degradation.

When considering the role of humidity in accelerated aging, it is important to realize that relative humidity is exactly that; it is the amount of water suspended in the air *relative* to its capacity at that temperature. As such there is an inherent danger in maintaining the same percentage of relative humidity as ambient levels during an accelerated aging study, as it necessarily results in higher moisture exposure than is typically seen during real time aging. For a detailed discussion of this topic see Reference.[107]

A.12.4 Another aspect of sterile barrier system testing relates to environmental challenging or conditioning material at various different temperatures and humidity levels in order to simulate exposure to various conditions from shipping to different climates. Hot/cold cycling can be used to mimic seasonal extremes to which packaged medical devices can be subjected, however attention should be paid to the rate of change.

Once again, the temperature and humidity levels should be chosen carefully based on an understanding of the product distribution and use conditions. The discussion of temperature and humidity above, with the exception of linearity concerns, is also pertinent to environmental challenging. One approach for a commonly used distribution system can be found in ASTM F2825.

A.12.5 The medical device manufacturer should make the final decision regarding the suitability of a packaging material and/or system to ensure efficacy of a sterilized medical device. This discussion is intended to serve as a guide in choosing the conditions for testing a sterile barrier system and/or packaging system or packaging material so that informed judgments can be made regarding the performance of the sterile barrier system and/or packaging system over time, and to separate shelf life testing from the environmental impact of temperature and humidity.

Annex B
(informative)

Sterilization considerations — Guidance for industry and health care facilities

B.1 Overview

B.1.1 Full consideration of the sterilization process for a terminally sterilized medical device needs to be included during medical device and sterile barrier system and/or packaging system design and verification to determine compatibility (ISO 11607-1:2006, 5.3). Very often, the sterilization method will dictate aspects of material selection, sterile barrier system and/or packaging system configuration, size, and medical device logistics.

Some aspects to be considered are:

a) material selection — porous or impermeable;

b) gaseous sterilization methods typically require porous sterile barrier systems;

c) irradiation sterilization methods may use impermeable or porous sterile barrier systems. Sometimes porous sterile barrier systems are used to enable abatement of odours that can develop during irradiation;

d) compatibility — Ability to withstand the process:

   Consider the medical device and sterile barrier system and/or packaging system performance after exposure to the chosen sterilization method at the process extremes or after multiple process exposures. For example, it is important to understand what physical properties (functional or cosmetic) may change with a given material undergoing irradiation and that the differences between e-beam and gamma sterilization methods and or dosage may have different degrees of effect on materials.

e) density/orientation:

   Consider shadowing effects of other medical devices in the same container or adjacent containers (gamma and e-beam.)

f) special totes/conveyor limitations:

   Consider constraints of the sterilization process, i.e. tote size for gamma sterilization, conveyor clearances for e-beam, pallet sizes for EO sterilization, etc.

g) pallet configurations:

   Consider pallet configuration for minimum reconfiguration needed at the sterilizer (if contract sterilized), optimum space utilization and shipping efficiency.

B.1.2 Some guidelines on the factors to consider for specific commonly used methods of industrial sterilization are listed below. The science of sterilization processing continues to be developed. New technologies should be studied closely to determine which material properties and design characteristics are crucial to successful processing.

B.2 Ethylene oxide

B.2.1 Process summary: Sterilization by alkalizing gas with moisture and heat.

B.2.2 Medical device/sterile barrier system considerations:

a) The medical device, sterile barrier system, and inks should be able to withstand elevated humidity and temperatures (typically ≤ 60 °C, high humidity), deep repeated vacuums, nitrogen and EO. Temperature and humidity ranges will vary with the design of the sterilization cycle.

b) The medical device needs to have areas that can allow gas penetration throughout and allow sustained contact with all areas of the medical device.

c) The sterile barrier system needs to have porous areas that allow gas to pass in and out. Gas transport through the permeable portion needs to occur at a rate sufficient to maintain sterile barrier system integrity during the vacuum and/or fill process. Care should be taken to ensure that the configuration of individual sterile barrier systems contained in a sterile barrier system and/or packaging system does not impede their permeability. Avoid close contact of the permeable material with a non-permeable one as this may prevent the gas from penetrating.

B.2.3 Process considerations:

a) Timing: the process may take several days for pre-conditioning, sterilization, and aeration. Wait time is needed for biological indicator release unless parametric release is used.

b) Efficiency will also depend on manufacturing time to build the full load; which is often several to many pallets in size.

c) Load size: based on the chamber size and considerations during the sterilization validation.

d) The sterilization cycle can be somewhat customized to meet medical device and microbiological requirements.

e) Remaining amounts of EO are out gassed to be within safe limits as a part of the sterilization process cycle settings, and the medical device needs to be tested for residual by products of sterilization (see ISO 10993-7).

B.2.4 For further information on EO sterilization see:

— ISO 11135-1;

— ISO 10993-7*;*

— ISO/TS 11135-2;

— AAMI TIR15;

— AAMI TIR16;

— AAMI TIR19;

— AAMI TIR20;

— AAMI TIR28.

B.3 Gamma irradiation

B.3.1 Process summary: The packaged medical device is subjected to ionization radiation in the form of high energy gamma photons released from a radioactive source such as cobalt-60, which disrupts the molecular structure of microbes, disabling reproduction.

B.3.2 Medical device/ sterile barrier system and/or packaging system considerations:

a) The medical device sterile barrier system and/or packaging system and inks needs to utilize materials that can withstand ionizing radiation. Cross-linking and chain scission can cause cosmetic and functional physical property changes, and or evolvement occurs with some materials. Radiation stable material replacements may be available.

b) Elevated temperatures may occur when using this method and should be taken into consideration.

c) Packaged case density is an important factor and should be controlled to be consistent in the process to maintain dosimetric release.

d) This method should be considered if the medical device has closed in areas that cannot be sterilized with a gas or a non-porous sterile barrier system and/or packaging system is needed.

e) Case size should be optimized to be compatible with the irradiator carrier size.

B.3.3 Process considerations:

a) Timing: the process is relatively short, however waits may occur since medical devices of similar densities should run together. Since the process uses dosimetric release, post-sterilization waits are not needed.

b) Load size is based on carrier size used at the irradiator and dose mapping studies.

B.3.4 For further information on radiation sterilization see:

— ISO 11137-1;

— ISO 11137-2;

— ISO 11137-3;

— AAMI TIR17;

— AAMI TIR29;

— AAMI TIR33;

— AAMI TIR35.

B.4 Electron beam sterilization (E-Beam)

B.4.1 Process summary: An accelerator-based system sterilizes medical devices by directing a concentrated stream of electrons at sterile barrier system and/or packaging systems containing finished medical device.

B.4.2 Medical device/ sterile barrier system and/or packaging system considerations:

a) The materials of the medical device, sterile barrier system, and inks should be carefully selected to withstand E-beam radiation. The effects on materials may be less dramatic than with gamma radiation.

b) Packaged case density is an important factor and should be controlled to be consistent in the process to maintain dosimetric release.

c) This may be a good choice for medical devices that have closed in areas that cannot be sterilized with a gas.

B.4.3 Process considerations:

a) Timing: the sterile barrier system runs through the process on a conveyor, sometimes two passes are needed. Since the process uses dosimetric release, post-sterilization waits are not needed.

b) Orientation of medical device/sterile barrier system and/or packaging system should be controlled so all parts of the medical device are exposed to the beam, i.e. take care to avoid the issue known as "shadowing."

c) Load size: limited by density requirements and equipment/conveyor criteria.

d) When incorporated into a production line, this can be an efficient, sterilization methodology.

B.4.4 For more information on E-beam sterilization see:

a) ISO/ASTM 51649;

b) Standards in gamma irradiation (see B.3.4).

B.5 X-ray sterilization

B.5.1 Process summary: The packaged medical device is exposed to radiation via ionized particle acceleration, which creates X-rays called bremsstrahlung radiation. This process alters the chemical and molecular bonds causing the destruction of reproducing microorganisms.

B.5.2 Medical device/sterile barrier system and/or packaging system considerations:

a) The medical device or sterile barrier system and/or packaging system needs to utilize materials that can withstand ionizing radiation. Although this process has shorter exposures at lower doses, cross-linking can cause cosmetic (yellowing) and functional physical property changes.

b) Sterile barrier system and/or packaging system does not require a porous membrane as X-rays can penetrate through packaging materials and into medical device structures.

c) The cycle has limited stress on sterile barrier system seals because cycle does include vacuum phases.

d) Pallet or tote configuration density is an important factor and should be controlled to be consistent in the process to maintain dosimetric release.

e) Consider the contract sterilizers pallet or tote material handling system to optimize the sterile barrier system and/or packaging system design to reduce dead space in the sterilization cycle.

B.5.3 Process considerations:

a) Efficiency will also depend on sterile barrier system and/or packaging system, shipper, and pallet configurations of the finished medical device.

b) Load size: based on the facility limitations and validations considerations derived from manufacturing schedules and inputs considered during the sterilization validation.

B.6 Moist heat (steam) sterilization

B.6.1 Process summary: the packaged medical device is subjected to saturated steam and elevated temperatures. Steam is the sterilizing agent and needs to pass through the sterile barrier system and/or packaging system in order to contact the medical device.

B.6.2 Medical device/sterile barrier system and/or packaging system considerations:

a) The medical device, sterile barrier system and/or packaging system, and inks should not be sensitive to water vapour or condensate and elevated temperatures.

b) The sterile barrier system and/or packaging system needs to have porous areas that allow steam to pass into and out of the sterile barrier system and/or packaging system. Steam transport through the permeable portion needs to occur at a rate sufficient to maintain sterile barrier system integrity during the vacuum and/or fill process. Care should be taken to ensure that the configuration of individual sterile barrier systems contained in a sterile barrier system and/or packaging system does not impede their permeability. Avoid close contact of the permeable material with a non-permeable one as this may prevent the steam from penetrating.

c) The medical device needs to have openings that can allow steam penetration with sustained contact with all areas of the medical device.

B.6.3 Process considerations:

a) Timing: the process usually takes less than 2 hours with no aeration required. Unless parametric release is used to release sterilized product the product needs to be held pending satisfactory results of biological indicator tests.

b) Load size: limited by equipment criteria and sterilization process validation for the medical device.

B.6.4 For further information on steam sterilization, see:

— ISO 17665-1;

— ISO/TS 17665-2.

B.7 Sterilization using moist heat and non-porous packaging

B.7.1 Process summary: Steam or pressurized hot water is used as a media to heat the packaged medical device.

B.7.2 Medical device/ sterile barrier system and/or packaging system considerations:

a) The medical device, sterile barrier system and/or packaging system, and inks should not be sensitive to humidity saturated steam and elevated temperatures.

b) Moisture needs to be present inside the sterile barrier system in order to create the steam and pressure that will sterilize the medical device.

c) The medical device needs to have openings that can allow steam and/or pressurized water penetration with sustained contact with all areas of the medical device.

B.7.3 Process considerations:

a) Timing: the process takes only a few hours, with no aeration required. Unless parametric release is used to release sterilized product the product needs to be held pending satisfactory results of biological indicator tests.

b) Load size: limited by equipment criteria and sterilization process validation for the medical device.

c) Overpressure control typically is needed to process peelable sterile barrier systems.

B.7.4 For further information on steam sterilization, see ISO 17665-1.

B.8 Dry heat

B.8.1 Process summary: the packaged medical device is subjected to high temperatures for an extended period of time.

B.8.2 Medical device/sterile barrier system and/or packaging system considerations:

The medical device, sterile barrier system and/or packaging system, and ink should withstand elevated temperatures. This typically may be 160° C or higher, for several hours, or may be a longer cycle at lower temperatures.

B.8.3 Process considerations:

a) Timing: the process takes only a few hours, with no aeration required. Unless parametric release is used to release sterilized product the product needs to be held pending satisfactory results of biological indicator tests.

b) Load size: limited by equipment criteria and sterilization process validation for the medical device.

B.8.4 For further information on dry heat sterilization, see ISO 20857.

B.9 Peroxide sterilization

B.9.1 The two common types of peroxide sterilization are:

a) Gas plasma is also known as low-temperature hydrogen peroxide gas plasma (LTHPGP) sterilization.

b) Hydrogen peroxide that is vaporized is similar to, but not identical to, gas plasma sterilization. Both utilize hydrogen peroxide that is vaporized, but gas plasma includes a plasma generation step.

B.9.2 Process summary: the packaged medical device is placed in a chamber at low temperatures and subjected to hydrogen peroxide gas that is vaporized or a gas plasma process.

B.9.3 Medical device and sterile barrier system and/or packaging system considerations:

a) The medical device, sterile barrier system and/or packaging system, and ink to withstand temperature up to 55 °C with humidity up to 80 % RH for the duration of the validated cycle.

b) If plasma is used, the medical device, sterile barrier system and/or packaging system, and ink should be compatible with the plasma, and with the plasma generation process.

c) The medical device, sterile barrier system and/or packaging system, and ink should not be sensitive to deep vacuum or hydrogen peroxide.

d) The medical device needs to be capable of withstanding the rates of pressure change allowed by the equipment.

e) The medical device needs to have areas that can allow gas penetration throughout and allow sustained contact with all areas of the medical device.

f) The sterile barrier system and/or packaging system need to have porous areas that allow gas to pass into and out of the sterile barrier system and/or packaging system. Gas transport through the permeable portion needs to occur at a rate sufficient to maintain sterile barrier system integrity during the vacuum and/or fill process.

g) Cellulosic materials cannot be used for the process.

B.9.4 Process considerations:

a) Timing: the process takes approximately one hour. Normally, aeration is not required. Some loads may require aeration or extra vacuum/pressure purges to ensure no out-gassing occurs into the workplace. If parametric release is not available there is a need to wait for biological indicator release.

b) Load size: limited by equipment criteria and sterilization process validation for the medical device.

c) The chamber exhaust should be directed through a pollution control device to destroy peroxide before it can enter the workplace or ambient atmosphere.

B.10 Ozone

B.10.1 Process summary: ozone sterilization is a low temperature gas sterilization process. The packaged medical device is subjected to elevated humidity levels and to ozone. Inactivation of microorganisms is achieved by oxidative mechanisms.

B.10.2 Medical device/ sterile barrier system and/or packaging system considerations:

a) The medical device and sterile barrier system and/or packaging system (including inks) should be able to withstand elevated humidity, deep repeated vacuums and ozone. The medical device manufacturer and the sterilizer manufacturer should be consulted to determine the compatibility of the medical device with ozone.

b) The sterile barrier system and/or packaging system need to have porous areas that allow gas to pass into and out of the sterile barrier system and/or packaging system. Gas transport through the permeable portion needs to occur at a rate sufficient to maintain sterile barrier system integrity during the vacuum and/or fill process.

c) The medical device needs to have areas that can allow gas penetration throughout and allow sustained contact with all areas of the medical device.

B.10.3 Process considerations:

a) Timing: the process takes only a few hours, with no aeration required. Chemical indicators and self-contained biological indicators (using *Geobacillus stearothermophilus*) cleared by FDA for use with the ozone sterilizer should be used to monitor the process. Sterilized product needs to be held pending satisfactory results of biological indicator tests. At the present time, there is no parametric release available for this sterilization method.

b) Load size: limited by equipment criteria and sterilization process validation for the medical device. The sterilizer should be loaded as recommended in the sterilizer manufacturer's instruction for use.

B.10.4 For further information on ozone sterilization, see ANSI/AAMI ST58.

B.11 Chlorine dioxide (ClO_2 or CD)

B.11.1 Process summary: Chlorine dioxide gas is a low temperature sterilization process. The process is similar to EO. Chlorine dioxide is an oxidizing agent and inactivation of microorganisms is achieved

by oxidative mechanisms. Its sporicidal effects can be compared with those of hydrogen peroxide that is vaporized and formaldehyde.

B.11.2 Medical device/sterile barrier system and/or packaging system considerations:

a) Nonwoven polyolefine as well as many transparent films, foil composites and rigid plastics are compatible with chlorine dioxide. Some papers may be acceptable. Unbleached, corrugated paper cartons should not be used.

b) The medical device and sterile barrier system and/or packaging system (including inks) should be able to withstand oxidizing conditions and elevated humidity (typically 55 %RH to 70 %RH). Gas concentration (typically 5 mg/L to 30 mg/L) and humidity will vary with the design of the sterilization cycle.

c) The medical device needs to have areas that can allow gas penetration throughout and allow sustained contact with all areas of the medical device.

d) The sterile barrier system and/or packaging system need(s) to have porous areas that allow gas to pass into and out of the sterile barrier system and/or packaging system. Gas transport through the permeable portion needs to occur at a rate sufficient to maintain sterile barrier system integrity during the vacuum and/or fill process.

B.11.3 Process considerations:

a) Timing: The process steps typically include

   1) preconditioning or humidification;

   2) CD charge;

   3) exposure; and

   4) CD removal and medical device aeration.

   The total process may take several hours (depending on the relative humidity, medical device volume and the size of the sterilization chamber). Preconditioning time is similar to typical EO processes while aeration time tends to be somewhat shorter. If biological indicators are used to release product, then sterilized product needs to be held pending satisfactory results of biological indicator tests. Parametric release is possible since there can be direct monitoring of CD concentration throughout the sterilization process.

b) Load size: limited by equipment criteria and sterilization process validation for the medical device.

c) Efficiency will also depend on manufacturing time to build the full load; which is often several to many pallets in size.

d) The sterilization cycle can be somewhat customized to meet medical device and microbiological requirements.

e) The chlorine dioxide concentration is reduced to a safe level as part of the sterilization process. The medical device needs to be tested for sterilization residuals and by-products.

Annex C
(informative)

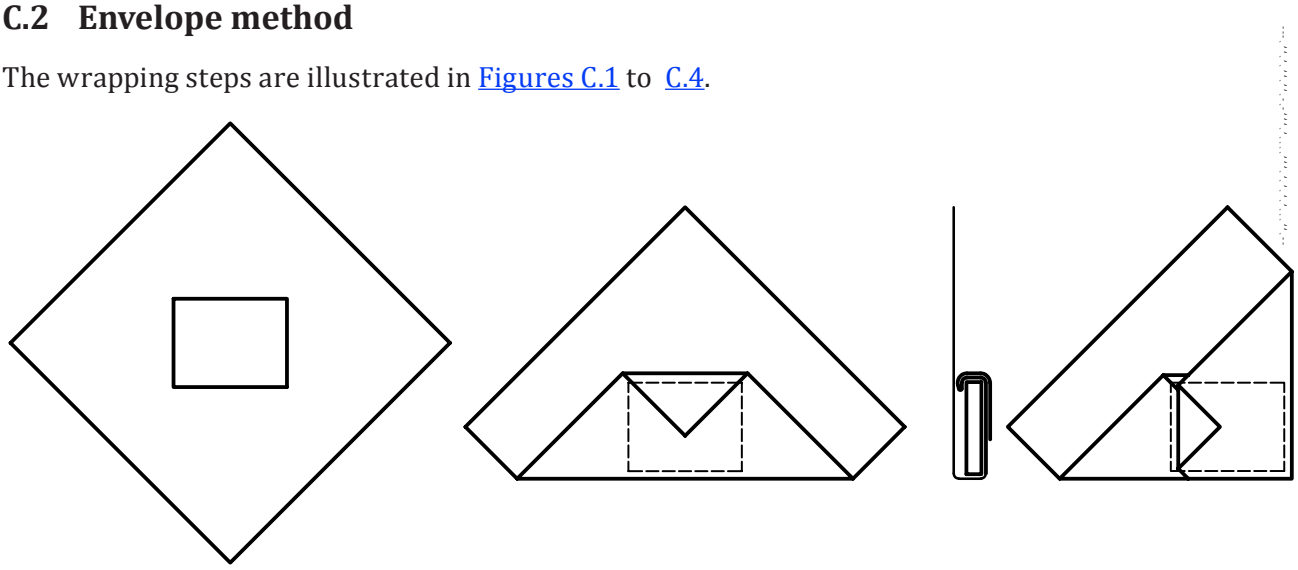
Examples of wrapping methods — Guidance for health care facilities

C.1 General

The drawings below illustrate several methods for wrapping medical devices prior to sterilization. These examples are not intended to describe the only methods for wrapping as there are other acceptable methods available. Wrapping may be performed sequentially or simultaneously. Different methods can be used for the different layers. Care should be taken to limit the area covered by tape and labels to ensure adequate porous area for effective sterilization and drying. The acceptability of a wrapping method is dependent upon the medical devices to be wrapped and should be determined by the user.

C.2 Envelope method

The wrapping steps are illustrated in Figures C.1 to C.4.



step 1 step 2 step 3

Figure C.1 — Envelope method steps 1 to 3

Step 1:

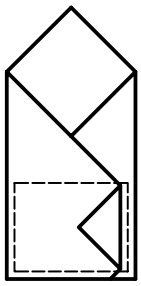
The medical device(s) is/are placed on the middle of the sheet in such a way that its edges form a right angle with the sheet diagonals.

Step 2:

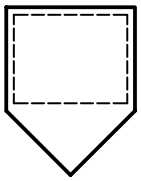
The sheet is drawn upwards over the broader side of the medical device(s) and folded back parallel to the longitudinal edge so that the sterilization load is completely covered. Thereby, a triangle (corner) is formed which enables aseptic opening.

Step 3:

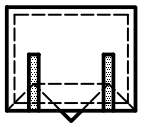
The same procedure as shown in step 2 is carried out from the right to the left.



step 4



step 5



step 6

Figure C.2 — Envelope method steps 4 to 6

Step 4:

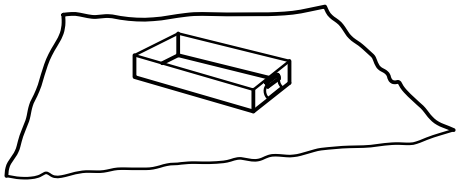
The same procedure as shown in step 3 is carried out from left to right.

Step 5:

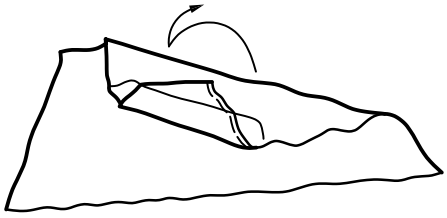
The last part of the sheet is now drawn over the medical device(s) to be wrapped. The corner of the sheet to be covered is tucked into the envelope until it just sticks out.

Step 6:

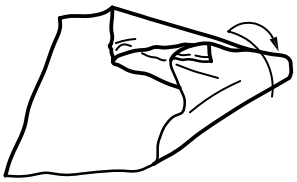
The sheet is closed with a suitable closure system with or without process indicator.



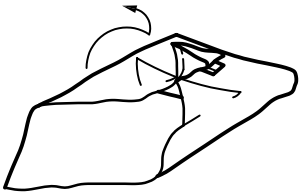
step 1



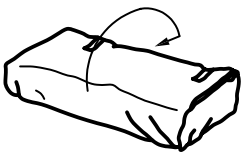
step 2



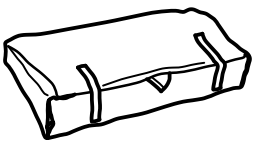
step 3



step 4

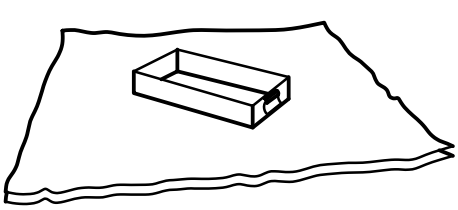


step 5

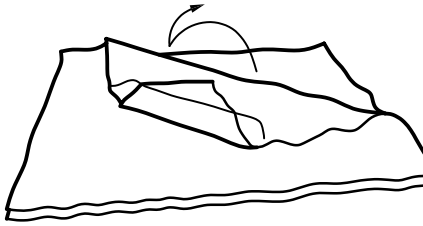


step 6

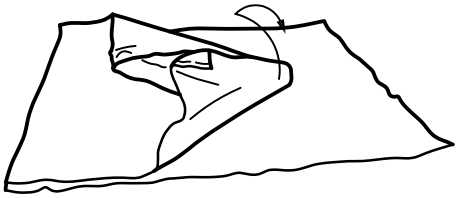
Figure C.3 — Envelope method simultaneous double wrapping



step 1

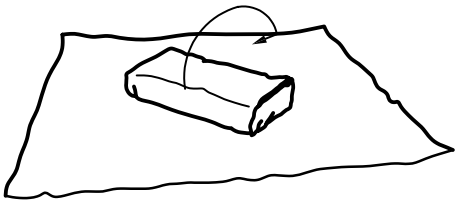


step 2

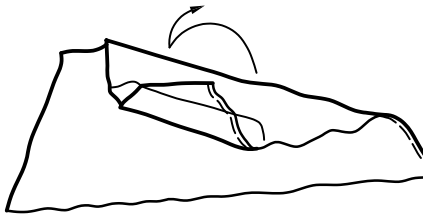


step 3

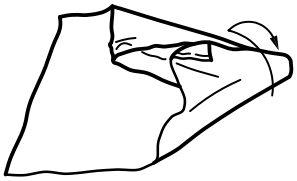
step 4



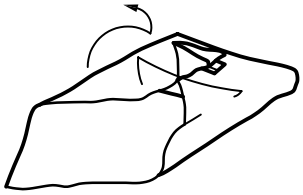
step 5



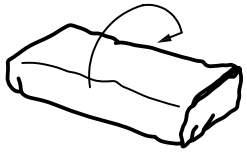
step 6



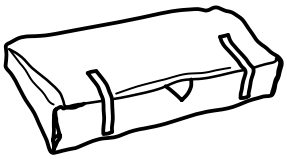
step 7



step 8



step 9

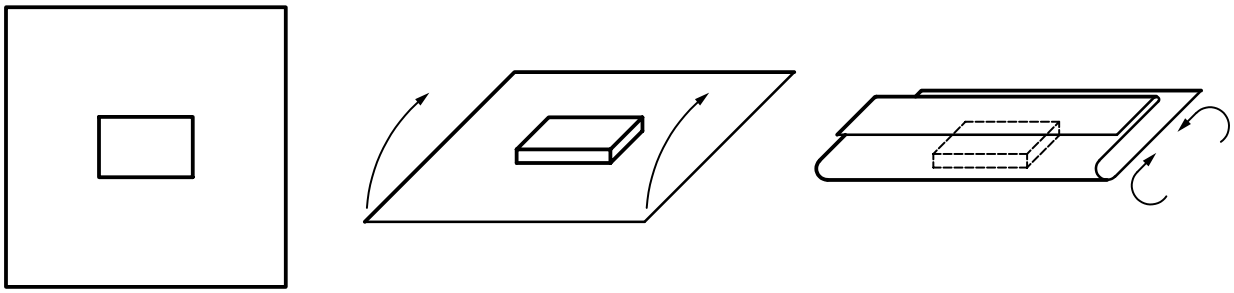


step 10

Figure C.4 — Envelope method sequential double wrapping

C.3 Parallel packaging/square fold method wrapping

The steps for parallel wrapping are illustrated in Figures C.5 to C.9.



step 1 step 2 step 3

Figure C.5 — Packaging/square fold method steps 1 to 3

Step 1:

The medical device(s) is/are placed in the middle of the sheet.

Step 2:

The front side of the sheet is wrapped over the medical device(s).

Step 3:

The edge of the sheet is folded back outward approximately to the level of the medical device(s).

step 4 step 5 step 6 step 7

Figure C.6 — Parallel wrapping steps 4 to 7

Step 4:

The back side of the sheet is folded forward.

Step 5:

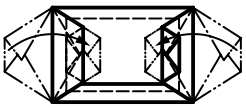
The edge of the sheet is folded outward so that the sheet ends with the forward upper edge.

Steps 6, 7 and 8:

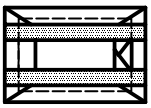
The wrap is folded at the sides and laid over the medical device(s).

Step 9:

The sheet is closed with a suitable closure system with or without process indicator.

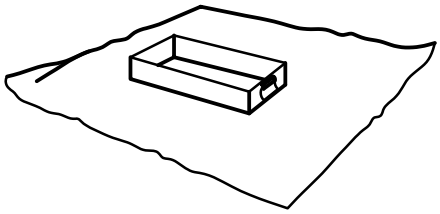


step 8

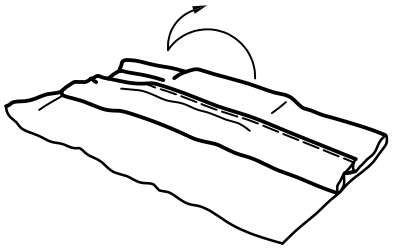


step 9

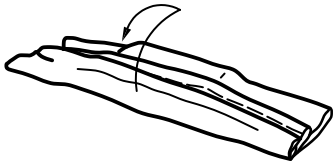
Figure C.7 — Parallel wrapping steps 8 and 9



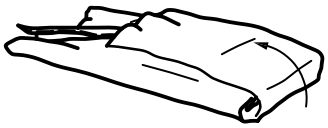
step 1



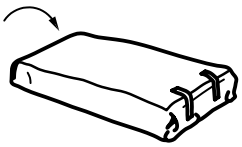
step 2



step 3

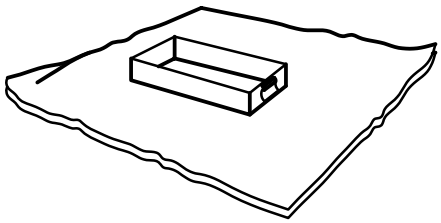


step 4

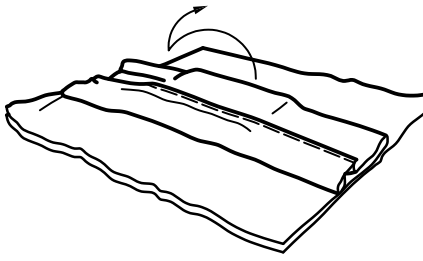


step 5

Figure C.8 — Square fold method simultaneous double wrapping



step 1



step 2

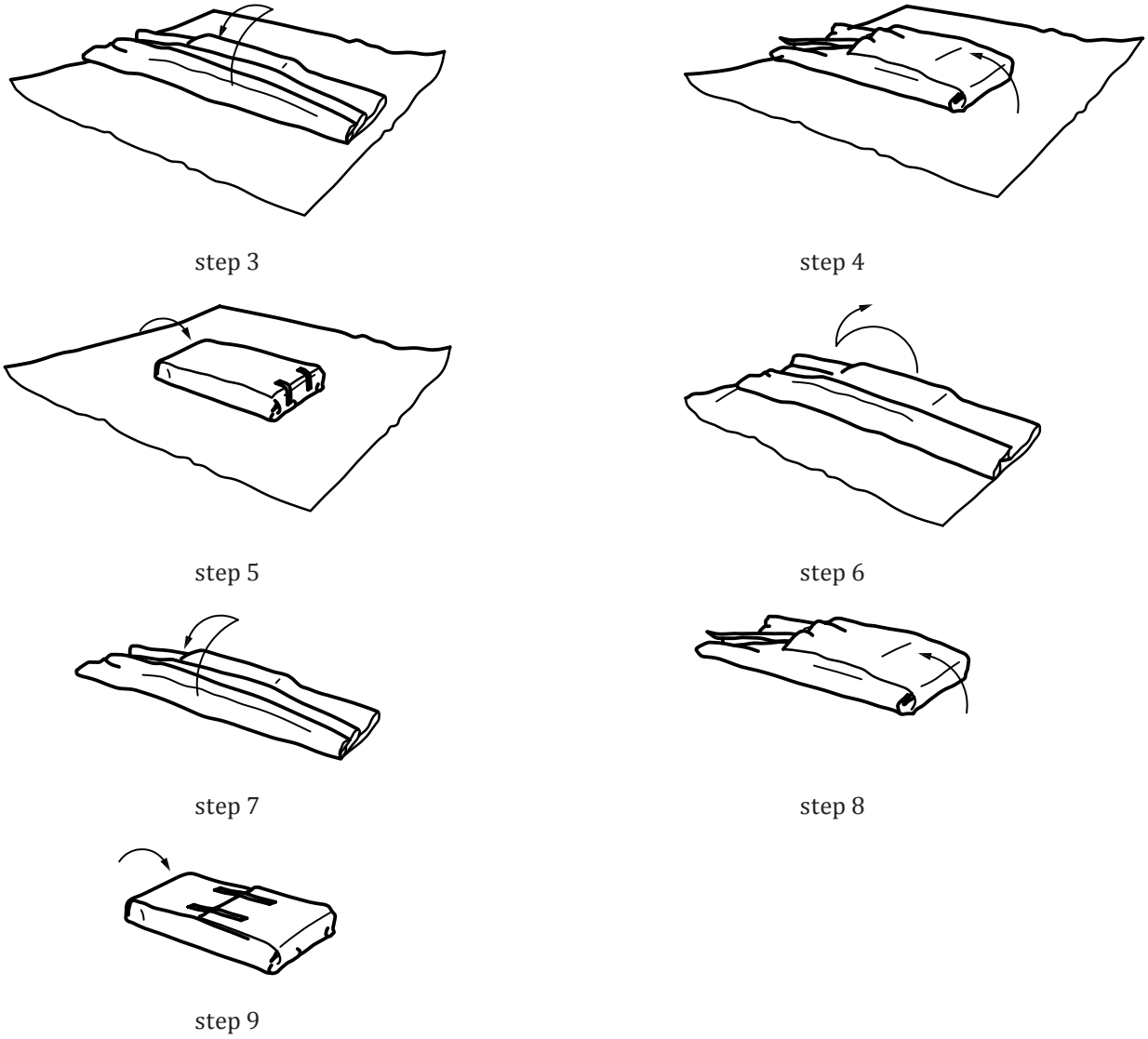
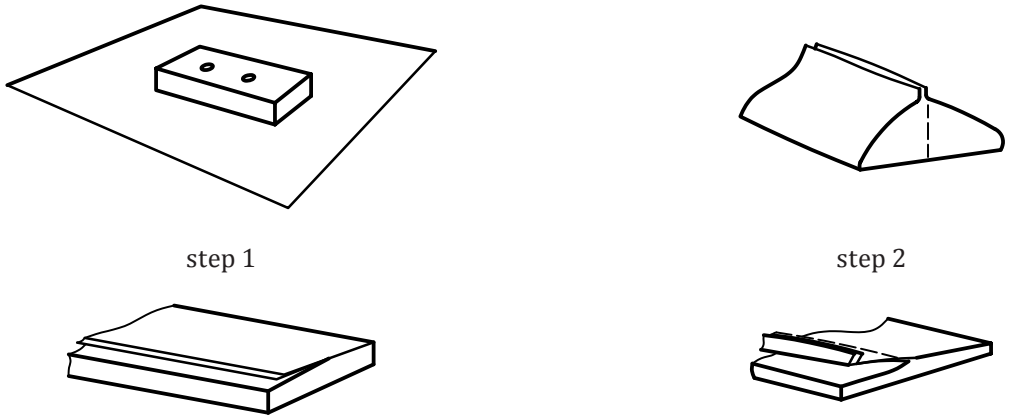


Figure C.9 — Square fold method sequential double wrapping

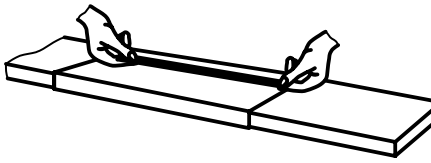
C.4 Pasteur or roll method

The steps for Pasteur or roll method wrapping are illustrated in Figure C.10.

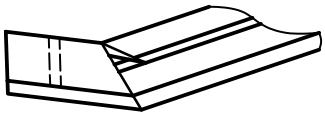


step 3

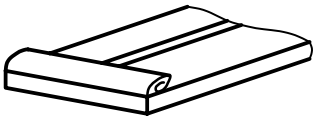
step 4



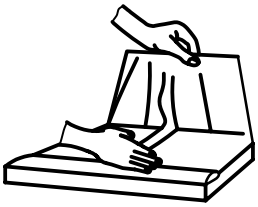
step 5



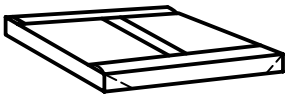
Hands position for step 4,5,6



step 6



step 7



step 8

step 9

step 10

Figure C.10 — Pasteur or roll method

Annex D
(informative)

Validation plan documents — Guidance for health care facilities

REMARK Users of the forms given in Annex D are permitted to produce copies of these forms, notwithstanding the fact that ISO retains all other rights regarding the entirety of the document.

D.1 General

The checklists available in Annex D can be used for the implementation and documentation of the validation of the packaging processes. This can be combined with the validation and/or revalidation of the sterilization process and documentation. The following table can be used to organize the number of validations.

Table D.1 can be used to determine the number of process validations to be performed.

Table D.1 — Number of process validationst

Configuration[a]	Steam[b]			LTFS	EO	H_2O_2
	134 °C	121 °C	____°C			
A						
B						
C						
D						

LTFS low temperature formaldehyde steam sterilization
EO ethylene oxide sterilization
H_2O_2 hydrogen peroxide sterilization

[a] Configuration includes material and closure system.
[b] If both vacuum and gravity displacement cycles are used in the facility, these three columns should be replicated.

D.2 Validation plan checklist: Heat Sealing Process Preformed Sterile Barrier Systems (PSBS: Pouches, Reels, etc.)

☐ **Validation** ☐ **Revalidation**

a) Responsibilities

Name of facility	
Location	
Validation participants	
Person responsible for the entire validation	
File location	

b) Description of the assembled sterile barrier systems

Contents of sterile barrier system	
Is this the worst-case scenario? If so, describe rationale:	
Number of sterile barrier systems assembled	
Approved procedure or SOP used to assemble	
Was internal organizing tray, tip protector for sharp medical devices etc. to support the medical device and protect the sterile barrier system used?	☐ yes ☐ no
If internal support/protection was used, describe:	

c) Description of sterilization processes

Manufacturer of sterilizer and model number			
Serial number of sterilizer			
Is this a contract sterilizer?	☐ yes ☐ no		
Sterilization cycle Attach printout if available	☐ Steam (highest temp./ longest time) ☐ Ethylene oxide (EO) ☐ other _____	☐ Plasma ☐ Low temperature steam formaldehyde (LTSF)	
Is this the worst-case cycle?	☐ yes	☐ no	cycle parameters: _____
Approved SOP or loading procedure used			
Process validated?	☐ yes	☐ no	
Validated by:			
Date of last validation:			
Date of next validation:			

d) Description of pouches and reels (preformed sterile barrier system)

Manufacturer of preformed sterile barrier systems			
Type/Grade			
Supplier contact information: Name: Address: Phone:			
Is supplier also the manufacturer of the pouches and /or reels?	☐ yes	☐ no	
Does manufacturer provide documented evidence of a quality management system (e.g. QM certificate, registration, etc.)	☐ yes	☐ no	
Has manufacturer validated their pouch/reel manufacturing process?	☐ yes	☐ no	☐ verification
Does supplier provide documentation demonstrating they have fulfilled the requirements of ISO 11607-1?	☐ yes	☐ no	☐ verification

If applicable, does supplier provide documentation of fulfilling requirements of regional product specific document (e.g. EN 868-5)?	☐ yes	☐ no	☐ verification
Sealing temperature range (in °C)*?	from _____to _____ Data from:_____ ☐ Verification available		
Sterilization process to be used:			
Is the preformed sterile barrier system compatible to the sterilization process?	☐ yes	☐ no	
Is the storage and handling of preformed sterile barrier systems in the hospital in accordance with regional/ national/local standards or requirements?	☐ yes	☐ no	☐ not available

e) Description of the sealing device

Sealing device manufacturer			
Type of sealing device			
Serial number (SN)			
Does temperature switch-off tolerance exist? [e.g. according to DIN 58953-7 (±5 °C)] Enter tolerance.	☐ yes	☐ no	Tolerance
Supplier of the sealing device.			
Supplier contact information: Name: Address: Phone:			
Date of last calibration.			
Does manufacturer provide documentation demonstrating that the equipment is capable of meeting the requirements of ISO 11607-2?	☐ yes	☐ no	☐ verification
Are manufacturer's directions for use available?	☐ yes	☐no	
When were they updated and where are they archived?			

f) Description of the protective packaging as well as handling, distribution and storage challenges

Protective packaging		
— Describe type of protective packaging	☐ yes	☐ no
— Applied after item is cool	☐ yes	☐ no
— Clearly labelled as protective packaging	☐ yes	☐ no
— Transport trays		
Description of handling, distribution and storage Has documentation been completed, e.g. see D.5?	☐ yes	☐ no

How often are sterile items moved or handled before arriving at their final point of use? — Number of events with risk of loss of integrity?	
Consider worst-case for Performance Qualification of the packaging system (combination of protective packaging and sterile barrier system) — What is the worst-case? — What is the rational for selection?	

g) Acceptance criteria — define method and acceptance criteria

Attribute	Method for evaluating	Acceptance criteria	
Seal integrity		Intact and continued seal Meets specified width No channel openings No wrinkles, creases or bubbles	
Package integrity		No punctures, tears, breaks	
Seal strength			
Aseptic presentation		Able to open without damage or contamination of the contents	
Peel ability	**Peelable without** material rupture, delamination, separation or degradation	☐ yes	☐ no
Other			

h) Qualification steps

Installation Qualification (IQ)	☐ executed	
	☐ previously executed in the validation dated: _____	
	☐ pass	☐ fail
	Date/Signature:	
Operational Qualification (OQ)	☐ executed	
	☐ date previously executed in the validation on _____	
Was acceptance criteria defined in (g) above met? Attach results	☐ pass	☐ fail
	Date/Signature:	
Performance Qualification (PQ)	☐ executed	
Was acceptance criteria defined in (g) above met? Attach results	☐ pass	☐ fail
	Date/Signature:	

i) Summary approval of the validation

☐ All parts of the validation passed, results attached.

☐ The following parts of the validation failed (please name):

_____

Follow-up or corrective actions to be taken:

_____

☐ Follow-up actions were determined and documented, results attached

Date of next scheduled review _____

_____
Signature

_____ _____
Place, Date Name in block print

D.3 Validation plan checklist: wrapping process

☐ **Validation** ☐ **Revalidation**

a) Responsibilities

Name of facility	
Location	
Validation participants	
Person responsible for the entire validation	
File location	

b) Description of sterilization wrap

Manufacturer of sterilization wrap			
Type/Grade	☐ Crepe paper ☐ Nonwoven ☐ Textile ☐ Plain paper	☐ Others If others, specify:	
Supplier contact information: Name: Address: Phone:			
Is supplier the manufacturer of the wrap?	☐ yes		☐ no
Does manufacturer provide documented evidence of a quality management system (e.g. QM certificate, registration, etc.)	☐ yes	☐ no	
Does supplier provide documentation demonstrating they have fulfilled the requirements of ISO 11607-1?	☐ yes	☐ no	☐ verification
If applicable, does manufacturer provide documentation of fulfilling requirements of regional product specific document (e.g. EN 868-2)?	☐ yes	☐ no	☐ verification
Sterilization process to be used:			

Is the sterile barrier system compatible with the sterilization process?	☐ yes	☐ no	
Is the storage and handling of wrap in the hospital in accordance with regional/ national/local standards or requirements?	☐ yes	☐ no	

c) Description of the wrapping closure system

Manufacturer of closure			
Type/Grade/lot number	☐ Adhesive tape		☐ Label
	☐Indicator tape		☐ Others If others, specify:
Lot number of closure system (tape)?			
Supplier contact information: Name: Address: Phone:			
Is supplier the manufacturer of the closure system?			
Does manufacturer provide documented evidence of a quality management system (e.g. QM certificate, registration, etc.)	☐ yes	☐no	
Does manufacturer provide documentation demonstrating they have fulfilled the requirements of ISO 11607-1?	☐ yes	☐ no	☐ verification
If applicable, does manufacturer provide documentation of fulfilling requirements of regional product specific document?	☐ yes	☐ no	☐ verification
Sterilization process to be used:			

d) Description of assembled sterile barrier systems (wrapping)

Contents of sterile barrier system	
Is this worst-case configuration? If so describe the rationale.	
Number of sterile barrier systems assembled	
Approved procedure or SOP used to assemble	
Was internal organizing tray, tip protector for sharp medical devices, corner protectors between tray and wrap, tray liner etc. to support the medical device and protect the sterile barrier system used?	☐ yes ☐ no
If internal support/protection was used, describe, like:	

e) Description of sterilization processes

Manufacturer of sterilizer and model number		
Serial number of sterilizer		
Is this a contract sterilizer?	☐yes	☐ no

Sterilization cycle Attach printout if available	☐ Steam (highest temp./ longest time) ☐ Ethylene oxide (EO) ☐ other _____		☐ Plasma ☐ LTSF (low temperature steam formaldehyde)
Is this the worst-case cycle?	☐ yes	☐ no	cycle parameters: _____
Approved SOP or loading procedure used			
Process validated?	☐ yes	☐ no	
Validated by:			
Date of last validation:			
Date of next validation:			

f) Description of protective packaging as well as handling, transportation, distribution and storage challenges

Protective Packaging	☐ yes	☐ no
— Describe type of protective packaging	☐ yes	☐ no
— Applied before sterilization	☐ yes	☐ no
— Applied after item is cool	☐ yes	☐ no
— Clearly labelled as protective packaging	☐ yes	☐ no
— Dust cover		
— Transport trays		
Description of handling, distribution and storage Has documentation been completed, e.g. see D.5?	☐ yes	☐ no
How often are sterile items moved or handled before arriving at their final point of use?		
— Number of events with risk of loss of integrity?		
Consider worst-case for Performance Qualification of the packaging system (combination of protective packaging and sterile barrier system)		
— What is the worst-case?		
— What is the rational for selection?		

g) Acceptance criteria — define method and acceptance criteria

Attribute	Method for evaluating	Acceptance criteria
Closure integrity		continuous, no opening or breaches, no channels
Package integrity		No punctures, tears, breaks,
Aseptic presentation		able to open without damage or contamination of the contents
Assembly (folds, etc.) according to documented procedure/assembly instructions		The opened sterile barrier system conforms to the documented procedure/ assembly instructions

Attribute	Method for evaluating	Acceptance criteria
Packaging configuration processed in the defined cycle		Have all sterilization parameters for the defined packaging configuration been met [see 3.2.3 b)]?
Other		

h) Qualification steps

Installation Qualification (IQ)	☐ executed	
	☐ previously executed in the validation dated:_____ _____	
	☐ pass	☐ fail
	Date/Signature:	
Operational Qualification (OQ)	☐ executed	
	☐ date previously executed in the validation on _____	
Was acceptance criteria defined in (f) above met?	☐ pass	☐ fail
Attach results	Date/Signature:	
Performance Qualification (PQ)	☐ executed	
Was acceptance criteria defined in (f) above met?	☐ pass	☐ fail
Attach results	Date/Signature:	

i) Summary approval of the validation

All parts of the validation passed, results attached.

The following parts of the validation failed (please name):

_____

Follow-up or corrective actions to be taken

_____

Follow-up actions were determined and documented, results attached

Date of next scheduled review _____

_____
Signature

_____
Place, Date

_____
Name in block print

D.4 Validation plan checklist: container process

☐ **Validation** ☐ **Revalidation**

a) Responsibilities

Name of facility	
Location	
Validation participants	
Person responsible for the entire validation	
File location	

b) Description of the rigid container

Manufacturer of rigid container				
Type/Grade	gasket	single use filter	re-usable filter	other
Supplier contact information: Name: Address: Phone:				
Is supplier the manufacturer of the rigid container?	☐ yes	☐ no		
Does manufacturer provide documented evidence of a quality management system (e.g. QM certificate, registration, etc.)	☐ yes	☐ no		
Does supplier provide documentation demonstrating they have fulfilled the requirements of ISO 11607-1?	☐ yes	☐ no	☐ verification	
If applicable, does supplier provide documentation of fulfilling requirements of EN 868-8?	☐yes	☐ no	☐ verification	
Is the filter used provided or recommended by the manufacturer of the container?	☐ yes	☐ no	☐ verification	
If not, did the filter supplier provide documented evidence of its efficacy and compatibility with the specific container and sterilization process that was used?	☐ yes	☐ no	☐ verification	
Sterilization process to be used:				
Is the sterile barrier system compatible to the sterilization process?	☐ yes	☐ no		
Is the storage and handling of containers in the hospital in accordance with regional/ national/ local standards or requirements?	☐ yes	☐ no		

c) Description of the tamper evident system used to demonstrate the closure integrity

Manufacturer tamper evident system	
Type/Grade	

Supplier contact information: Name: Address: Phone:			
Is supplier the manufacturer of the tamper evident system?	☐ yes		☐ no
Does the tamper evident system provide the following characteristics? — provide visual indication of tampering — hinders opening of the container and provides visual indication or tampering (physically blocks opening of the container) — indicate that the lid has been physically secured to the bottom part of the container since sterilization	☐ yes ☐ yes ☐ yes		☐ no ☐ no ☐ no
If a single use tamper evident system is used is there a lot number?	☐ yes LOT-No.:		☐ no
Does manufacturer provide documented evidence of a quality management system (e.g. QM certificate, registration, etc.)	☐ yes	☐ no	
Does supplier provide documentation demonstrating they have fulfilled the requirements of ISO 11607-1?	☐ yes	☐ no	☐ verification
Sterilization process to be used:			
Is the closure system compatible to the sterilization process?	☐ yes	☐ no	

d) Description of assembled container

Contents of sterile barrier system		
Is additional packaging used within the container?	☐ yes	☐ no
Is the additional packaging a sterile barrier system?	☐ yes	☐ no
Is this the worst-case configuration, if so describe the rationale		
Number of sterile barrier systems assembled		
Procedure or SOP used to assemble		
Was internal organizing tray, tip protector for sharp medical devices etc. to support the medical device and protect the sterile barrier system used?	☐ yes	☐ no
If internal support/protection was used, describe:		

e) Description of sterilization processes

Manufacturer of sterilizer and model number		
Serial number of sterilizer		
Is this a contract sterilizer?	☐ yes	☐ no
Sterilization cycle Attach print-out if available	☐ Steam (highest temp./ longest time) ☐ Ethylene oxide (EO) ☐ other _____	☐ Plasma ☐ Formaldehyde (FO)

Is this the worst-case cycle?	☐ yes	☐ no	cycle parameters: _____
SOP or loading procedure used			
Process validated?	☐ yes	☐ no	
Validated by:			
Date of last validation:			
Date of next validation:			

f) Description of the handling, distribution and storage challenges

Has documentation been completed, e.g. see D.5?	☐ yes	☐ no
How often are sterile items moved or handled before arriving at their final point of use? — Number of events with risk of loss of integrity?		
Consider worst-case for Performance Qualification of the packaging system (combination of protective packaging and sterile barrier system) — What is the worst-case? — What is the rational for selection?		

g) Acceptance criteria- define method and acceptance criteria

Attribute	Method for evaluating	Acceptance criteria
Latching mechanism and Closure continuity/integrity		Closure continuity/integrity maintained without closure rupture
Filter/valve integrity		No punctures, tears, channels, damage
Gasket integrity		No damage (see 3.3.2.9.2)
Aseptic presentation		able to open without damage or contamination of the contents
Other		

h) Qualification steps

Installation Qualification (IQ)	☐ executed	
	☐ previously executed in the validation dated: _____	
	☐ pass	☐ fail
	Date/Signature:	
Operational Qualification (OQ)	☐ executed	
	☐ date previously executed in the validation on _____	
Was acceptance criteria defined in (f) above met? Attach results	☐ pass	☐ fail
	Date/Signature:	
Performance Qualification (PQ)	☐ executed	
Was acceptance criteria defined in (f) above met? Attach results	☐ pass	☐ fail
	Date/Signature:	

i) Summary approval of the validation

☐All parts of the validation passed, results attached.

☐ The following parts of the validation failed (please name):

_____

Follow-up or corrective actions to be taken

_____

☐ Follow-up actions were determined and documented, results attached

Date of next scheduled review _____

_____
Signature

_____ _____
Place, Date Name in block print

D.5 Handling and distribution checklist: handling, distribution and storage

The following checklist should help to make the choice of the sterile barrier system used.

Anticipated challenges that effect integrity of sterile barrier systems

Does the manufacturer provide recommendations for the conditions of handling, storage and distribution?

— Temperature	☐ yes	☐ no
— Relative humidity	☐ yes	☐ no
— Handling requirements	☐ yes	☐ no
— Restrictions on agitation	☐ yes	☐ no
— Bumps and other movement	☐ yes	☐ no

Description of handling and staff attire

Is there an education program for staff who handles sterile barrier systems?	☐ yes if yes describe	☐ no
Is there a hand hygiene protocol?	☐ yes if yes describe	☐ no
Is there a dress code?	☐ yes if yes describe	☐ no
Is the number of times a sterile barrier system is handled from point of sterilization to point of use known?	☐ yes if yes describe	☐ no

Description of distribution/transport means

On site transportation

— Can the clean and/or sterile medical devices be transported and stored separately from soiled medical devices?	☐ yes	☐ no
— Are these sterile medical devices covered or enclosed during transport?	☐ yes	☐ no

— Are the compartments cleaned and disinfected prior to transporting sterile medical devices if, previously contaminated items were transported?	☐ yes	☐ no
— If transport systems left unattended in public areas are they able to be locked and secured?	☐ yes	☐ no
Off-site transportation — Applicable?	☐ yes	☐ no
— Are the vehicles used to transport appropriate for the use?	☐ yes	☐ no
— Has the pneumatic suspension in the transport vehicles been considered?	☐ yes	☐no
— Can and will the vehicles be routinely cleaned and maintained?	☐ yes	☐ no
— Have the extremes of temperature and humidity been considered?	☐ yes	☐ no
— Are the compartments cleaned and disinfected prior to transporting sterile medical devices if, previously contaminated items were transported?	☐ yes	☐ no
— Are transport carts dedicated for sterile stock able to be locked and secured?	☐ yes	☐ no
— Are transport personnel trained in handling sterile barrier systems?	☐ yes	☐no

Storage aspects

Are there dedicated storage areas for sterile barrier systems?	☐ yes	☐ no
Is there a system to stock rotation based on date of sterilization?	☐ yes	☐ no
Is it a dust free environment?	☐ yes	☐ no
Is overhead lighting fitted flush with the ceiling?	☐yes	☐ no
Is there a routine for regularly cleaning of floor?	☐yes If yes, how often?	☐ no
Is the shelving made of non-porous material?	☐ yes	☐ no
Is there a routine for regularly cleaning of shelf/basket?	☐ yes If yes how often	☐ no
Can storage on shelf/ basket be without any risk of damage?	☐ yes	☐ no
Is there enough space between floor and sterile items?	☐ yes cm/inch	☐no
Is there enough space between ceiling and sterile items?	☐ yes cm/inch	☐ no
Is direct sunlight able to be avoided?	☐ yes	☐ no
Are the manufacturer's requirements of humidity being followed?	☐ yes Result %	☐ no
Are the manufacturer's requirements of temperature being followed?	☐ yes Result °C/ °F	☐ no
Is the air filtered?	☐ yes State %	☐ no

Is the air changed every hour?	☐ yes ☐ no Amount:
Is there positive pressure?	☐ yes ☐ no
Are airborne particles or microorganisms counted?	☐ yes ☐ no Result particle or cfu/m^3
Is there a separate room for unpacking industrial goods?	☐ yes ☐ no

Annex E
(informative)

Installation qualification documentation — Guidance for health care facilities

REMARK Users of the forms given in Annex E are permitted to produce copies of these forms, notwithstanding the fact that ISO retains all other rights regarding the entirety of the document.

E.1 Checklist installation qualification (IQ): heat sealing process

a) General data

Sealing device		
Manufacturer		
Manufacturer's address		
Quality management system	☐ Verification available	
Type		
Serial number		
Year of manufacture		
Location		
Person responsible for validation		
Additional operators for IQ		
Date of IQ		
Type of sealing device	☐ Bar/impulse ☐ Bar/continuously heated ☐ Rotary sealer	☐ Series model ☐ Special sealing device from manufacturer ☐ Modified sealing device Modified by: _____
If applicable, European Union CE conform?	☐ yes ☐ no	☐ verification
Service team		
Address		
Telephone number		
Contact person		
Authorization	☐Yes, by:_____	☐No

b) Installation conditions

Parameter	Postulated	Available (measured)
Voltage		☐ yes
Frequency in Hz		☐ yes
Fuse protection in Ampere		☐ yes
Conforms to local electric code		☐ yes
Compliance	☐ **Yes** ☐ **No**	**Date/Signature:** _____

c) Documentation

Document	Available		Location (repository)
Instruction manual	☐ yes	☐ no	
If applicable, European Union CE-Declaration of conformity	☐ yes	☐ no	
Replacement parts and order-List	☐ yes	☐ no	
SOP approved	☐ yes	☐ no	
Purchase Order verification	☐ yes	☐ no	
Electrical drawings and installation schematics	☐ yes	☐ no	
Compliance	☐ yes	☐ no	**Date/Signature:** _____

d) Security characteristics

Parameter	Required	Available	
Seal seam width			
Distance to medical product			
Process course	Automatic	☐ automatic	☐ manual
Compliance	☐ yes ☐ no	**Date/Signature:** _____	

The service instructions in general suffice for verification of these aspects. Furthermore, the following aspects to be checked by an authorized person:

Description	Compliance		Remarks
Is the sealing device connected according to manufacturer's instructions?	☐ yes	☐ no	
Is it demonstrated that the sealing device has no optical security defects (defect in the casing cover, power supply line, plug, etc.)?	☐ yes	☐ no	
Is it demonstrated that the sealing device has no operational defects (unknown running noises, rattling, squeaking, etc.)?	☐ yes	☐ no	
Compliance	☐ yes	☐ no	**Date/Signature:** _____

e) Critical parameters

The following additional aspects to be determined by the user or checked (partial verification required):

Which parameters were designated as critical during process development? (Ask the manufacturer). — at least temperature, pressure and time (speed)	☐ Temperature ☐ Sealing / dwell time (bar sealer) ☐ Other (please specify)	☐ Pressure ☐ Sealing speed (rotary sealer)
Question	**Compliance**	**How**
Are these critical process parameters controlled and monitored?	☐ yes ☐ no	
Are systems available, which in case of deviation from previously determined limit values of operational parameters raise an alarm or warning or a stop of the machine will be initiated?	☐ yes ☐ no	
Are these critical process parameters routinely documented?	☐ yes ☐ no	
Compliance	☐ yes ☐ no	**Date/Signature:** _____

The following additional aspects to be confirmed with verification:

Question	**Compliance**		**Proven by**
Is the sealing device serviced/do written service plans exist?	☐ yes	☐ no	
Is the sealing device calibrated?	☐ yes	☐ no	
Compliance	☐ yes	☐ no	**Date/Signature:** _____

Do the parameter settings remain following a power failure?	☐ yes	☐ no	
Compliance	☐ yes	☐ no	**Date/Signature:** _____

f) Training and work area

Training

Name of employee	**SOP**	**Training**			**Signature**	
		Trained by	**Qualification**	**Date**	**Trainer**	**Trainee**

Work area

Have the following been verified?

Table surface smoothness (no sharpness or any foreign matter embedded potentially damaging the wrapping process raw material)	☐ yes	☐ no
Table surface cleanliness and ability to be maintained clean	☐ yes	☐ no
Table environment to be design offering enough empty room to fold	☐ yes	☐ no
Are the appropriate SOP's available in the work area?	☐ yes	☐ no
Date/Signature: _____		

E.2 Checklist Installation Qualification (IQ): Wrapping Process

Typically an IQ is only performed when there is equipment to be installed. Alternatively, for a process that involves only people and their execution of tasks, the development of the SOP's and the training on them may be considered by some facilities to be an IQ. The training of the specific operators employed for the OQ and PQ should be documented in those reports.

Training

Name of employee	SOP	Training			Signature	
		Trained by	Qualification	Date	Trainer	Trainee

Work area

Have the following been verified?

Table surface smoothness (no sharpness or any foreign matter embedded potentially damaging the wrapping process raw material)	☐ yes	☐ no
Table surface cleanliness and ability to be maintained clean	☐ yes	☐ no
Table environment to be design offering enough empty room to fold	☐ yes	☐ no
Are the appropriate SOP's available in the work area?	☐ yes	☐ no
Date/Signature: _____		

E.3 Checklist installation qualification (IQ): container process

Typically an IQ is only performed when there is equipment to be installed. Alternatively, for a process that involves only people and their execution of tasks, the development of the SOP's and the training on them may be considered by some facilities to be an IQ. The training of the specific operators employed for the OQ and PQ will be documented in those reports.

Training

Name of employee	SOP	Training			Signature	
		Trained by	Qualification	Date	Trainer	Trainee

Work area

Have the following been verified?

Table surface smoothness (no sharpness or any foreign matter embedded potentially damaging the wrapping process raw material)	☐ yes	☐ no
Table surface cleanliness and ability to be maintained clean	☐ yes	☐ no
Table environment to be design offering enough empty room to fold	☐ yes	☐ no
Are the appropriate SOP's available in the work area?	☐ yes	☐ no
Date/Signature: _____		

Annex F
(informative)

Operational qualification documentation — Guidance for health care facilities

REMARK Users of the forms given in Annex F are permitted to produce copies of these forms, notwithstanding the fact that ISO retains all other rights regarding the entirety of the document.

F.1 Checklist operational qualification (OQ): heat sealing process

Seal Temperature	**Lower limit (LL)**	**Upper limit (UL)**
1. Temperatures recommended by the preformed sterile barrier system manufacturer		
2. Actual temperature achieved during the test		
Temperatures achieved during the test were within the limits recommended by the preformed sterile barrier system manufacturer		☐ yes ☐ no
Sealing temperature range (in °C)*?	from _____to _____ Data from:_____ ☐ Verification available	

Process	
SOP/Procedure(s) used **Approval date and version**	
Operator training on procedure **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____**	

Maintenance	
SOP/Procedure(s) used **Approval date and version**	
Operator training on procedure **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____**	

Number of samples evaluated

Attribute	Acceptance criteria	Compliance			
		Lower Level		Upper Level	
Seal integrity	Intact seal for a specified seal width	☐ yes	☐ no	☐ yes	☐ no
	Verified by: _____ Test method: _____				
	No channels or open seals.	☐ yes	☐ no	☐ yes	☐ no
	Verified by: _____ Test method: _____				
Package integrity	**No** punctures or tears	☐ yes	☐ no	☐ yes	☐ no
	Verified by: _____ Test method: _____				
Seal strength	Meets specified criteria _____	☐ yes	☐ no	☐ yes	☐ no
	Verified by: _____ Test method: _____				
Peelability	Peelable without material rupture, delamination, separation or degradation	☐ yes	☐ no	☐ yes	☐ no
Aseptic presentation	Able to open without damage or contamination of the contents	☐ yes	☐ no	☐ yes	☐ no
	Verified by: _____ Test method: _____				
Other	Specify: _____	☐ yes	☐ no	☐ yes	☐ no
	Verified by: _____ Test method: _____				
Temperature (T) determined for the PQ (Average between lower limit and upper limit is typically the Actual-Temperature during the test)	T = _____				

F.2 Checklist operational qualification (OQ): wrapping process

Process	
SOP/Procedure(s) used **Approval date and version**	
Operator training on procedure **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____**	

Number of samples evaluated

Attribute	Acceptance criteria	Compliance
Closure integrity	Continuous, no opening, or breaches, no channels Verified by: _____ Test method: _____	☐ yes ☐ no
Package integrity	**No** punctures, tears, breaks Verified by: _____ Test method: _____	☐ yes ☐ no
Aseptic presentation	Able to open without damage or contamination of the contents Verified by: _____ Test method: _____	☐ yes ☐ no
Assembly (folds, etc.) according to documented procedure/ assembly instructions	Open and assessed package conforms to documented procedure/assembly instructions Verified by: _____ Test method: _____	☐ yes ☐ no
Other	Specify: _____ Verified by: _____ Test method: _____	☐ yes ☐ no

Maintenance	
SOP/Procedure(s) used **Approval date and version**	
Operator training on procedure **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____**	

F.3 Checklist operational qualification (OQ): container process

Process	
SOP/Procedure(s) used **Approval date and version**	
Operator training on procedure **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____**	

Number of samples evaluated

Attribute	Acceptance criteria	Compliance
Latching mechanism and closure continuity/integrity	Closure continuity/integrity maintained without seal/closure rupture Verified by: _____ Test method: _____	☐ yes ☐ no
Tamper evidence system	Tamper evidence system intact and place verified Verified by: _____ Test method: _____	☐ yes ☐ no
Filter/valve integrity	No punctures, tears, channels, damage, Verified by: _____ Test method: _____	☐ yes ☐ no
Gasket integrity	No damage Verified by: _____ Test method: _____	☐ yes ☐ no
Aseptic presentation	Able to open without damage or contamination of the contents Verified by: _____ Test method: _____	☐ yes ☐ no
Other	Specify: _____ Verified by: _____ Test method: _____	☐ yes ☐ no

Maintenance	
SOP/Procedure(s) used **Approval date and version**	
Operator training on procedure	
Operator Name:_____ Date Trained: _____ **Operator Name:_____ Date Trained: _____** **Operator Name:_____ Date Trained: _____**	

Annex G
(informative)

Performance qualification documentation — Guidance for health care facilities

REMARK Users of the forms given in Annex G are permitted to produce copies of these forms, notwithstanding the fact that ISO retains all other rights regarding the entirety of the document.

G.1 Checklist performance qualification (PQ), sealing process

Temperature defined for the sealing process (copy from OQ Checklist)	T = _____			
Actual-temperature for the Operational Qualification (copy from OQ Checklist)	Lower limit (LL) LL:		Upper limit (UL) UL:	
Switch-off tolerance in degrees (according to sealing device manufacturer's specifications)	Aberration (A) A = _____			
Results lower and upper value	T– A	=	T+ A	=
Conditions	**T – A ≥ LL**		**T+ A ≤ UL**	
Compliant with conditions?	☐ yes	☐ no	☐ yes	☐ no

Criteria						
Process SOPs are approved and used	☐ yes		☐ no			
Person(s) have been trained on SOPs	☐ yes		☐ no			
Sterilization process	**Sterilization-cycle A**		**Sterilization-cycle B**		**Sterilization-cycle C**	
Date/time of sterilization						
Sterilization protocol attached?	☐ yes	☐ no	☐ yes	☐ no	☐ yes	☐ no

Sealing parameters			
Temperature			
Pressure			
Time dwell/speed			
Others (please specify)			

Number of samples evaluated
Samples should be evaluated after sterilization, distribution and handling [see 3.2.3 b)].

Attribute criteria

Attribute	Acceptance criteria	Compliance
Seal integrity	Intact seal for a specified seal width Verified by: _____ Test methods: _____	☐ yes ☐ no
	No channels or open seals, no bubbles. Verified by: _____ Test methods: _____	☐ yes ☐ no
Package integrity	**No** punctures or tears Verified by: _____ Test methods: _____	☐ yes ☐ no
Seal strength	Meets specified criteria Verified by: _____ Test methods: _____	☐ yes ☐ no
Peelability	**Peelable without** material rupture, delamination, separation or degradation	☐ yes ☐ no
Aseptic presentation	Able to open without damage or contamination of the contents Verified by: _____ Test methods: _____	☐ yes ☐ no
Other	Specify: _____ Verified by: _____ Test methods: _____	☐ yes ☐ no

G.2 Checklist performance qualification (PQ), wrapping process

Criteria					
Process SOPs developed and used	☐ yes		☐ no		
Person(s) have been trained on SOPs	☐ yes		☐ no		
Sterilization process	Sterilization-cycle A		Sterilization-cycle B		Sterilization-cycle C
Date/time of sterilization					
Sterilization protocol available?	☐ yes	☐ no	☐ yes	☐ no	☐ yes ☐ no
Number of samples evaluated Samples should be evaluated after sterilization, distribution and handling [see 3.2.3 b)].					

Acceptance criteria

Attribute	Acceptance criteria	Compliance
Closure integrity	Continuous, no opening, or breaches, no channels Verified by: _____ Test methods: _____	☐ yes ☐ no

Attribute	Acceptance criteria	Compliance
Package integrity	**No** punctures, tears, breaks, stains Verified by: _____ Test methods: _____	☐ yes ☐ no
Aseptic presentation	Able to open without damage or contamination of the contents Verified by: _____ Test methods: _____	☐ yes ☐ no
Assembly (folds, etc.) according to documented procedure/assembly instructions	Open and assessed package conforms to documented procedure/assembly instructions Verified by: _____ Test methods: _____	☐ yes ☐ no
Other	Specify: _____ Verified by: _____ Test methods: _____	☐ yes ☐ no

G.3 Checklist performance qualification (PQ), container process

Criteria						
Process SOPs approved and used	☐ yes ☐ yes		☐ no ☐ no			
Person(s) have been trained on SOPs	☐ yes		☐ no			
Sterilization process	Sterilization-cycle A		Sterilization-cycle B		Sterilization-cycle C	
Date/time of sterilization						
Sterilization protocol available?	☐ yes	☐ no	☐ yes	☐ no	☐ yes	☐ no
Number of samples evaluated Samples should be evaluated after sterilization, distribution and handling [see 3.2.3 b)].						

Acceptance criteria

Attribute	Acceptance Criteria	Compliance
Latching mechanism and closure continuity/integrity	Closure continuity / integrity maintained without seal/closure rupture caused Verified by: _____ Test methods: _____	☐ yes ☐ no
Filter/valve integrity	No punctures, tears, channels, damage, Verified by: _____ Test methods: _____	☐ yes ☐ no
Gasket integrity	No damage Verified by: _____ Test methods: _____	☐ yes ☐ no
Aseptic presentation	Able to open without damage or contamination of the contents Verified by: _____ Test methods: _____	☐ yes ☐ no
Tamper evidence	Is the tamper evidence mechanism intact and effective? Verified by: _____ Test methods: _____	☐ yes ☐ no
Other	Specify: _____ Verified by: _____ Test methods: _____	☐ yes ☐ no

Annex H
(informative)

Addressing worst-case requirements — Guidance for industry and health care facilities

H.1 Overview

ISO 11607-1 addresses "worst-case" in three areas and in each case, it means something slightly different. In order to correctly interpret and apply these clauses dealing with worst-case, it is important to understand the terms that are used.

Specifically:

— *sterile barrier system* — minimum package that prevents ingress of microorganisms and allows aseptic presentation of the product at point of use;

— *protective packaging* — configuration of materials designed to prevent damage to the sterile barrier system and its contents from the time of their assembly until the point of use;

— *packaging system* — combination of the sterile barrier system and protective packaging.

H.2 Worst-case configuration — Medical devices

In ISO 11607-1:2006, 6.1.6, it states: "When similar medical devices use the same packaging system, a rationale for establishing similarities and identifying the worst-case configuration shall be documented. As a minimum, the worst-case configuration shall be used to determine compliance with this part of ISO 11607."

Within medical device product families (i.e. medical devices that are similar but not identical), a common sterile barrier system can be used to protect a variety of medical devices. The worst-case is established by identifying the medical device(s) that apply the most stress to the packaging system. The worst-case configuration may be the bulkiest or heaviest item in an otherwise common group of medical devices or an item with the greatest number of fitments or other medical device features. Often, the determination of the worst-case configuration is clear. However, in some cases it may be necessary to test more than one medical device (e.g. the heaviest medical device as well as the medical device with the most fitments) to ensure that the packaging system has been fully challenged. Properly characterizing and evaluating the worst-case configuration will ensure that the other medical devices in the product family will be appropriately protected by the packaging system.

H.3 Worst-case — Sterile barrier system

Additional direction regarding worst-case testing is provided in ISO 11607-1:2006, 6.3.4 on packaging system performance testing, *"Performance testing shall be conducted on the worst-case sterile barrier system at the specified process limits of forming and sealing and after exposure to all the specified sterilization processes."* There are two predominant approaches to addressing the key issues of this section.

The first and most common approach utilizes sourcing preformed sterile barrier systems manufactured using a fully validated process. Sterile barrier systems that have been produced as lots run at typical operating conditions within the validated window are tested and evaluated. By choosing an appropriate sample size from multiple lots (typically three), one can be assured, at a given confidence level, that the full range of package characteristics (e.g. seal strength) have been represented. Hence, sample size

selection and number of lots to be evaluated are important components of the documented rationale. Numerous reference materials exist to assist in sample size determination.

The second approach involves producing sterile barrier systems at the worst-case conditions of manufacture, generally the extremes of the validated window. In some cases, sterile barrier systems may be produced at the lowest validated temperature, the lowest validated pressure, and the shortest validated dwell to yield sterile barrier systems with the low-end worst-case seal quality. Typically, the parameters used to establish the OQ are used to produce the sterile barrier systems needed to assess the packaging system performance. This approach can be costly as specific and separate production runs will need to be performed to create the sterile barrier systems at the worst-case conditions of manufacture.

Under both of these approaches, make the final closure seal (whether on a preformed sterile barrier system, tray/lid system, or via the form fill seal process) at or beyond the specified process limits of sealing to ensure that a worst-case sterile barrier system has been produced.

The approach to achieving compliance to ISO 11607-1 will vary between medical device manufacturers, but in each case the approach chosen should be supported by an appropriate rationale, to be included in the documented package validation protocol. The choice will be dependent on corporate risk policy and economic considerations.

H.4 Worst-case configuration — Sterile barrier system manufacturing process

Worst-case configuration is again discussed in ISO 11607-2:2006, 5.1.5, “When similar preformed sterile barrier systems and sterile barrier system manufacturing processes are validated, a rationale for establishing similarities and identifying the worst-case configuration shall be documented. As a minimum, the worst-case configuration shall be validated to determine compliance with this part of ISO 11607.” In this case, worst-case configuration applies to the sterile barrier system manufacturing processes not to the medical device itself. When validating manufacturing processes, the (preformed) sterile barrier systems may be grouped into families, for example chevron pouches using the same top and bottom materials but of different sizes. To ensure that the validation is meaningful for the entire sterile barrier system family, the worst-case configuration(s) for the (preformed) sterile barrier family need to be identified. When heat sealing, it is important to look at the extremes of seal area. For example, both small and large seal areas on pouches, blister packs present unique challenges and should both be assessed. For thermoformed trays and lids, the total square centimetres in the sealing array (i.e. total square centimetres of seal under the sealing platen) could be considered. This approach allows the impact of oversealing and undersealing as well as temperature and pressure distribution to be assessed.

It is important to also consider that the worst-case package configuration for sealing purposes may not be the same as the worst-case for sterilization validation.

Annex I
(informative)

Generating a final packaging system validation protocol — Guidance for industry

NOTE Validation of the final packaging system, including the sterile barrier system and any protective packaging, consists of the preparation of an appropriate validation protocol, execution of that protocol, and a critical examination of the test results to determine whether the desired packaging system requirements are met (ISO 11607-1:2006, 4.3, 6.3, and 6.4).

I.1 Plan objectives and background on protocol development

A critical element in the validation process is to document the plan by which the packaging system will be tested. This is typically done by writing a detailed protocol that describes the plan objectives, packaging system design details, sampling plan(s) to be employed, required sterile barrier or packaging system shelf life, test methods and equipment to be used, acceptance criteria, and other pertinent information. The protocol should be detailed enough for the test engineer to understand what should be done to satisfy the validation requirements.

The protocol will describe the test methods appropriate for the type of packaging system being evaluated, including methods for package (sterile barrier system) integrity. (Further discussion of test methods can be found in Annexes A and O). An appropriate and rigorous shipping and handling test method should be chosen that will realistically challenge the package (sterile barrier system) integrity and ensure a high probability that the sterile barrier system and packaging system will reach its destination in a useable condition. The protocol should describe the shelf life requirements of the packaged medical device and the method for verifying this aspect of the packaging system design (for further information on use of accelerated aging to evaluate sterile barrier system or packaging system shelf life, see Annex A). Sample sizes for all test methods should be large enough to provide for significant statistical analysis, so as to provide a high degree of reliability. Once the protocol is developed for the packaging system design and system being evaluated, it should be approved by all pertinent parties before testing is begun, and that approval, like all aspects of the protocol, needs to be documented.

NOTE The development of a sterile barrier system is a balance of available time and resources, and it may be that the parameters to produce the packaged medical device undergo refinement during the execution of the protocol. Experienced companies will employ a flexible approach, but always document any design or process changes with a defendable rationale.

I.2 Understanding the packaging system design configuration

An important aspect of the packaging system design validation is having an understanding of the different levels of packaging that might be used. A complete packaging system may have a sterile barrier system (for example, a pouch or tray), additional levels of protective packaging (e.g. carton, shelf pack), as well as the shipping container. When testing, the definitive indicator of acceptance of the packaging system design is maintenance of the sterile barrier system (the primary package), which is judged by integrity tests. In addition, secondary and tertiary levels of packaging, which provide dispensing, labelling, and protective functions, may often be discreetly evaluated in the protocol, as they contribute to the efficacy of the complete packaging system.

Prior to preparation of a validation protocol, the biocompatibility of the sterile barrier system typically has been assessed. Any potential medical device/packaging system interactions (if relevant) should be considered by the medical device manufacturer in advance of investing resources aimed at validating a sterile barrier system.

I.3 Grouping packaging systems for validation

When determining and assessing the packaging system, thought should be given to other packaging system designs and medical devices that may require validation. Many times similar medical devices, comprising a "medical device family," may be validated together, where package materials, packaging machinery, sterilization processes, and other aspects of the medical device use and life cycle are similar. Choosing a device/packaging system combination that represents a "worst-case" example may be advisable, in order to ensure less demanding variants of the sterile barrier system and associated medical device are covered. In all such cases the protocol should include the rationale for this approach. It is also sometimes possible to leverage existing packaging systems for medical devices to reduce the burden associated with the validation protocol, or to validate a worst-case scenario that covers multiple packaging system/medical device combinations. Medical devices with similar physical dimensions and/or packaging system configurations similar to validated structures may provide the basis for a valid rationale to limit the amount of testing required to establish efficacy of a sterile barrier system.

I.4 Determining sample size for final packaging system validation

The sample size chosen will vary depending upon the packaging system that is being tested (e.g. sterile barrier system, protective packages, shipping box), the type of response of the test (attribute or variable) and considerations regarding acceptable levels of risk, (ISO 11607-1:2006, 4.3).

a) For the sterile barrier system, which will ultimately determine the acceptability of the entire packaging system, tests should be performed using a sample size that will provide statistically significant data.

b) For attribute data (e.g. pass/fail) the sample size will be dependent upon the desired level of confidence and the desired reliability of the outcome.

c) For variable data tests, where an actual value is obtained as opposed to a pass/fail result, fewer samples are required to obtain a statistically significant value. Therefore, it is advisable where possible to convert attribute tests to variable tests (for example through the use of a grading scale) in order to reduce the required sample size.

d) The shipping box, which will contain either individual sterile barrier systems or secondary and tertiary boxes, may have sample sizes as small as one, if the one shipping box contains enough sterile barrier systems to perform adequate test replicates for packaging system tests.

NOTE It is important to understand the unit of test configuration: for example, a packaging system containing twelve (12) sterile barrier systems is not a sample size of twelve (12). It is a sample size of one (1) and each sterile barrier system is 1/12 of a whole sample.

I.5 Defining acceptance criteria

A critical component of the validation is to define what constitutes a positive outcome for the validation. The acceptance criteria should be established prior to beginning the validation and should be centred on delivery of the medical device to the end user in an undamaged and sterile condition. Detailed acceptance criteria may allow for accepting specified damage to a medical device or its packaging system. The form and content of acceptance criteria may vary widely, in accordance with the particular situation. Methods may range from simple pass-fail judgments to highly quantitative scoring or analysis systems. Protocol acceptance criteria and packaging system specifications are closely linked, though a protocol will probe more aspects of a packaging system than are typically monitored during routine production.

I.6 Sterile barrier system preparation for testing

Sterile barrier systems submitted for the packaging system design validation should be manufactured under standard operating procedures. Packaging systems needs to be sterilized using a validated sterilization process. The sterilization may be elevated to a worst-case situation by performing multiple sterilization cycles. The packaging systems should contain the actual medical device or a surrogate of

the medical device, appropriate labelling, and IFU's expected to be included in the final market packaging system (see DIN 58921).

I.7 Define the shipping environment

Based on the design inputs regarding the global logistics and distribution anticipated for the medical device, shipping and handling test should be defined (ISO 11607-1:2006, 5.5). This test may be designed by several means:

— actual shipment (see note);

— standardized laboratory simulations;

— laboratory simulations based on measured field data;

— environmental challenging (climatic stressing) if appropriate.

For guidance on choosing an appropriate distribution challenge method see ASTM D4169. For further information on environmental challenging see Annex A.

NOTE Actual shipment is not recommended as the only method used for evaluations. Typically, there is no way to document whether the packaging system receives the harshest or least challenging modes of shipping and handling.

I.8 Defining shelf life

One important aspect of a validation protocol is the rationale and test parameters for establishing medical device shelf life (ISO 11607-1:2006, 6.4). When indicated on a medical device packaging system, the FDA requires documented evidence to support these claimed expiration dates. The European Union requires expiration dates on all medical device packages as specified in the EC Directive 93/42/EEC which states in part, "the label must bear where appropriate, an indication of the date by which the medical device should be used, in safety, expressed as the year and month".

Using accelerated aging to test sterile barrier system shelf life is generally accepted as valid for new medical device introductions, provided real time aging is in place to confirm accelerated aging test results. The accelerated aging protocol should be based on a conservative temperature that is carefully chosen so that the materials (both of the medical device and the packaging materials) are not damaged due to extreme conditions that are outside the range of use for those materials. Typically, a series of tests is carried out to evaluate package (sterile barrier system) integrity, opening features (if applicable), and the general properties of the packaging materials themselves.

For a discussion of stability testing, see 4.8.2 and Annex M.

NOTE Additional information may be found in the EU-MEDDEV 2.2/3 guidance document.

Annex J
(informative)

Design inputs — Medical device attributes — Guidance for industry

J.1 Introduction

Before the design of a packaging system for a terminally sterilized medical device can begin, it is critical to examine all attributes and requirements of the medical device, which could affect the design of the packaging system (ISO 11607-1:2006, Clause 6). The best way to accomplish this is for those responsible for the design of the packaging system to be involved in the overall product development at an early stage. Obtaining the pertinent information required to begin the design process should be a cross-functional activity requiring input from a number of organizations. These organizations include but are not limited to engineering, manufacturing, marketing, and regulatory.

At a high level, design inputs can be thought of as product attributes and product specific requirements. Product attributes are generally the physical characteristics of the medical device, which will need to be contained. The product specific requirements, however, can be divided into several categories. These categories are product protection requirements, manufacturing requirements, sterilization process requirements, storage distribution and handling requirements, marketing requirements, budget requirements, customer requirements and regulatory requirements. Each of these categories is interrelated, developed in parallel during the product development cycle, and each plays a role in determining the final packaging system design.

Each of these categories will be discussed in Annex J to provide baseline guidance for gathering design inputs prior to designing a packaging system for a terminally sterilized medical device product.

J.2 Product attributes

The first phase of gathering design inputs should involve analysing medical device attributes. These are the physical characteristics of the medical device that will help guide some basic decisions regarding what type of packaging system is necessary for containing the medical device.

Physical characteristics include but are not limited to:

a) **Size**: The dimensions of the medical device should be understood, including length, width, diameter and profile of the medical device and all accessories that will be part of the total medical device.

b) **Weight**: Determine the total weight of the medical device and all accessories to be packaged.

c) **Centre of gravity**: Determine whether the medical device is balanced or offset, this will help determine the orientation of the medical device in the packaging system.

d) **Profile**: Determine the profile of the medical device and all accessories.

e) **Sharp edges/points**: Determine whether there are any sharp edges or points on the medical device and accessories that could damage the sterile barrier system. Also, determine if the end user, or person opening the packaging system, needs to be protected from any sharp edges or points on the medical device and accessories.

f) **Surface characteristics**: Determine if the surface of the medical device or accessories have any special protection requirements. For example, it is possible to have a medical device that is coated,

a medical device with a rough surface that could abrade sterile barrier materials, or a polished medical device that could be scuffed by the sterile barrier materials.

g) **Shelf life**: It is important to understand if the medical device has an expiration date. Also, if the shelf life will be extended once additional validation data are available.

h) **Ability to reconfigure**: Determine whether or not the medical device can be manipulated in order to fit in the packaging system. Some packaging systems require the medical device to be placed in the packaging system in a specific orientation. The ability to reconfigure the medical device is often an opportunity to decrease the size of the packaging system.

J.3 Medical device protection guidance

One of the main functions of a packaging system is to protect the medical device up to the point of use. In order to design a cost effective packaging system for a medical device, an assessment of the medical device sensitivities should be conducted. These sensitivities, along with factors such as the processing in manufacturing, sterilization, and handling in distribution and at the point of use will aid in determining the overall medical device protection requirements. Understanding these requirements will help to make decisions regarding material selection for both the sterile barrier system and the protective packaging.

An assessment of medical device protection requirements should at minimum include the following:

a) **Temperature sensitivities**: Determine if there are any limitations on the exposure of the medical device to temperature extremes. This could determine whether or not the medical device will require a controlled environment during distribution.

b) **Humidity/moisture**: Determine if there are any limitations on the exposure of the medical device to humidity extremes.

c) **Light**: Determine if there are any limitations on the exposure of the medical device to ultraviolet (UV) or visible light.

d) **Oxygen**: Determine whether the medical device is sensitive to oxygen.

e) **Shock**: Determining the amount of shock the medical device can handle without packaging will help determine the amount of shock protection required from the packaging system. It is also important to understand if the medical device is more susceptible to shock forces in a particular orientation.

f) **Vibration**: Determine if the medical device is sensitive to vibration. It is often helpful in the design of a packaging system to know the resonant frequency of the medical device; this will help determine the amount of protection required.

J.4 Storage, distribution, and handling guidance

J.4.1 The packaging system designer should understand the stresses imposed upon the packaging system through its total life cycle. This includes all factors of storage, distribution and handling. The requirements for these environments are determined largely by the type of medical device, type of packaging system, and the type of distribution. A thorough understanding of these factors will help to address all pertinent medical device protection requirements.

J.4.2 An assessment of storage, distribution and handling requirements should at a minimum include the following:

a) **Storage**: A thorough assessment of storage environments should be conducted. This assessment should include the storage environments at the manufacturing facilities, the distribution centres and by the end users. The key factors are space limitations, stacking or shelving issues and the temperature/humidity exposures. The storage environment of the end users can be difficult to

quantify, however, at a minimum there should be an understanding of any variability of how the end user will be storing the medical device. This could include storage at a hospital, at a regional centre, or medical devices being carried between clinical sites by sales force personnel.

b) **Distribution/Transportation**: An assessment of the distribution environment should be conducted. A complete evaluation of a distribution environment can be time consuming and costly, however, there should be a basic understanding of the factors involved in distribution in order to design a cost effective packaging system. Determine basic factors such as the transportation means used to move medical devices between: the manufacturing facility, the remote or contract sterilization facility (if applicable); the distribution centre, and the customer. Distribution assessment should also include any distribution by the customer. The methods of accomplishing all of this medical device movement are critical design inputs.

c) **Handling**: An assessment of medical device handling should be completed. This assessment includes several factors from the manufacturing, distribution and customer environments. Medical device protection requirements are often directly related to how the medical device is handled, whether it is manual handling or machine handling. The means in which the medical device is handled is often determined by the packaging configuration, whether it is a single unit or a palletized unit, and how it arrives at the point of use.

J.5 Manufacturing guidance

J.5.1 Prior to the design of the packaging system for a medical device, there should be a thorough understanding of the manufacturing processes to which the medical device and packaging system will be subjected. The designer should understand all of the processes involved in forming, sealing and labelling the packaging system.

J.5.2 An assessment of manufacturing requirements should at minimum include the following:

a) **Location**: Determine where the medical device will be built and packaged. This should include multiple locations if the medical device, a subassembly or raw materials will be shipped between facilities prior to final packaging. The location should be assessed to determine whether there are any environmental factors, which will affect the decisions to be made for packaging system design. Also, if the same medical device is to be manufactured at multiple locations, any differences between those facilities should be identified.

b) **Equipment**: A thorough assessment of available packaging equipment should be completed in order to design a cost effective packaging system. This assessment will identify opportunities to design packaging system to be compatible with existing machinery. Also, it will identify any gaps that need to be filled through the acquisition of additional packaging equipment.

c) **Validation**: A key component of developing manufacturing processes for sterile barrier systems is sterile barrier system process validation. The time and cost of validation activities for sterile barrier forming, sealing and assembly should be addressed prior to sterile barrier system design.

d) **Training**: The time and cost of training operators to assemble the packaging system or run assembling equipment should be considered for new packaging system designs.

J.6 Sterilization process guidance

The sterilization process for the medical device should be understood prior to designing the packaging system. Knowing the sterilization process will help guide key decisions regarding the materials of construction for the sterile barrier system. Additional information on sterilization process requirements and references can be found in Annex B.

J.7 Marketing guidance

J.7.1 The packaging designer should understand the fundamentals of how the medical device will be marketed. A basic marketing plan will provide insights regarding the customers, markets and the overall medical device plan for the medical device. This information will be used to drive several key decisions regarding packaging system design.

J.7.2 An assessment of the medical device marketing requirements should at a minimum include the following:

a) **Customers**: The marketing plan can give key insights into who will be using the packaging system. Factors related to the customer, and how the packaging system is used will help guide basic decisions regarding packaging system design.

b) **Markets**: The marketing plan will determine what markets the medical device will be submitted to and eventually sold. This can be used to determine country specific requirements concerning materials, labelling and distribution, which could affect the design of the packaging system.

c) **Configuration**: A marketing plan can dictate whether the medical device needs to be packaged in single units, multi-packs or even whether the medical device needs to be part of a kit with other medical devices. Typically, marketing will determine the need for these configurations based on the anticipated volume, the scope of the launch, average selling price in intended markets and the logistics associated with distribution. Though the packaging system designer does not always participate in these decisions, they are key inputs to the design of the packaging system.

J.8 Budget guidance

J.8.1 A factor that is common to all design projects, whether the project is for the design of a packaging system for a terminally sterilized medical device or not, is the budget. Prior to the design of the packaging system for a medical device, there should be a thorough understanding of the budget for the packaging system design. Understanding the budget will help guide critical decisions through all phases of the design of the packaging system.

J.8.2 An assessment of budget requirements should at minimum include the following:

a) **Material**: Determine that the cost of packaging system materials selected is appropriate for the medical device. Additionally, consider the costs of needed setup materials.

b) **Manufacturing**: Determine the costs associated with assembling the packaging system. This includes the cost of tooling, equipment, facility space, overhead, and labour.

c) **Supply chain**: Determine the costs associated with sending the medical device through the distribution system. This includes cost of interplant shipments, shipments to distribution centres and shipments to customers.

J.9 Customer guidance

J.9.1 The packaging system designer needs to understand the basic customer requirements regarding the packaging system for a terminally sterilized medical device. The basic requirements are that the sterile barrier system as part of a packaging system needs to maintain sterile integrity and allow for aseptic presentation at the point of use. Beyond that, assessing customer requirements can be a daunting process. However, it is essential to understand as much about the customer and the environment of the customer as possible in order to design an effective packaging system.

J.9.2 An assessment of customer requirements should at minimum include the following:

a) **Customer**: It is important to understand who will be using the packaging system. For a terminally sterilized medical device this is often an operating room technician, however, it could also be a variety of personnel in a number of circumstances. Understanding as much about the customer as possible will help the design decision-making process.

b) **Customer environment**: Determine the use environment where the sterile barrier system will be opened. For a terminally sterilized medical device this is usually an operating room or hospital environment. This can often be a high stress environment; steps should be taken to ensure that using the packaging system does not add to the stress level in the use environment.

c) **Ease of opening**: The sterile barrier system should be easy to open in order to allow for the medical device to be dispensed aseptically. This is fundamental for sterile medical device packaging. If the sterile barrier system is difficult to open, the likelihood of contamination increases. When a sterile medical device is contaminated, it is useless.

d) **Medical device identification**: Consider any medical device identification requirements specific to the customer needs, or that will help the customer in the use environment. Additional information and references on medical device identification requirements can be found in Annex N.

J.10 Regulatory guidance

It is critical to understand the regulatory path of the markets the medical devices will be distributed in. The requirements for regulatory approval often vary throughout different international regions and can affect the decision making process in the design of the packaging system. Additional information on the regulatory requirements and references can be found in Annex N.

Annex K
(informative)

Risk analysis tools — Guidance for industry and health care facilities

K.1 Applications

There are a multitude of applications for risk analysis that may include:

K.1.1 Use/applications/system: this analysis looks at the packaged medical device from the user's perspective once the medical device is shipped:

a) understand user requirements and hazards;

b) ease of use, i.e. opening/presentation;

c) understand medical device application and hazards;

d) medical device misidentification order of use.

K.1.2 Design: The design analysis process allows for developers to design quality and reliability into the medical device and packaging system knowing the potential failures they are attempting to prevent. List potential failure modes of the design:

a) processing;

b) sterilization;

c) distribution;

d) human interaction;

e) consider unique failure modes;

f) consider specific barrier property failure(s).

K.1.3 Process: The manufacturing process may significantly contribute to potential failures in the field. The process analysis identifies potential failures that should be addressed during the medical device development process:

a) machinery (setting variability);

b) materials (lot-to-lot variability);

c) environment (location variability);

d) personnel (skill set/experience).

K.2 Risk analysis tools

K.2.1 Failure modes and effects analysis (FMEA): This methodology helps to rank possible failures that could require additional attention or more in-depth analysis. FMEA provides a disciplined analysis

of a specific function to identify and rank by severity any known or potential failure modes before they occur. Typical FMEA steps include:

a) identify important functional steps, i.e. process;

b) translate characteristics into potential failure mode format;

c) identify potential effects and causes of associated failure;

d) determine current controls;

e) assign severity, occurrence, and detection ranking;

f) calculate RPN (Risk Priority Number);

g) rank RPNs (Pareto format) and determine recommended action;

h) record action taken and determine the resulting RPN;

i) follow-up.

K.2.2 Fault tree analysis (FTA): FTA is a deductive, "top-down" approach to failure mode analysis. It provides a logical, structured process that can identify a failure and its effects before it actually occurs. Typical FTA steps include:

a) list possible hazards;

b) determine failures, or combination of failures, that will lead to the named hazards;

c) prepare a diagram of a fault tree;

d) use the fault tree to intercept or design out unacceptable consequences.

K.2.3 Hazard analysis and critical control points (HACCP): HACCP is a systematic approach to the identification, evaluation, and control of hazards. Typical HACCP steps include:

a) conduct a hazard analysis;

b) determine the critical control points (CCPs);

c) establish critical limits;

d) establish monitoring procedures;

e) establish corrective actions;

f) establish verification procedures;

g) establish recordkeeping and documentation procedures.

Annex L
(informative)

Considerations for sampling plans — Guidance for health care facilities

ISO 11607-1:2006 and ISO 11607-2:2006 both state in 4.2:

> The sampling plans used for selection and testing of packaging systems shall be applicable to packaging systems being evaluated. Sampling plans shall be based upon statistically valid rational.
>
> NOTE Examples of suitable sampling plans are given in ISO 2859-1 or ISO 186. Additional sampling plans may be specified by countries or regions.

There are ongoing questions in health care facilities about the requirements for a statistically valid sampling plan; wondering what does that mean and how do I prove it? Annex L outlines guidance on how to answer that question for single use or reusable sterile barrier system. If your facility does not have a background in statistics, the Working Group developing this document would suggest that you enlist the aid of a statistician. Additionally, a significant amount of information is available on the internet by searching for "sampling plans" or "sample size". There are even programs available on the web that will calculate your sample size after inputting the required information.

The goal of a sampling plan is to provide confidence that the predetermined acceptance criteria are met not only in the samples, but also in all populations or lots which are produced by the process. One way is to test every member of a population or lot. For instance, if you sterilize a load containing 50 wrapped devices, inspecting all of the wrapped packages is a statistically valid rational. Another way is to sample a smaller number of packages. However, if you decided to just inspect one packaged device it would not provide enough information to ensure the rest of the load is acceptable. In the same way, if the one packaged device that was inspected was unacceptable, would you reprocess the entire load?

Sterility Assurance Level (SAL) is a result of sterilization and is normally intended to imply a certain degree of microbial inactivation imparted by a sterilization process using heat, chemicals, radiation or a combination of these agents. SAL is not intended to apply to other safety aspects as the level of inactivation during a sterilization process, and is not intended to describe the safety level for maintenance of sterility after sterilization. Maintenance of sterility is influenced by the SBS itself, but mainly by the practiced procedures of handling and storage in a health care facility. The health care facility will therefore need to define these procedures and the way of - and level of safety for – verification.

There are several factors that should be considered in determining sample plans with the goal of determining that the entire population or lot of packages meets the predetermined acceptance criteria.

— The number of packages in the population or lot. If your facility has a packaged product and you only produce 1 per month, the only valid sampling plan is to test every package. However, if the facility produces a packaged product and the population or lot is 1000 per month, it could be uneconomical to test them all and establishing a sampling plan reduces the cost since testing is only performed on a subset of the population or lot.

— The way that the lot is produced and defined.

NOTE 1 ISO 2859-1 is primarily used in case of continuing series of lots (see ISO 2859-1, 1.2). Hospitals, however, do not typically produce continuing series of lots of identical packages.

NOTE 2 Hospitals might consider the forming, sealing and sterilizing of similar packaging concepts (i.e. pouches) as continuous production, although different sizes and loads are involved.

Consequently a lot might be considered to be the number of produced packages within a defined time frame (i.e. per day, per person, per pack table etc.)

— The type of data your test method produces. Data can be continuous (a number such as seal strength) or discrete (pass/fail such as visual inspection) and require different statistical methodologies and sampling plans. For example, ANSI/ASQ Z1.9 addresses variable (continuous) data, and ANSI/ASQ Z1.4 addresses discrete (attribute) data.

— The variability (standard deviation) that the test method produces in testing. The higher the variability the more samples that will have to be tested. This is one of the reasons that the Working Group developing this document recommends the use of test methods with established P&B statements, those statements will provide a demonstration of the variability in the test method.

— The level of risk that is acceptable in your facility. There are two types of risks associated with any sampling plan. One risk is accepting a population or lot even though several packages do not actually meet the acceptance criteria. This is referred to as "consumer's risk" or β. The other risk is rejecting a population or lot of packages even though it shouldn't be because of an abnormal defect. This is known as "producer's risk" or α.

— The costs associated with the sampling plan and testing. If the costs are too high, the sample size can be decreased but it is important to realize that this will increase the level of risk.

As indicated above, a factor that increases the sample size needed is variability in the test method; therefore, it is crucial to take steps to minimize that variability. One of the keys to success is to establish explicit, clearly defined acceptance criteria and methodologies.

There needs to be a clear acceptance criteria for every attribute tested. Visual inspection of sterile barrier systems is easy to define. This may simply be that the package is intact.

Seal strength testing of the seals formed at your facility on pouches and reel goods requires the establishment of upper and lower limits. If the seal strength is too low, integrity may not be maintained. If it is too high, opening the package may result in fibre tear or delamination of the materials. Frequently there is a minimum seal strength value established in seal strength acceptance criteria and a hand peel test demonstrating ability of aseptic presentation is used as the upper limit. There are several ways to run seal strength and it is important to decide on a method and stay with that method. The seal strength measurement using the three different methods of positioning the test sample in the testing device can produce very different results. It is also important to establish the locations that will be sampled. The pouch, reel, and sealing equipment supplier may be able to provide information that may assist your facility in establishing limits.

When conducting OQ and PQ, the sampling plan will be different than the routine sampling plan for packages produced at the facility. These steps are designed to establish the capability of the process used to package a device and more data will be required to achieve this. The results of OQ and PQ can be used to establish an estimate of variability. This can be used in the establishment of routine sampling plans.[106]

Annex M
(informative)

Stability testing (ISO 11607-1:2006, 6.4) — Guidance for industry

M.1 A packaging system which has labels or labelling that make claims of product expiry dates should have stability data that demonstrates that the sterile barrier system seals and materials remain stable enough to maintain integrity over the time stated. Seal strengths can be evaluated using tensile (peel) or burst testing. Sterile barrier system materials can be tested for such key attributes as tensile strength, elongation, puncture and tear resistance, barrier properties and others (see 4.3).

M.2 The requirement of ISO 11607-1 is that stability testing shall be performed using real-time aging. Accelerated aging stability data are commonly used until the results from real-time aging is available. When preparing sterile barrier system samples for stability testing, the same number of samples as designated for accelerated aging should be assembled, sterilized and placed into real-time storage. Aged samples are often tested at intervals shorter than the end date indicated on the sterile barrier system labelling, especially when evaluating new materials where limited or no stability data are available.

M.3 ASTM F1980 provides valuable guidance regarding the development of accelerated aging conditions and discusses the importance of selecting aging temperatures that do not exceed the limitations of the sterile barrier system materials. The standard also discusses the separation of the stability study from packaging system performance testing and further points out the fact that it is not necessary to include medical devices in the sterile barrier system stability samples.

M.4 It is understood that pass/fail criteria data can be obtained from accelerated or real time aging. However, accelerated aging temperatures can create an extreme challenge condition to a material and sterile barrier system that may not be found in real world situations, and thereby create false interpretations of the failure mode. Diligence should be used when determining aging temperatures and acceptance criteria. The user can look for trends that indicate that the materials and seals may be changing in a manner that may affect sterile barrier integrity over time. For example, if the trending is significantly negative, the materials may not be suitable for use. The decision to use the candidate materials and sterile barrier system is based on risk level and the criticality of the attribute to the function of the sterile barrier system and the packaging system during handling, distribution and storage and should be documented in the rationale.

M.5 ISO 11607-1 is quite clear regarding the separation of sterile barrier system stability testing from packaging system performance testing and regards them as separate entities. The standard does not preclude the user from combining these tests but doing so imposes unrealistic stresses on the test samples which can result in failures not experienced during normal storage and distribution. There are several reasons why stability testing and packaging system performance testing should not be combined:

a) ISO 11607-1 regards the loss of sterility as event related rather than time related. Such events occur during the handling, storage and distribution of medical device products and are usually catastrophic in nature.

b) Combining both stability and design performance tests could expose the packaging systems to excessive conditions and stresses not seen in normal distribution environments. For example, accelerated aging quite often exposes sterile barrier system samples to continuously elevated temperatures (≥55 °C) for extended periods of time (several months). Protective packaging can be significantly weakened to an extent that could cause failures during performance testing.

c) If a failure occurs during performance testing of aged packaging systems or sterile barrier systems, it is difficult if not impossible to determine the root cause. Was it a failure due to aging (time) or was it a package design performance issue (event)?

Annex N
(informative)

Use of the Internet — Guidance for industry and health care facilities

The Internet has become a useful tool for medical device and related professionals for finding information. Since web addresses are constantly changing, the best tool is to use a search engine. Usually searching for "medical device regulations in (country)" results in plenty of links. Often there are links to translations of the regulations in other languages.

Annex O
(informative)

Test method validation — Guidance for industry

O.1 ISO 11607-1:2006 and ISO 11607-2:2006, Clause 4 state that all test methods must be validated. Test method validation has been interpreted in many ways. Annex Q will provide guidance to validate a test method.

O.2 Test methods that have been subjected to formal inter-laboratory studies (ILS, also known as round-robin studies) are beneficial because the ILS will always provide the user with a statement indicating the repeatability and reproducibility of the test method. Repeatability is a measure of the variation within a laboratory and can be due to several variables including operators, test apparatus, variation over time etc. Reproducibility is a measure of the variation between laboratories. In many instances, an ILS will also provide the user with an indication of the sensitivity of the test method, which is a measure of the limits of the test method. An ILS can also provide an indication of the robustness of the test method. All of these indicate that the test method *can* be validated however it is important to note that it is *not* validated in a new laboratory without additional steps.

O.3 When adopting an ILS test method into the laboratory, steps need to be taken to demonstrate that the test method performs in a comparable way to the performance in the ILS. Typically, an ILS test report will use samples of different materials that produce measurements over the range of the test method results. While these samples are typically not identified in the ILS, frequently, those in the trade can determine the source of these samples. It is therefore possible to perform a limited internal study to determine the repeatability within your laboratory. This study might take into consideration factors such as multiple operators or apparatus etc. The results of this validation study need to be documented (ISO 11607-1:2006, 4.4.1). An appropriate acceptance criterion is that the internal repeatability should be equal to or better than the ILS reproducibility (ISO 11607-1:2006, 4.4.2).

O.4 It is not necessary to demonstrate that the test method sensitivity is the same as determined in the ILS. This can be accomplished by documenting in the rationale that the sensitivity limits in your laboratory are a subset within the range of the ILS. For example, if the laboratory only performs hydrostatic head testing on materials within the range of 20 to 50, there is no need to validate the test method for values below 15 and above 60. However, this limitation needs to be noted and if a sample is tested above or below the specified limits the test method would have to be validated within this new range.

O.5 There are many acceptable test methods that have not been subjected to an ILS. These may be from the scientific literature, national standard methods, or developed by the laboratory. The most important issues with these tests are: demonstrating that the test is actually measuring the property intended to be measured; determining the sensitivity and accuracy are sufficient to measure the intended property over the specified range of values: determining the repeatability of the test method. These can be determined by application of the scientific process through carefully designed experiments. Again, the results of this experimentation needs to be documented (ISO 11607-1:2006, 4.4.1).

O.6 In summary, validation of test methods in a laboratory requires the demonstration through experimentation that the test method performs as intended and is shown to be repeatable within that laboratory. Without this validation step, the user cannot determine if the data they gather is appropriate or not.

Annex P
(informative)

Use of contract packagers — Guidance for industry and health care facilities

P.1 General

Contract packagers, sometimes referred to as contract manufacturers or external manufacturers, are suppliers of packaged medical devices ready for sterilization or already sterilized. These manufacturers provide a service to the medical device company in cases where the additional expertise, capability, or capacity to package the medical device is needed, or the company may wish to outsource the packaging for economic reasons.

P.2 Functions performed by contract packagers

The contractor may perform one, or any combination, of the following functions:

a) full final packaging system design, development, and validation;

b) package the provided medical device in its sterile barrier system, additional protective packaging, and/or the entire packaging system;

c) material and component procurement to the contractor's or medical device manufacturer's specification;

d) terminally sterilize or subcontract the sterilization of the packaged medical device.

P.3 Responsibilities

Contractors should comply with the same current good manufacturing practices (cGMPs) and regulatory and quality systems requirements to include ISO 11607-1 and ISO 11607-2 as any medical device manufacturer.

Medical device manufacturers, as the customer, should ensure that the contract supplier meets the same conditions as if they were producing the packaged medical device themselves. This includes design control, quality systems, packaging systems, and process validation, and sterilization validation where appropriate. Ultimate responsibility and liability lies with the medical device manufacturer holding regulatory approval.

Annex Q
(informative)

Guidance on establishing process parameters — Guidance for industry

Q.1 General

Annex Q is applicable to industrial manufacturers of both preformed sterile barrier systems and sterile barrier systems.

Critical process parameters, including ranges and tolerances, are necessary to ensure that a product satisfies the defined requirements under all the anticipated conditions of manufacturing. These parameters should be established using statistically valid techniques. Examples of tools that can be used include:

— FMEA (Failure modes and effects analysis);

— DOE (Design of experiment);

— heat seal curve analysis;

— visual attributes.

Q.2 EXAMPLE Forming and lidding a tray

Q.2.1 FMEA (Failure modes and effects analysis)

Failure modes and effects analysis is a systematic method for studying failure. It can be used for both product development and process control. It determines the severity and likelihood of potential failure modes which are normally identified on the bases of past experience with similar products or processes. In this case (product development), it is used to establish the process parameters for equipment at each stage of the fabricating, loading, sealing and packing process whereas in Annex K it is one of the risk analysis tools.

The procedure involves the following stages:

— identifying which defects will cause the product to be rejected (failure mode);

— establishing the cause of failure and how likely it is to occur;

— establishing the consequences of each failure mode;

— grading the severity, frequency and ease of detection of each failure mode;

— identifying the controls currently in place and the probability of detecting failure;

— calculating the Risk Priority Number (RPN) for each failure mode using the equitation Q.1:

RPN = Severity Number x Frequency Number x Ease of Detection Number (Q.1)

— recommending actions to reduce the RPN.

An example for failure modes and effects analysis is given in Table Q.1.

Table Q.1 — FMEA Example

Process	Function	Failure Mode	Effect of Failure	Severity	Cause	Frequency	Current Controls	Ease of Detection	RPN	Actions
Forming	Forming trays	Poor forming. Pinholes	Damage to product	10	Incorrect Machine settings	2	Leak tester	2	40	
Sealing	Heat sealing materials	Open seal	Product integrity	10	Incorrect machine settings	1	Leak tester	3	30	
Sealing	Heat sealing materials	Channel in seal	Product integrity	10	Creases in material	4	Visual	3	120	
Sealing	Heat sealing materials	Channel in seal	Product integrity	10	Incorrect Machine settings	4	Leak tester	5	200	
Sealing	Heat sealing materials	Spotty seals	Product integrity	10	Incorrect Machine settings	3	Visual	1	30	
Bar code scanner	Registration of packs	Unable to read bar code	Machine won't run	1	Failure of Software or Poor Print quality	1	Machine won't run	1	1	

Q.2.2 Design of Experiment (DOE)

Design of experiment is used to establish the optimum process parameter window. In other words, to identify the process conditions that will ensure that good quality product is produced consistently. The more detailed the information obtained at this stage, the easier it is to maintain control of the process.

Forming of a tray and subsequent heat sealing of the lid require consideration of temperature, pressure and dwell time. In both cases it is necessary to identify the range of process conditions that will have the minimum effect on the resulting sterile barrier system.

For example, the process conditions necessary to ensure an acceptable seal strength when heat sealing the lid should be:

— sufficiently removed from those which will result in failure of the seal;

— produce a good quality seal;

— show minimum variation in seal strength.

Various levels of experiments can be conducted – from simple, linear screening studies to determine the relative effect of various parameters on resulting seal – to highly complex, fractional factorial quadratic studies. Often a simple, linear experiment is conducted to confirm the significance of parameters – followed by a more complex study – with centre points – to ensure a good mathematical model of the process is generated which fits the data. It is often found that temperature is the most important variable, followed by time and then finally, pressure is rarely significant over a large range.

The tools used to establish the optimum conditions for heat seals are:

— heat seal curve analysis;

— visual assessment of the seal areas;

— a combination of the heat seal curve analysis and visual assessment;

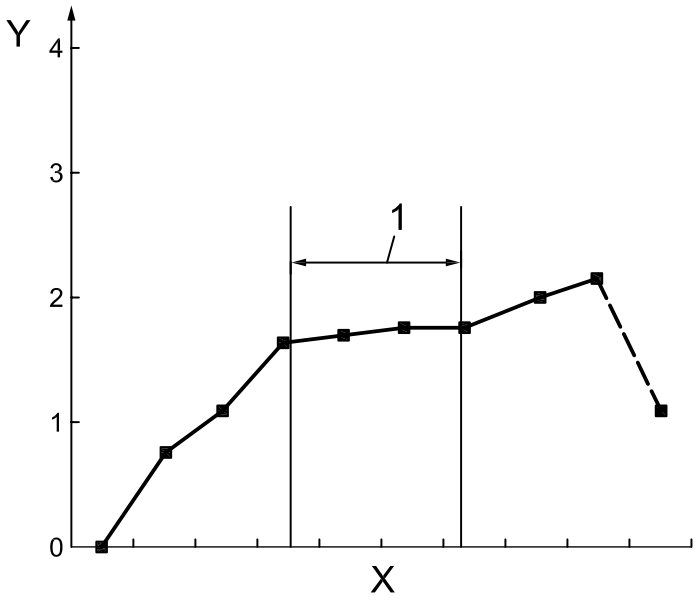
— determination of process capability

— seal integrity;

— seal quality (visual assessment).

Q.2.3 Heat seal curve analysis (Process range assessment)

This procedure involves evaluating how a matrix of temperature, pressure and dwell time will impact on the seal strength. Curves constructed to determine the consequences of the various parameters normally show that varying pressure and dwell time have a less effect on seal strength so these are kept constant while the temperature is varied. The process limits are then established over the range where the seal strength meets specification. Sterile barrier systems with seals just beyond these limits should still maintain pack integrity but the seals are likely to show slight visual defects (see Figure Q.1).



Key

X temperature

Y seal strength

1 proposed process limits

Figure Q.1 — Heat seal curve for optimum process parameters

Q.2.4 Visual scoring method for heat seals

Seals are graded for visual defects at both ends of the process range. Higher values indicate better quality. For example:

a) Lower end of sealing range

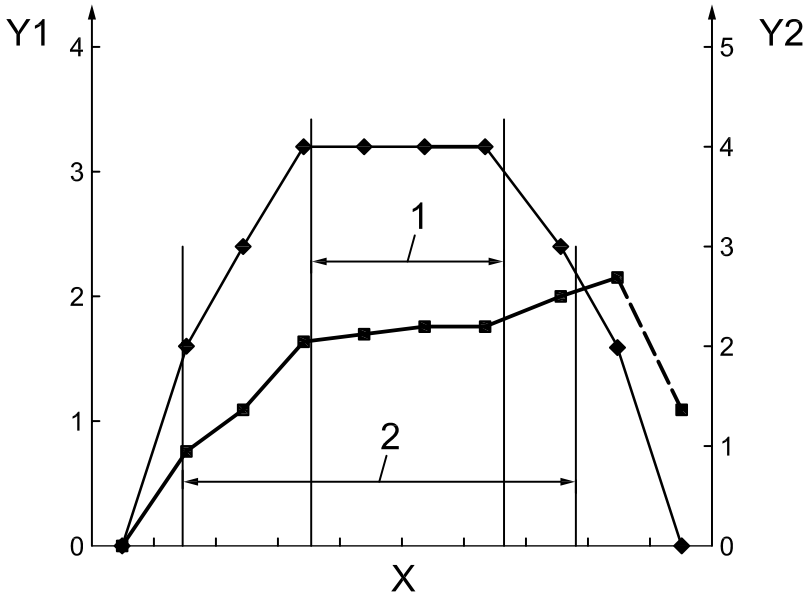
Grade	Defect
0	Open seals
1	Seal width less than 50 % of the specified value
2	> 25 % spotty seals
3	≤ 25 % spotty seals
4	Seal width slightly less than the specified value Slightly spotty seals
5	Good quality seals

b) Upper end of sealing range

Grade	Defect
0	Holes in polymers
1	Welded seals/melted polymer Severe curl of the flange of the tray Severe transparentization of polymer based nonwoven lids Severe fibre tearing of paper based lids
2	Moderate curl of the flange of the tray Moderate transparentization of polymer based nonwoven lids Significant fibre tear of paper based lids
3	Mottled seals Moderate fibre tearing of paper based lids
4	Slight curl of the flange of the tray Slight transparentization of polymer based nonwoven lids Occasional mottling Slight fibre tearing of paper based lids
5	Good quality seals

Q.2.5 Combining heat seal curve analysis and visual scoring

The results obtained from the analysis of heat seals can be combined with those obtained using the visual scoring method to produce the Figure Q.2.



Key

X temperature
Y1 seal strength
Y2 visual seal quality
1 proposed process limits
2 proposed specification limits

Figure Q.2 — Seal strength and visual seal quality vs. temperature

Q.2.6 Determination of process capability

The purpose of process validation is to demonstrate that the process is under statistical control and consistently producing product within specification. A best practice is to calculate the process capability Cp/Cpk:

If the process is centred, Formula (Q.2):

$$Cp = \frac{USL - LSL}{6\sigma} \tag{Q.2}$$

where

σ sample standard deviation

USL upper specification limit

LSL lower specification limit

If the process is not cantered, Formula (Q.3):

$$\text{Cpk} = \frac{\text{CSL} - X}{3\sigma} \quad \text{(Q.3)}$$

where

CSL closest specification limit

X process average

Guidelines for Cp/Cpk values are given in Table Q.2.

Table Q.2 — CpK value example

	Cpk	Sigma level (σ)	Process yield	Process defects (PPM)
	0,33	1	68,27 %	317311
	0,67	2	95,45 %	45500
	1,00	3	99,73 %	2700
Target	1,33	4	99,99 %	63
Better	1,67	5	99,9999 %	1
Best	2,00	6	99,9999998 %	0,002

To maximize the Cp/CpK it is useful to achieve a minimum of variability, while keeping the specification window as large as reasonable or possible. The specifications should be validated, in other words, within those limits, the integrity of seals should be guaranteed and the package should withstand the sterilization process and resist the hazards of transport, distribution and storage. For these reasons, it is essential to have a good understanding of the process window for the specific material and sealing equipment combination.

If studies are undertaken and the minimum desired Cpk is not obtained, then an analysis of the process should be conducted, keeping in mind that excessive variation always has a source. Material thickness variation, deviations in the temperature and flatness across the sealing surfaces and temperature controllers with excessive fluctuations can all be examined in order to pinpoint the sources which contribute the most to the excessive variation.

Multiple lots of materials — sufficient to provide a representative look at expected variation should be used in order to check the robustness of the process development – prior to entering in to more formal validation activities.

Annex R
(informative)

Investigation failure — Guidance for industry and health care facilities

R.1 Evaluating failure

R.1.1 If, during the validation process, defects are found in candidate packaging materials or systems, there are several approaches that can be taken to resolve the issue. Most of these involve analysis of the defects to determine the source or failure mode. Tools available to assist with this analysis include:

a) microscopic analysis;

b) polymeric analysis;

c) manual manipulation.

R.1.2 If these approaches prove unfruitful, several problem-solving approaches may be applied to determine the root cause and finally, a corrective action plan should be put in place to ensure the solution actually solves the problem.

R.2 Determining the source of the defect

R.2.1 In terms of analysing the defect, the first place to start is generally determining what caused the problem. Defects can be created by five major sources:

— medical device;

— process;

— packaging system;

— people;

— environment.

R.2.2 Medical device induced defects can be related to the weight or sharpness of the medical device. The defective sterile barrier system and medical device should be reassembled, taking care to align in the same manner, so that any correlations to shape or rubbing pattern may be determined. It is important to reassemble the complete packaging system configuration, including the sterile barrier system and protective packaging. Often, an individual sterile barrier system or packaging system will not clearly show the source of the defect, but when the stack of packaged medical devices is reassembled, it allows visual identification of the source.

R.2.3 Process induced defects are related to the equipment — including inadequate equipment maintenance. Excessive variation of key process parameters should have been addressed at the IQ stage of validation, but should not be overlooked as possible root causes. Sharp burrs on packaging equipment, conveyors with brads and staples protruding, worn gaskets and inadequate machine repairs should all be investigated as possible root causes. Equipment induced defects often manifest themselves in a repetitive manner that suggests a specific portion of the process. It is important to track the sterile barrier system or packaging system with a defect back to a particular location in the packaging process. Which cavity

produced the medical device, which lane was it packed on, and what side of the machine, are all important considerations. By physically bringing the defective sterile barrier system or packaging system back to the packaging process and retracing the production steps, important correlations may be discovered.

R.2.4 Defects that are not traceable to medical device or process may be related to the packaging system. Examination should be made of the materials of construction to determine if the material selected met the requirements for puncture, flex crack, abrasion or any of the other attributes see Annex A. Defects in sterile barrier or packaging system fabrication should be investigated to determine if the defect occurred before incoming raw material inspection, during handling within the production facility or after shipment from the plant. The packaging system design should be evaluated. This would include the significant design criteria such as dimensions and seal configuration as well as the protective packaging arrangement.

R.2.5 One should consider punctures created in loading, cuts or abrasions caused during handling, and incorrect loading configurations as possible areas for further exploration. Human causes of defects are often very difficult to resolve, as information is sometime difficult to obtain. It is important to speak with the individuals involved in the generation of the packaging systems themselves and inquire about what actually took place. It is also important to determine whether standard procedures and protocols were followed.

R.2.6 Environmentally induced failures can come from many different sources. Changes to air flow around equipment that requires temperature control sometimes may result in overheating or under heating of dies and/or materials. For example, the periodic cycling of an overhead air conditioner directed at a heat seal platen may be an elusive offender. In some cases, extreme fluctuations in humidity or temperature environments or prolonged exposure to UV light can contribute to the formation of defects such as ink or label adhesion issues, packaging system embrittlement, or discoloration.

R.3 Chemical vs. mechanical causes

R.3.1 While researching the sterile barrier system or packaging system defect cause, it is important to try to differentiate between chemical and mechanical causes.

R.3.2 Chemical causes should be thought of in 3 categories:

a) chemical changes within a given material (e.g. degradation due to ongoing cross-linking or slip bloom)

b) chemical interaction between packaging materials and medical devices (e.g. leaching of plasticizers or additives from either medical device or sterile barrier system or packaging system damaging the other).

c) chemical interaction between the protective packaging and sterile barrier systems (e.g. yellowing of the sterile barrier system due to transference of BHT antioxidants from corrugated materials or poly liners). Chemical causes are the result of reactions or changes of a molecular nature — such as oxidation or crystallization of packaging materials. Material additives (e.g. heat seal coating components, paper additives, slip, anti-block, processing aid, or contaminants) should be checked to confirm they have not changed or are not interacting with the packaging system or medical device to create the opportunity for a defect.

R.3.3 In contrast, mechanical failures such as flex cracking, punctures, abrasion, and/or cuts/shear defects should be differentiated from chemical failures. Discussions with suppliers are often an important step at this point to determine possible historical failure mechanisms. Often anecdotal memories on the part of experts in the industry may lead to a fruitful path of problem solving.

R.3.4 It is important to reassemble the package system in its entirety, much as a crime scene investigator would do. Important geometries of medical device and packaging system should be returned to their original orientation. Medical device caught in seals, sterile barrier systems impinging on one another, the

weight of a stack of medical device on a bottom medical device are all possible failure modes that can best be determined when the entire case is examined. Often removal of one panel of a corrugated shipper may provide insight into the failure. This may be done in combination with vibration testing or drop testing. High speed video analysis may assist in seeing how the defect develops.

R.4 Other tools

R.4.1 A microscope, whether stereo, polarizing or hot stage is a very important tool in the effort to sort out potential causes. A true stereo microscope that provides for three dimensional viewing can determine if defects originated inside the sterile barrier system or outside of the sterile barrier system — providing a good next step in the search for the culprit. A polarizing microscope reveals otherwise invisible stresses embedded in plastic film. These stresses can be used to determine if a puncture has stretched and pushed the film in a particular direction. This can help to differentiate between flex crack, abrasion and puncture failure modes. Finally a hot stage microscope has the ability to melt plastic film under the microscope. An embedded particulate can be heated and determined to be a gel or a foreign contaminant by seeing at what temperature, if any, the particle melts. Defects smaller than the resolution of optical microscopes (less than 5 microns) can be evaluated using scanning electron microscopy (SEM).

R.4.2 Polymeric testing tools abound and are especially useful in determining if plastics have changed.

a) **DSC:** Differential scanning calorimeters or DSCs can provide data regarding softening points and, in addition to helping to determine what materials are present, can provide melt points and insight into differences in crystallinity.

b) **FTIR:** Infrared spectroscopy can determine what molecular functional groups exist and therefore provide insight into the material composition. Surface A.T.R. scans can help to determine if slip bloom or other contaminants that can affect seal strength are present.

c) **GC:** Gas Chromatography can provide information regarding residual solvents, monomers and plasticizers.

d) There are many other physical test methods that may be helpful in a particular circumstance including mass measurement, wear and abrasion tests, density, and dimensional, fatigue and flex cracking, strength and stiffness properties, adhesion and permeability. More advanced laboratory tests that may be of help include high performance liquid chromatography (HPLC), gel permeation chromatography (GPC), atomic adsorption spectroscopy (AAS), atomic emission spectroscopy (AES), mass spectroscopy (MS), auger microprobe analysis, electron stimulation for chemical analysis (ESCA), and transmission electron microscopy (TEM). Raw materials suppliers can be of assistance in selecting the appropriate test methods.

R.4.3 One last "test method" that has proven to be helpful is the attempt to recreate the defect through gross manual manipulation. This class of tests seeks to apply excessive force in an attempt to recreate the defect mode. Often insights into the strength of materials, packaging system designs, and interactions can only be obtained by first hand viewing of forces and package reactions. Gross manipulation tests may give insight into directions to be explored.

R.5 Problem solving approach

If laboratory test methods do not reveal the source of the problem further investigation using process flow diagrams, production line audits, design of experiments, fishbone diagrams, as well as a listing of all possible variables may be helpful. Returning to the FMEA document (see Annex K) to review possible sources of error is also a good approach. Additionally, a careful analysis of what may have changed or what is different from other validated packaging systems may provide a direction for the next step of problem solving. The steps of accurately and precisely describing the problem, gathering existing data, and identifying and testing possible root causes followed by a determination and verification of the solution, are all critical. In summary, a confirmation study, which recreates the problem, implements the corrective action, and then tests for the elimination of the problem, is important.

Annex S
(informative)

Packaging manufacturing process and packaging system design feasibility evaluation — Guidance for industry

S.1 Feasibility evaluation for initial and full-scale packaging manufacturing process

Evaluate the feasibility of both the initial and full-scale packaging manufacturing process for the type of packaging system chosen in 4.4.2.1 and 4.4.2.2. Typical considerations are listed below. At this point, use of a contract packager may also be appropriate; for guidance on the use of a contract packager, see Annex P.

S.1.1 Projected volume

Primarily due to costs of equipment, smaller volume items are generally packaged in preformed sterile barrier systems, and very high volume items are often packaged in a form fill seal process. An exception to this may be if form fill seal equipment already exists that has capacity for the item, see Annex Q.

S.1.2 Equipment/staff availability

If packaging line already exists, assess if there is capacity available for projected volume of this item.

S.1.3 Capital guidance

If a packaging line with capacity for the projected volume of this item exists, calculate the estimated costs of training applicable personnel, purchasing any new tooling, and validating this packaging system. If a new line is required, calculate the estimated costs of new equipment and its ancillary requirements (e.g. space, electricity, and compressed air), personnel and their training, and validation of the packaging line and of this particular packaging system.

S.1.4 Total packaging system cost

It may be helpful to define process (4.5.2) first. Add together:

a) costs of components, including any anticipated waste created in sealing process;

b) costs of fabricating/sealing, including initial equipment and running costs;

c) cost of direct labour;

d) costs of quality assurance/engineering and other support staff;

e) costs of any additional labelling or marking;

f) costs of protective packaging required for particular type of sterile barrier system, allocated over units per secondary package or further packaging;

g) sterilization cost per sterile barrier system.

Consider that different packaging system volumes or configurations may result in different utilization rates of sterilization process.

S.2 Packaging system design feasibility evaluation

Evaluate the feasibility of packaging system chosen in 4.4. Typical considerations are listed below:

NOTE Feasibility is not a requirement of ISO 11607-1 or ISO 11607-2. This section is used to assess the feasibility of the packaging system.

S.2.1 Packaging system design feasibility evaluation

S.2.1.1 This is an engineering evaluation in which the entire packaging system (possibly only a prototype at this point) is subjected to physical and climatic stresses and post stress testing analysis. Results of this testing determine if the design is worth pursuing.

S.2.1.2 This post stress testing typically assesses:

a) if the condition of the post stress protective packaging, labels and labelling;

b) whether the sterile barrier system contained the medical device(s) and protected it from being physically damaged;

c) possible physical interactions between sterile barrier system and the contents;

d) if the sterile barrier system maintained its microbial barrier.

S.2.1.3 While this step is frequently not a full-scale validation, useful guidance may be found in Annex I, Generating a final packaging system validation protocol.

S.2.2 Packaging system design feasibility plan

S.2.2.1 Use a documented plan employing validated test methods, specifications, guides, and practices (ISO 11607-1:2006, 6.3.2). See Annex A for further information on test methods.

S.2.2.2 This test plan should include pass-fail criteria.

S.2.2.3 Sterile barrier system tests should be conducted on samples that have been built considering the worst-case elements laid out in 4.6.3 (ISO 11607-1:2006, 6.3.4).

S.2.2.4 Samples should be exposed to physical or dynamic and climatic stresses which simulate those present in the expected distribution handling and storage environments (ISO 11607-1:2006, 6.3.5).

S.2.3 Worst-case feasibility condition

NOTE Further guidance on addressing worst-case may be found in Annex H.

To aid in the validity of the feasibility evaluation, determine worst-case conditions, or what at this point what are believed to represent a worst-case, for a number of factors related to the packaging system. These include but are not limited to:

a) sterile barrier system manufacturing (sealing parameters, etc.);

b) sterilization (parameters, number of cycles, etc.): It may not be necessary for the samples to be sterilized for initial feasibility testing;

c) packaging system configuration: This requires an understanding of how the medical device will be sold, what the unit of sale and the unit of test will be. The same medical device may be sold in many packaging system configurations. As an example, it may be sold as a single medical device in a sterile barrier system with protective packaging in a box with the necessary labels and labelling. It may also be sold as a box of 12, 12 sterile barrier systems with protective packaging in a single

box with the required labels and labelling. It may also be sold as 50 sterile barrier systems with protective packaging in a single box with all the required labels and labelling. There may be pallet size units of sale as well.

d) shipping configuration: This requires an understanding of how the packaging system will be shipped to the customer; if the packaging system is over packed during the customer order filling process;

e) distribution environment: This requires an understanding of how the packaging system will be shipped to the customer.

S.2.4 Pass/fail status of packaging system

S.2.4.1 Upon completion of the sample stressing, it is necessary to determine whether the packaging system passed or failed.

S.2.4.2 The packaging system passes the feasibility testing if it met all the pass/fail criteria set forth in the Packaging System design feasibility plan. This establishes confidence that the design will work, it will function as intended. Begin preparing for packaging system validation, typically performed on a validated manufacturing process as in 4.7.

S.2.4.3 If the packaging system failed to meet all of the criteria set forth in the plan, the failure modes should be determined and investigated. Corrective action(s) for the failures should be put in place. This may include redesigning the packaging system concept and repeating feasibility. Guidance on determining failure mode and appropriate corrective action may be found in Annex R.

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