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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 (see www.iso.org/directives).

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights. Details of any patent rights identified during the development of the document will be in the Introduction and/or on the ISO list of patent declarations received (see www.iso.org/patents).

Any trade name used in this document is information given for the convenience of users and does not constitute an endorsement.

For an explanation of the voluntary nature of standards, the meaning of ISO specific terms and expressions related to conformity assessment, as well as information about ISO's adherence to the World Trade Organization (WTO) principles in the Technical Barriers to Trade (TBT), see www.iso.org/iso/foreword.html.

This document was prepared by Technical Committee ISO/TC 198, *Sterilization of health care products*, in collaboration with the European Committee for Standardization (CEN) Technical Committee CEN/TC 102, *Sterilizers and associated equipment for processing of medical devices*, in accordance with the Agreement on technical cooperation between ISO and CEN (Vienna Agreement).

This second edition cancels and replaces the first edition (ISO/TS 16775:2014), which has been technically revised.

The main changes compared to the previous edition are as follows:

— updates to reflect ISO 11607-1:2019 and ISO 11607-2:2019 editions;

— intent and guidance is provided for each clause of the standard to improve usability of this document.

— new annexes have been added;

— some annexes have been removed.

Any feedback or questions on this document should be directed to the user's national standards body. A complete listing of these bodies can be found at www.iso.org/members.html.

Introduction

Sterile barrier systems are intended to allow for sterilization, provide physical protection, maintain the sterility of their contents until the point of use and ensure aseptic presentation. The sterile barrier system, depending on conditions of handling, distribution or storage, can be combined with additional protective packaging to create a packaging system.

ISO 11607-1 specifies the requirements for materials, sterile barrier systems, and packaging systems, including the validation of the packaging system design while ISO 11607-2 specifies the requirements for packaging process validation. The requirements outlined in these standards are generic and are applicable to healthcare 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 healthcare facility, by a medical device manufacturer or reprocessor.

This document provides guidance on the application of ISO 11607-1 and ISO 11607-2. This latest revision has been completely reorganised following the structure of ISO 11607-1 and ISO 11607-2 and referring to individual or groups of clauses or subclauses while indicating the intent of the requirements followed by relevant guidance. It can be used for the systematic application of ISO 11607-1 and ISO 11607-2 or as a reference when questions come up about specific requirements. Clause 4 covers the general requirements that are identical in ISO 11607-1 and ISO 11607-2, while Clause 5 applies to ISO 11607-1:2019 and Clause 6 to ISO 11607-2:2019. Guidance on the application of risk management over the packaging life cycle has been added in anticipation of the upcoming amendments to ISO 11607 (all parts).

This guidance document is applicable to healthcare facilities and to industry while differences for the two environments are addressed as necessary. Although healthcare facilities are usually not involved in sterile barrier system design tasks, their part in the sterile barrier system and packaging system design process consists of carefully selecting an appropriate sterile barrier system and protective packaging based on the identified risks related to the content, sterilization method, transport, storage and aseptic presentation. Sterile barrier and packaging systems and the related processes must then be properly validated, and sealing, closure and assembly processes must be controlled and monitored. To ensure patient safety, healthcare facilities should develop written procedures to be implemented by adequately trained personnel. Guidance given in the annexes of this document is applicable to healthcare facilities and/or industry, as indicated.

The conditions of use of this guidance can vary widely around the world and can be subject to interpretation by circumstances and regulatory environments.

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

1 Scope

This document 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 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 ISO 11607-2 and illustrates 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 conformity with them.

Guidance is 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 document provides information for both healthcare facilities and the medical devices industry for terminally sterilized medical devices.

This document 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 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 11607-1:2019, *Packaging for terminally sterilized medical devices — Part 1: Requirements for materials, sterile barrier systems and packaging systems*

ISO 11607-2:2019, *Packaging for terminally sterilized medical devices — Part 2: Validation requirements for forming, sealing and assembly processes*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11607-1:2019 and ISO 11607-2:2019 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— ISO Online browsing platform: available at https://www.iso.org/obp

— IEC Electropedia: available at http://www.electropedia.org/

3.1
process
set of interrelated or interacting activities that use inputs to deliver an intended result

Note 1 to entry: Whether the "intended result" of a process is called output, product or service depends on the context of the reference.

Note 2 to entry: Inputs to a process are generally the outputs of other processes and outputs of a process are generally the inputs to other processes.

Note 3 to entry: Two or more interrelated and interacting processes in series can also be referred to as a process.

[SOURCE: ISO 9000:2015, 3.4.1, modified — Notes to entry 4, 5 and 6 are deleted.]

3.2
risk
combination of the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO/IEC Guide 63: 2019, 3.10, modified — Note 1 to entry deleted.]

3.3
risk control
process (3.1) in which decisions are made and measures implemented by which *risks* (3.2) are reduced to, or maintained within, specified levels

[SOURCE: ISO/IEC Guide 63: 2019, 3.12]

3.4
risk estimation
process (3.1) used to assign values to the probability of occurrence of harm and the severity of that harm

[SOURCE: ISO/IEC Guide 63: 2019, 3.13]

3.5
risk evaluation
process (3.1) of comparing the estimated *risk* (3.2) against given risk criteria to determine the acceptability of the risk

[SOURCE: ISO/IEC Guide 63: 2019, 3.14]

4 Guidance on Clauses 1-4 of ISO 11607-1:2019 and ISO 11607-2:2019

4.1 Scope (ISO 11607-1:2019, Clause 1 and ISO 11607-2:2019, Clause 1)

4.1.1 Intent

The objective of the scope is to outline the purpose of the standard, its applicability, as well as any exclusions or limitations.

4.1.2 Guidance

ISO 11607-1:2019 and ISO 11607-2:2019 are "group standards" as defined in ISO 16142-1[1] as it applies to a wide range of packaging types that are intended to maintain sterility of terminally sterilized medical devices until the point of use. Group standards are horizontal in nature within the medical device sector and are developed to address the essential principles that are applicable to a wide range of medical devices. Furthermore, as defined by ISO 16142-1, ISO 11607-1:2019 and ISO 11607-2:2019 are also process standards. Process standards provide the requirements for manufacturers to develop, implement, and maintain processes applicable to all stages of the lifecycle of a medical device. These processes are typically established in the frame of a quality management system like ISO 13485[2] or

ISO 9001[3], although these standards are not a normative requirement as outlined in Clause 4 of this document.

The scopes of ISO 11607-1 and ISO 11607-2 apply to healthcare facilities, medical device manufacturers and wherever medical devices are placed in sterile barrier systems (SBSs), packaged and sterilized. It is recognized that the circumstances of the application of these documents will be different when they are used in a healthcare facility compared with when they are used by a medical device manufacturer or reprocessor.

ISO 11607-1:2019 and ISO 11607-2:2019 can also be applied by any suppliers of packaging materials or preformed SBSs. In this case the conformity statements will be limited to what the manufacturer can claim since full conformance is only possible for the completely sealed or closed SBS validated for a specific device or family of devices. Manufacturers of materials and preformed SBSs should clearly indicate what is covered and not covered in their conformity statements.

As a summary, ISO 11607-1:2019 and ISO 11607-2:2019 are horizontal group standards and process standards applicable to several stages of the lifecycle of sterile medical packaging providing the requirements for:

a) packaging materials, preformed SBSs and SBSs (ISO 11607-1:2019, Clause 5);

b) the development process of the SBSs and the packaging system including:

- the required forming, sealing and assembly processes;
- the design validations;
- the process validations;
- revalidations, periodic, if applicable, and in case of changes;
- change controls;
- the controls during routine operations.

It addresses materials, packaging, and also combination of packaging and device. It covers also sterile fluid path packaging where the SBS functionality is integrated with the construction of the device. ISO 11607-2 is applicable wherever a seal or closure is formed and was never intended to cover manufacturing of materials like sheets of sterilization wrap or rigid trays that are manufactured outside of a form-fill-seal process.

4.2 Normative references (ISO 11607-1:2019, Clause 2 and ISO 11607-2:2019, Clause 2)

4.2.1 Intent

Normative references list standards which are required to understand and to apply the standard.

This clause provides the normative references to other standards that apply as well to conform with the requirements of ISO 11607-1:2019 and ISO 11607-2:2019.

4.2.2 Guidance

Normative references are referred to in the text of a standard in such a way, that some or all of the cited content constitutes requirements for the document. In order to be able to apply the standard, all normatively cited references should be available to the user.

4.3 Terms and definitions (ISO 11607-1:2019, Clause 3 and ISO 11607-2:2019, Clause 3)

4.3.1 Intent

Many terms used in a standard document can, depending on the context in which they are used, have a slightly different meaning. This clause refers to the definitions of key terms in order to clarify their intent and meaning for the purpose of this document.

4.3.2 Guidance

The definitions of ISO 11607-1:2019 and ISO 11607-2:2019 apply and it is recommended to review those along with this document. Definitions in the current editions of these documents align with the definitions in ISO 11139:2018[4].

4.4 Quality and risk management (ISO 11607-1:2019, 4.1, 4.2 and ISO 11607-2:2019, 4.1, 4.2)

4.4.1 Intent

This subclause introduces the need to have formal systems for quality and risk management to support appropriate execution and documentation of the activities described to conform with ISO 11607-1:2019 and ISO 11607-2:2019.

4.4.2 Guidance

4.4.2.1 Guidance on quality system requirements (4.1)

A quality management system is a formalized system that documents processes, procedures, and responsibilities for achieving quality policies and objectives.

Such a formal quality management system helps to coordinate and direct activities to meet customer and regulatory requirements and improve the effectiveness and efficiency on a continuous basis.

Examples of standards describing such quality management systems include but are not limited to ISO 9001[3], ISO 13485[2], US FDA Quality System regulation[5,6] and ANSI/AAMI ST90[7]. Implementing a third-party audited quality management system is a good practice, but not a requirement of ISO 11607 (all parts).

ISO 11607-1:2019 and ISO 11607-2:2019 emphasise the need to formalize quality system elements to have appropriate control of records, design and development, product realization, measurements, calibration, data analysis and decisions taken to improve outcomes or to correct non-conformities. The quality system should also consider training of personnel, change management and revalidations as well as supplier controls.

4.4.2.2 Guidance on risk management requirements (4.2)

Risks to the user and patient, defined as the combination of the probability of occurrence of harm and the severity of that harm, are by nature inherent to medical devices and related activities and need to be minimized.

Risk management requirements are applicable to all stages of the life cycle of a terminally sterilized medical device, its accessories, and packaging related activities. ISO 11607-1:2019 and ISO 11607-2:2019 cover specifically the packaging life cycle phases of packaging design and development, validation and production.

An ongoing risk management process should be established, implemented, documented and maintained to minimize the risk for the user and the patient. This process should include:

1) identification of hazards and hazardous situations associated with the packaging system,

2) risk estimation and risk evaluation against defined criteria for risk acceptability,

3) risk control,

4) monitoring the effectiveness of the risk control measures.

NOTE 1 Local regulatory requirements can provide mandatory criteria for risk acceptability or these criteria can be based on the generally accepted state of the art.

NOTE 2 PFMEA (Process Failure Mode and Effect Analysis) is an example of a risk analysis tool that is used widely in the industry.

This process should apply throughout the phases of design and development, validation and production of the packaging system. The following life cycle phases should be included:

a) Design and development phase

- Packaging system design (see ISO 11607-1:2019, Clause 6)
- Sealing and assembly process development (see ISO 11607-2:2019, 5.1)

b) Validation phase

- Performance and stability testing (see ISO 11607-1:2019, Clause 8)
- Usability evaluation (see ISO 11607-1:2019, 7)
- Process validation (see ISO 11607-2:2019, 5.2, 5.3, 5.4 and 5.5)

c) Production phase

- Process control and monitoring (see ISO 11607-2: 2019, 5.6)
- Assembly (see ISO 11607-2: 2019, Clause 6)
- Use of reusable SBSs (see ISO 11607-2: 2019, Clause 7)
- Process changes and revalidation (see ISO 11607-2: 2019, 5.7)
- Packaging system changes (see ISO 11607-1: 2019, Clause 9)

NOTE 3 ISO 14971[8] provides requirements for application of risk management to medical devices.

A risk management plan should be documented in accordance with the risk management process for each packaging system including as minimum

- scope of the planned risk management activities
- criteria for risk acceptability,
- activities for verification of the implementation and effectiveness of risk control measures.

Risk management plans for similar packaging systems can be combined, in such case the rationale for these similarities should be documented. Risk management plans and related documentation for packaging systems can be combined with those for the medical device.

Packaging related risk management is understood as a continuous iterative process throughout the phases of design and development, validation and production of the product, requiring regular system evaluation and updating. Risk management and risk-based decision making are elements of state-of-the-art quality management.

For further guidance on risk management and risk analysis tools during design and development, users should refer to the following annexes of this document:

— Annex A Design and development for packaging systems – guidance for industry

— Annex B Guidance on the application of the ISO 11607 series in healthcare facilities

— Annex C Risk analysis tools – Guidance for industry and healthcare facilities

4.5 Sampling (ISO 11607-1:2019, 4.3 and ISO 11607-2:2019, 4.3)

4.5.1 Intent

The purpose of this subclause is to make sure that the science of statistics is the basis of sampling plans so that results have acceptable confidence and are sufficiently reliable.

4.5.2 Guidance

Sampling plans should be risk based (considering the safety of patient and healthcare user) and suitable for the intended use, in other words depending on the device or the process (healthcare users should see also Annex D of this document).

The key elements of sampling plans reflecting the risk are the following:

a. **Quality level**

It is important to define what quality level is required and should be proven. This can be expressed in an AQL (acceptance quality limit)[9,10], a percentage of conforming products, a C_{PK} value (minimum process capability index)[11] and many other performance metrics.

b. **Confidence level**

Unless a 100 % inspection is performed, there is always an uncertainty in the outcome of test results based on sampling. Without having an 100 % inspection there are always situations where a good batch will be rejected, or a bad batch will be accepted based on the coincidence of the samples taken. The level of certainty is expressed in the confidence level.

NOTE 1 A 100 % inspection without uncertainty assumes that the inspection is based on a fail-safe non-destructive test method. A 100 % inspection does not ensure that 100 % of errors will be caught.

Other factors that influence the choice for a sampling system and related sample size:

c. **Type of test data / test data format**

Depending on the product characteristic measured and the chosen test method, the test will generate either discrete or continuous data. These data types are also sometimes referred to as attribute or variable data.

Discrete data can only take particular values. The number of those values can be infinite, but each is distinct and there is no grey area in between. Discrete data can be numeric, for example numbers of particles, but it can also be categorical, for example red or blue, or good or bad, or pass or fail.

Continuous data are not restricted to defined separate values but can take any value over a continuous range. Continuous data are numeric. Examples are seal strength, seal width, etc.

Each data type requires different suitable sampling plans. Because continuous data contains much more information than discrete data, the required sample size for continuous data is smaller than for discrete data if the same quality level and reliability level are required. To reduce the required sample size for pass/fail data it can be possible to use a grading scale to produce data with greater resolution (e.g. scoring of visual inspection of seals and ranking the results with a numeric value).

d. **Available process / product performance information**

Information available from engineering studies, similar processes, similar products or other sources can provide an indication for the process capability or product variability to be validated. This initial estimation can be used for sample size calculations.

NOTE 2 For example, if a process capability with a C_{PK} of 3 is expected, the sample size can be lower than for a process with an expected C_{PK} of 1,33.

e. **Population composition and available samples**

It is important to understand the difference between situations where the number of samples is taken from a larger batch and situations where the required number of pieces are built or manufactured for evaluation or validation purposes. The latter case could be for devices that are only built in small quantities. In both cases it is essential that samples represent the final process or the process settings that are being evaluated.

f. **Packaging configuration**

The packaging configuration (i.e. unit packages, number of SBSs and the protective packaging, shipper box, etc.) needs to be considered depending on the type of test and purpose of the test. For example, distribution simulation for performance testing (see 5.26 of this document) needs to include the entire packaging system while sealing process validation (see 6.2 through 6.9 of this document) may focus only on the SBS.

4.6 Test methods (ISO 11607-1:2019, 4.4 and ISO 11607-2:2019, 4.4)

4.6.1 Intent

The purpose of this subclause is to provide the necessary requirements for test methods to demonstrate conformity so that they produce meaningful and reliable data and that appropriate decisions can be taken based on the data generated.

4.6.2 Guidance

Test methods exist to provide measures of SBSs 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 Annex B of ISO 11607-1:2019. Not all test methods are appropriate all of the time; some test methods are most appropriate for research and development and others for conformity monitoring. The choice of which test method to employ is driven by the requirements of and applicability to the product (device and package) through its life cycle and should be chosen such that the parameters probed are closely related to medical device SBS and/or packaging system attributes.

NOTE 1 For a guide to available tests, see Annex B of ISO 11607-1:2019.

When evaluating the choice of materials for preformed SBSs or SBSs and for all validation activities, ISO 11607-1:2019 4.4.1 requires the rationale for the selection of an appropriate test to be established and recorded. It is recommended to document this in a formal test plan, which will then also include the respective acceptance criteria for the selected methods. Annex B of ISO 11607-1:2019 includes a selection of test methods, but it is perfectly acceptable to include other test methods, if conformity with ISO 11607-1:2019, 4.4, is demonstrated. For more information on generating a final packaging system validation protocol for healthcare facilities, see Annex B of this document.

A critical component of the packaging validation is to define what constitutes a positive outcome for the validation. The acceptance criteria (ISO 11607-1:2019 4.4.2) 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 can allow for accepting specified damage to a medical device or its packaging system. The form and content of acceptance criteria can vary widely, in accordance with the particular situation. Methods can 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.

NOTE 2 When providing test results to users of materials and preformed SBS in a healthcare facility, it can be helpful to fully explain rationale for acceptance criteria thresholds.

Subclause 4.4.3 of ISO 11607-1:2019 and ISO 11607-2:2019 requires that all test methods used to show conformity with this standard are validated. Test method validation has been interpreted in many ways. Validation confirms, through objective evidence, that requirements for a specific intended use or application have been fulfilled.

NOTE 3 For more information on validation of test methods, see ASTM F3263 Standard Guide for Packaging Test Method Validation[12] and the SBA guidance for test method validation[13].

Test methods that have been subjected to formal/systematic inter-laboratory studies (ILS, also known as round-robin studies) are beneficial because the ILS will provide the user with a statement which in turn provides some sense of the repeatability, reproducibility and in some cases the sensitivity 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.

Sensitivity of the test method is a measure of the limits of the test method.

The precision and bias statement contained in an ASTM standard indicates 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. 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 11607-1:2019, 4.4.3). An appropriate acceptance criterion is that the internal repeatability should be equal to or better than the ILS reproducibility (ISO 11607-1:2019, 4.4.2).

It is not necessary to demonstrate that an integrity 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 units, there is no need to validate the test method for values below 15 and above 60 units. 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.

Integrity test methods are key methods to be included into every validation protocol and they need to be validated considering the expected sensitivity, i.e. the smallest hole or leak rate that can be detected by the method or often referred to also as the precision of the test method. This is typically conducted by producing packages with a seal channel using a wire of a known size corresponding to the targeted sensitivity. If the method is capable to detect the simulated channel, then it is considered validated for this established sensitivity. A rationale needs to be established for the selection of a given sensitivity.

NOTE 4 ASTM test methods include a precision and bias section providing information on sensitivity of integrity test methods

There are many acceptable test methods that have not been subjected to an ILS. These can 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 and 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 need to be documented (ISO 11607-1:2019, 4.4.3).

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.

4.7 Documentation (ISO 11607-1:2019, 4.5 and ISO 11607-2:2019, 4.5)

4.7.1 Intent

This subclause defines the documentation requirements of all records that demonstrate conformity to ISO 11607-1:2019 and ISO 11607-2:2019.

4.7.2 Guidance

Records demonstrating the conformity to ISO 11607-1:2019 and ISO 11607-2:2019 are required.

ISO 11607-1 requires a specified retention period for all records which are used to demonstrate conformity. The retention period should be defined based on all applicable requirements such as customer and regulatory requirements, expiry date, traceability, period of time expected to be in the marketplace for example.

Some records can have different retention periods than others dependant on whether a record is related to a particular batch (e.g. seal strength of preformed SBS) or the lifetime of the material/SBS (e.g. training documentation and calibration certificates).

Records and documents to be retained include but are not limited to:

a) performance data (methods used, values, etc.);

b) specifications (drawings, composition, etc.);

c) evidence of test method validations;

d) validation protocols and conclusions.

Also, other data, such as production data and conditions, can be considered.

Modification of materials, SBSs, production methods (sealing equipment) or the intended use require a record of the decision and new documentation about the materials and production methods, or revision of the current documentation (see also ISO 11607-2:2019, 5.7).

Documentation and records can be in any format or type (e.g. hard copy or electronic media). Good recording practices should be followed. Documents and records should be easily identifiable concerning the product/product family in question, so considerations should be given to title, date of issue, author, etc.

When electronic records are used, degradation of storage media and availability of the software should be considered for the specified retention time. The method of storing the records should also be considered to allow access as and if needed (e.g. audits, customer complaints or post-market follow up).

5 Guidance on Clauses 5-11 of ISO 11607-1:2019

5.1 General requirements for materials, preformed sterile barrier systems and sterile barrier systems (ISO 11607-1:2019, 5.1.1 and 5.1.2)

5.1.1 Intent

These subclauses introduce requirements to qualify materials, preformed SBS and SBS.

5.1.2 Guidance

Choosing appropriate packaging materials for a sterilizable medical device requires careful consideration (ISO 11607-1:2019, 5 and 6). Aspects of the SBS to be considered include but are not limited to:

— compatibility with sterilization;

— robustness with respect to processing;

— storage;

— handling, and distribution;

— microbial barrier properties;

— ease of opening for aseptic presentation;

— a number of considerations regarding end use of the medical device.

It is advised 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 packaging materials or medical packaging can be a significant asset in determining suitable options.

Note 1 and 2 of ISO 11607-1:2019, 5.1.1 discusses use of the EN 868 series, however there is no prerequisite to conform with the EN 868 series in order to conform with ISO 11607-1:2019.

Consider the environmental impact of disposal of preformed SBS and SBS (see Annex D in ISO 11607-1:2019) which can include recycling. When selecting materials, consider the objective to enable recycling.

5.2 Conditions for production and handling (ISO 11607-1:2019, 5.1.3 and 5.1.4)

5.2.1 Intent

This subclause provides basic requirements to be put in place in order not to degrade or damage materials and/or preformed SBSs during processing.

5.2.2 Guidance

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 SBSs. Depending on the properties of the material, the equipment should be designed or adapted accordingly.

Manufacturers of materials or preformed SBSs can provide guidance based on the requirements of these subclauses and other known issues regarding the conditions of use. For example forming and

sealing parameters (as temperature, pressure, dwell time), storage conditions (humidity, temperature), etc. under which the material and/or preformed SBS shall be produced and handled.

Materials typically have temperature range limits that have to be considered during processing. For example, medical paper can be compatible with laser printing while nonwoven materials often are not, as the temperature exceeds the limits for these materials.

The pressure range can be important: e.g. for sealing processes, there could be limits regarding the maximum pressure that can be applied to the materials (concerning ISO 11607-1 5.1.4 b), downstream use conditions such as during sterilisation and shipping can also include environmental pressure ranges/changes that can influence SBS and material selections. See also 5.9.2 of this document (in particular the note) regarding compatibility with sterilisation methods and the rate of pressure change that can be applied.

Some materials are hygroscopic and humidity outside manufacturers' recommendations can affect some physical properties and cause issues with material properties during processing, for example sealing, printing or lamination. Recommendations issued by material or SBS manufacturers should be followed.

Some polymer materials are sensitive to exposure to UV light from sunlight or other sources. If UV stabilizers are required, care should be taken to ensure biocompatibility requirements can be met.

Consideration should be given to appropriately control the level of cleanliness and bioburden during storage, processing, and handling operations.

Electrostatic charging of some materials needs to be considered as it can lead to attraction of particles and/or sudden discharges of electrostatic charges via an operator. Electrostatic charges can be controlled by installing electrostatic bars (or other static dissipative technologies) to remove static electricity into strategic locations of a packaging process.

5.3 Source, history and traceability of materials (ISO 11607-1:2019, 5.1.5)

5.3.1 Intent

This section outlines the importance of controlling materials used as input to a process to manufacture SBSs and the need to maintain traceability information for follow up in case of issues.

5.3.2 Guidance

Complete traceability of an SBS and/or packaging system and its components is maintained, primarily as an aid in determining the root cause of any non-conformances. This is a requirement when conformity with 5.1.5 of ISO 11607-1:2019 is claimed or when a quality management system like ISO 9001[3] or ISO 13485[2] is implemented. In some jurisdictions, it can be a regulatory requirement as well.

Knowing the source and controlling materials is essential for producing a reliable preformed SBS and/or SBS. In this context, it is essential to deal with any deviations or changes that can have an impact on the output of the process by implementing corrective actions and/or performing change assessments. (For more information about change control, see 5.29.)

Material verification is a key procedural traceability element to avoid material mix ups, like combining incorrect top web and bottom web materials or using an incorrect polymer material for the manufacturing of a film.

5.4 Properties to be evaluated (ISO 11607-1:2019, 5.1.6)

5.4.1 Intent

The intent of this subclause is to be a general introduction to the key goals to be fulfilled by materials and/or preformed SBSs to secure the appropriate functionalities expected from a terminally sterilized medical device packaging system.

5.4.2 Guidance

The following list of general properties can be considered as a checklist of the items to be addressed in a packaging solution selection and/or validation to ensure the intended requirements are achieved. Documenting the review and assessment of each of these properties is the expected good practice to demonstrate conformity with applicable requirements of ISO 11607-1:2019:

— Microbial barrier evaluation can be addressed through guidance in this document related to 5.1.7 h), 5.2.1, 5.2.2 and 5.2.3 of ISO 11607-1:2019. Some standardized test methods, guides and procedures that may be used to support this evaluation are listed in ISO 11607-1:2019, Annex B (under microbial barrier and microbial barrier surrogate).

— Biocompatibility and toxicological evaluation can be addressed through guidance in this document related to subclauses 5.1.7 a), 5.1.7 g), 5.1.9 b), 5.4 c), 6.1.1 and 6.2.3 l) of ISO 11607-1:2019. Some standardized test methods, guides and procedures that may be used to support this evaluation are listed in ISO 11607-1:2019 Annex B (under biocompatibility).

— Physical and chemical properties evaluation can be addressed through guidance in this document related to subclauses 5.1.7 b), 5.1.7 c), 5.1.7 d), 5.1.7 e), 5.1.7 f), 5.1.9 b), 6.1.3, 6.1.4, 6.2.3 b), 6.2.3 c), 6.2.3 d) and 8.2.1 of ISO 11607-1:2019. Some standardized test methods, guides and procedures that may be used to support this evaluation are listed in ISO 11607-1:2019 Annex B (under basis weight, burst, chloride, cleanliness, conditioning, pH, printing & coating, sulphate, tear resistance, tensile properties, thickness).

— Compatibility with forming, sealing and assembly processes can be demonstrated through guidance in this document related to subclauses 5.1.11 c), 5.1.8 a), 5.1.8 b), 5.1.8 c), 5.1.9 c), 5.1.9 e), 5.1.9 f) and 8.1 of ISO 11607-1:2019. Some standardized test methods, guides and procedures that may be used to support this evaluation are listed in ISO 11607-1:2019 Annex B (under coat weight, peel-open characteristic, seal strength, sterile barrier seal integrity).

— Compatibility with intended sterilization process(es) can be demonstrated through guidance in this document related to subclauses 5.1.7 f), 5.1.7 g), 5.1.9 b), 5.1.10 b), 5.1.12 a), 5.3.1, 5.3.2, 5.3.3, 5.4 b), 6.1.5, 6.2.3 l) and 11 of ISO 11607-1:2019. Some standardized test methods, guides and procedures that may be used to support this evaluation are listed in ISO 11607-1:2019 Annex B (under air permeance, biocompatibility, peel-open characteristic, pH, pore size, seal strength, sterile barrier integrity, wet burst in wet conditions, wet tensile properties).

— Potential use-by-date limitations for pre-sterilization storage and shelf-life limitations for post-sterilization storage can be addressed through guidance in this document related to subclauses 4.5.2, 6.1.6, 6.2.3, 8.3.1, 8.3.2, 8.3.3, 8.3.4, 8.3.5, 8.3.6 and 11 of ISO 11607-1:2019. Some standardized test methods, guides and procedures that may be used to support this evaluation are listed in ISO 11607-1:2019 Annex B (under accelerated ageing, conditioning, performance testing).

5.5 General performance requirements for materials (ISO 11607-1:2019, 5.1.7 and 5.1.8)

5.5.1 Intent

The purpose of these subclauses is to define general performance requirements on materials for preformed SBSs, SBSs and packaging systems.

5.1.7 outlines basic considerations with respect to the material's sterility maintenance and medical device protection functionalities, covering barrier and integrity performances, consistent physical properties, non-detrimental chemical properties, as well as material safety considerations.

5.1.8 covers additional requirements related to the eventual addition of an adhesive layer on one surface of the material.

5.5.2 Guidance

5.5.2.1 Regarding requirements for leachables and odours [ISO 11607-1:2019, 5.1.7 a)]

Packaging material components could migrate into the medical device (i.e. leachables) and interact with its contents, which could lead to adverse effects. In the same way, medical device material components could migrate into the packaging system materials resulting in adverse effects. The risk needs to be assessed (see 4.4.2.2 for guidance on risk management) and appropriate compatibility studies should be performed, as chemical leaching can cause reactions or changes of a molecular nature — such as oxidation or crystallization of materials. Material additives (e.g. heat-seal coating components, film or paper additives, plasticizers, slip agents, anti-blocking agents, processing aids, polymer by-products) should be checked to confirm they have not changed (sterilization, aging, etc.) or are not interacting with the packaging system or medical device to create the opportunity for a defect. Potential chemical interaction between the protective packaging and SBS (e.g. yellowing of the SBS due to transfer of antioxidants from corrugated materials or poly-liners) also should be considered.

NOTE ASTM D4754[14] deals with extractables testing. ISO 10993-13[15] deals with degradation products from polymers.

Material's odours are usually readily evident, but it should be noted that if packs are gamma sterilized, odours related to the content which might develop, can abate when a porous SBS is used.

5.5.2.2 Regarding requirements for visible material defects (5.1.7 b) of ISO 11607-1:2019)

Visual inspection is a valuable means of monitoring material integrity to ensure that the integrity is consistent with the specified acceptance criteria. Localized thickening and/or thinning can be assessed by ensuring compliance with thickness variation specification.

5.5.2.3 Regarding material basis weight (5.1.7 c) of ISO 11607-1:2019)

The basis weight of a material is its mass per unit area. Test methods to determine basis weight include ISO 536[16], JIS P-8124[17], ASTM D4321[18], ASTM D3776-6M[19] and TAPPI T410[20]. EN 868[21-26] series specify an acceptable range of variations per major type of packaging materials.

5.5.2.4 Regarding material cleanliness (5.1.7 d) of ISO 11607-1:2019)

Regarding cleanliness, the expectation is that packaging materials should be adequately free of dirt, dust, grease, and other forms of contamination (hairs, insects, etc.). Particulates can be embedded or loose, foreign or bits of parent material. The level of particulate present can be controlled in a manufacturing process by implementing appropriate contamination and cross-contamination risk control measures at the source of the problem. Overall performance can be assessed based on specified acceptance criteria. As applicable, specific acceptance criteria should be established by categories of particulates or foreign materials.

Three main categories can be specified:

a) Loose particulates on the surface of the material of the SBS and/or packaging system that can be brushed or rubbed off.

b) Foreign material resulting from the manufacturing process and embedded between layers of a laminate or within a film, non-woven, or paper.

c) Particulates or visually displeasing items inherent to manufacturing raw materials such as, but not limited to, pulp shives, small particles of resins/polymers with higher-than-average molecular weight, gels or carbon particles resulting from localized excessive heat in processing. All these derive from parents' materials and should therefore be considered separately from process related embedded foreign material particulates.

NOTE TAPPI Dirt Estimation Chart provides a means of measurement which can be utilized for specifying product cleanliness levels and contamination control requirements. EN 13795[27] or IEST-STD-CC1246E[28] provide methods for specifying product cleanliness levels and contamination control requirements.

5.5.2.5 Regarding material physical properties (5.1.7 e) of ISO 11607-1:2019)

The SBS should be capable of protecting the medical device's sterility, efficacy, and/or functionality until time of use. Physical property requirements of the SBS or preformed SBS will depend on the mass and the profile of the contents, the type of protective packaging (if applicable), storage conditions and the distribution system.

There are several factors that affect material performance. Physical properties referred to in ISO 11607-1 5.1.7 e) are the following:

a) *Tensile strength*: The tensile strength of a material is the maximum force (tension) required to break or fracture the material and is expressed as force per unit area. ISO 1924-2[29] and ASTM D882[30] are normally used to provide guidance on testing tensile strength. Associated to tensile strength is elongation, defined as being 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.

b) *Thickness variation*: Thickness is the determination of a single layer of the material using a caliper and soft rubber platens. This soft platen method eliminates the surface roughness effect and, because the platen closing pressure is more uniformly distributed over the test area, partially eliminates the compressibility effect. Hence, the soft platen method is preferred when the measured thickness is used to calculate the material thickness variation, for instance expressed as "coefficient of variation" or "relative standard deviation" (ratio of the standard deviation σ to the mean μ). Test methods to determine thickness include but are not limited to ISO 534[31] and ASTM F2251[32].

c) *Tear resistance*: Tear resistance is the ability of a material to resist tearing and for the material to continue to propagate an initiated tear. Test methods to determine tear resistance include but are not limited to ISO 1974[33], ASTM D1922[34] and ASTM D1424[35].

d) *Air permeance*: Air permeance is the degree to which a material admits a flow of air through a sample. It can be measured using a range of air leakage instruments of different types such as the Bendtsen air permeance tester (this tool measures the flow of air through a fixed area in ml/min) or the Gurley tester (this tool measures the time for 100ml of air to flow through a set area). Other appropriate test methods can be found in Annex B of ISO11607-1: 2019. This property is considered as key to monitor material breathability and is expressed in μm/Pa.s as being the volume of air passing through a surface area of $1m^2$ under a pressure of 1Pascal during 1 second.

e) *Bursting strength*: This test method is designed to measure the maximum bursting strength defined as the pressure at which a sheet (e.g. paper or non-woven) will burst. The maximum pressure reading up to the rupture point is recorded as the bursting strength. Used as a measure of resistance to rupture, bursting strength is determined by procedures such as ISO 2758[36], JIS P-8112[37], TAPPI T403[38] and ASTM D3786[39].

For selected properties, EN 868 series[21-26] specify acceptance limits per major type of packaging materials. It is to be noted that these test methods to assess physical properties will characterize the material but are not directly predictive of the performance of the completed SBS performance. Further evaluation, such as laboratory simulated packaging system performance tests, frequently needs to be performed to assess material performance of the SBS for a specific medical device.

Some other properties can be relevant and therefore should be evaluated. ISO 11607-1:2019 Annex B and EN 868 series provide some additional properties to be specified, as appropriate.

5.5.2.6 Regarding material chemical and toxicological characteristics (5.1.7 f) and 5.1.7 g) of ISO 11607-1:2019)

When choosing a material for a sterile barrier or packaging system there are basic safety requirements that should be met. The source, history and traceability of manufacturing of the used raw materials should be known and controlled. Chemical properties should be evaluated. This will typically include toxicity tests and the evaluation of possible chemical interactions between material and medical device (through check of material neutral pH, low contents of sulfate or chloride. EN 868 series[21-26] specify an acceptable range of variations per major type of packaging material).

The following should be considered and/or evaluated for packaging materials:

— Presence of toxic heavy metals.

— Presence of natural rubber latex.

— Compliance with food packaging regulations (although not required by medical packaging regulations, this is commonly used as the first point of reference when evaluating the toxicological properties of packaging materials),

NOTE 1 Examples of regulations are FDA Code 21 CFR 170–189[40], BFR 36 XXXVI[41] and the European Commission Regulation No 10/2011[42] on plastic materials and articles intended to come into contact with food.

— Biocompatibility (testing is subsequently carried out depending on the specific application).

NOTE 2 Guidance to assess biocompatibility can be found in ISO 10993-1[43] and ASTM F2475[44].

5.5.2.7 Regarding microbial barrier properties (ISO 11607-1:2019, 5.1.7 h))

In non-porous materials, the microbial barrier requirement is met by demonstrating that the material does not permit the passage of air, as detailed in ISO 11607-1:2019, Annex C. In porous packaging materials, the microbial barrier can be assessed using test methods as listed in ISO 11607-1:2019, Annex B.

See also 5.8 of this document on microbial barrier properties.

5.5.2.8 Regarding materials with adhesive coatings (ISO 11607-1:2019, 5.1.8)

As the seal integrity depends on the coating pattern continuity and uniformity, attention is to be drawn on ensuring non-occurrence of any defects such as skips, voids or breaks in the pattern of the layer of adhesive added on one side of the material.

NOTE For information, EN 868-7[24] Annex E proposes a method for the determination of regularity of seal adhesive coatings on paper, which could not be applicable to other porous webs.

The coat weight of an adhesive coated substrate can affect its sealability, seal strength, and adhesive transfer (if required). 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 be within the specified acceptance criteria. EN 868 series[21-26] specify an acceptable range of variations of coating mass depending on coated substrates with associated test methods. Alternatively, ASTM F2217[45] provides a standard practice for coating/adhesive weight determination.

5.6 Additional requirements for sterile barrier systems and preformed sterile barrier systems (ISO 11607-1:2019, 5.1.9)

5.6.1 Intent

The purpose of this subclause is to provide guidance on additional requirements for preformed SBSs and SBSs, in order to minimize contamination and to ensure that specified seal and peel requirements are fulfilled. The examination of the seal performance contributes to demonstrating that the seal integrity and/or closure is effective, and that sterility is maintained until the point of use or expiry date.

5.6.2 Guidance

5.6.2.1 General

Conformity with ISO 11607-2 is required.

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

SBS chemical constituents 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.

NOTE 1 Not all SBSs or preformed SBSs are intended to be peelable.

A SBS should be opened according to the manufacturing instructions. If there is a specific orientation needed to prevent 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).

Seals should be tested for strength and reviewed to determine if the results meet the desired seal strength for the SBS. Other criteria include peelability, seal visual attributes, and failure of material(s) during opening, e.g. delamination. For guidance on how to establish sealing windows, users should refer to Annex E of this document.

NOTE 2 For aseptic presentation see ISO 11607-1:2019, Clause 7.

5.6.2.2 Seal strength

The primary means of characterizing package seal strength is to measure the force required to separate two packaging components. Such a separation can be part of the SBS and/or packaging system design, in order to facilitate aseptic presentation, or it can represent the force required to rupture a permanent (or "weld") seal. Seal strength measurements are key indicators of the sealing process. Measured seal strength values are dependent on but not limited to:

— the nature of packaging material(s) used;

— the set-up of the sealing equipment (e.g. sealing temperature, dwell time and sealing pressure);

— the materials and conditions of the sealing tool in the sealing equipment;

— the parameters of the method used to test the seal.

When determining specified seal strength values the characteristics of the materials and ability of sealing process should be considered.

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 seal strength and reviewed to determine if the results meet the specified seal strength

for the SBS 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 and for determining specified seal strength values. Thereafter, seal strength measurements can be used to monitor manufacturing and to ensure a process output is within specification limits as long as seal strength data has been demonstrated to be a suitable monitor of the process.

ASTM F88/F88M[46] is the definitive test method for characterizing seal strength. ASTM F88/F88M provides information on differences in technique. Seal strength assessed by different techniques (e.g. F88/F88M technique A, B and C) are likely to give different results so that consistency and specification of used technique is important when evaluating seal strength. EN 868-5[47] defines specific testing conditions based on ASTM F88/F88M, in order to align testing and make the results comparable. See Annex B of ISO 11607-1:2019.

5.6.2.3 Bursting strength

A means by which an entire SBS 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 bursting strength are measurements obtained by ASTM F1140[48] (unrestrained) and ASTM F2054[49] (restrained) test methods. While bursting strength testing probes the entire SBS 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 seal strength testing. Burst testing is more typically used for in-process control and is not considered to be a whole package integrity test. When it will be used as such a control, then concurrent seal strength and burst testing should be performed at the time of validation.

5.7 Reusable sterile barrier systems (ISO 11607-1:2019, 5.1.10, 5.1.11 and 5.1.12)

5.7.1 Intent

These subclauses list additional requirements for reusable SBSs like reusable rigid containers or reusable woven wrap materials in order to ensure that these reusable components comply to minimum performance requirements during each use of their serviceable life.

5.7.2 Guidance

ISO 11607-1:2019, 5.1.10 requires that for a reusable preformed SBS, the manufacturer recommends reprocessing steps and demonstrate, that when so reprocessed, the SBS will maintain the minimum performance characteristics, or the end of serviceable life shall be detectable.

ISO 11607-1:2019, 5.1.11 details specific requirements for rigid reusable containers. For healthcare facilities, guidance on application of ISO 11607-1:2019 and ISO 11607-2:2019 is given in Annex B.

Annex B also provides guidance on the use of sterilization wrap, as well as guidance on the specific additional requirements for reusable woven wrap as given in ISO 11607-1:2019, 5.1.12.

Information on further requirements on reusable sterilization containers can be found in ANSI/AAMI ST77:2013/(R)2018[50] and EN 868-8:2018[51].

5.8 Microbial barrier properties (ISO 11607-1:2019, 5.2)

5.8.1 Intent

This subclause provides the basic requirements for microbial barrier properties for impermeable and porous materials.

5.8.2 Guidance

All sterilizable medical packaging materials for SBSs need to provide an adequate microbial barrier.

The selection of appropriate materials will be influenced by the design decision taken under Clause 6 of ISO 11607-1:2019.

The NOTE under ISO 11607-1:2019, 5.2.3 refers to two types of tests, those based on microbiological methods and physical test methods based on challenging materials with particulates, also labelled as microbial surrogate methods in Annex B of ISO 11607-1:2019.

NOTE Whole package (SBS) microbial challenge testing is currently not standardized in any consensus standard. In these tests typically the SBS is 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. While proposed as an alternative to physical integrity testing, these methods are not particularly reliable and are technically challenging to execute and validate. When validated, these methods can be appropriate if they are the only possibility when physical testing is not achievable, e.g. for evaluating the integrity of tortuous path closure SBSs[52].

5.9 Compatibility with the sterilization process (ISO 11607-1:2019, 5.3)

5.9.1 Intent

Sterilization processes can interact with packaging to affect its properties, and therefore its suitability for an application. This subclause ensures this effect is properly evaluated.

5.9.2 Guidance

The ability of SBSs to withstand sterilization processes and maintain their structural integrity as well as other material characteristics and properties is a critically important requirement (ISO 11607-1:2019, 5.3 and 6.1.5). As a result, the method(s) of sterilization should be identified early so packaging materials, preformed SBSs or SBSs that are compatible with the sterilization method(s) can be selected.

Gaseous sterilization methods such as moist heat, ethylene oxide (EO), vaporized hydrogen peroxide (VH2O2) or others, require pressure driven gas exchange through the SBS and/or packaging system which can induce significant mechanical stress on the pack. This depends on a packaging design that is sufficiently porous, and with the porous areas located in an unhindered position in the packaging system. It can also be necessary to provide suitable room in all additional layers of packaging to accommodate SBS expansion during the sterilization cycle. These sterilization methods also require elevated temperature and humidity conditions, with which the materials chosen need to be compatible.

ISO 11607-1 requires assessment of the compatibility with sterilization processes. For sterilization methods like moist heat, EO, VH2O2 or others that can create rapid pressure changes, this includes an evaluation that the SBS is not adversely affected by the rate of change in pressure. This should be done on the actual process taking into account material variability (see ISO 11607-1:2019, 5.3.2).

NOTE ISO/TS 22421 includes a requirement that the technical description for a sterilizer includes a statement of the maximum rate of pressure change in an operating cycle. The rate of pressure change in ISO/TS 22421 is expressed as the pressure gradient calculated as a rolling average using a rate of measurement of 1 s and time interval for calculation of the rolling average of 3 s. The maximum calculated rolling average from at least three replicated operating cycles is to be given. This provides some information on the rate of pressure change that the SBS is likely to experience in an operating cycle but that assessment of compatibility of the SBS with the sterilization process should be done on the actual process taking into account material variability (see ISO 11607-1:2019, 5.3.2).

While the impact on material properties due to EO are often negligible, other methods, such as radiation or VH2O2, can induce significant changes in material properties, potentially impacting packaging stability and performance (ISO 11607-1:2019), see AAMI TIR17[53].

Initial selection of packaging materials or preformed SBSs can be made on the data and recommendations available from manufacturers and in the public domain which approximates to the anticipated conditions of use. However, it is imperative that the type and number of anticipated sterilization cycles are evaluated at some point, preferably on the final SBS, including the medical device or equivalent proxy, as part of the selection process. Evaluations of sterilization compatibility may be leveraged

between sterile product families and packaging families based on worst case considerations or other valid rationales (see ISO 11607-1:2019, 6.1.9). This can be the case, for example, where many similar but not identical medical devices or combinations of medical devices are packaged in the same or similar packaging. Evaluation of the effects of sterilization on the closure/seal integrity and opening features of the SBS should be included. Annex F offers a more detailed review of sterilization methods and their effects to assist with material selection.

5.10 Labelling system (ISO 11607-1:2019, 5.4)

5.10.1 Intent

This section governs the labelling of the SBS so that the product identification and instructions for use are clearly visible and readable by the end user, and that such labelling does not introduce unacceptable risk to the SBS or its contents or potential interference with the sterilization process.

NOTE ISO 11607-1 only addresses the presence of labelling, not the specific information to be printed on the label. Specific expectations for labelling content will vary by region and regulatory framework and specific regulations on label content (e.g. US FDA, European medical device regulation (MDR), ISO) apply.

5.10.2 Guidance

5.10.2.1 Type of labelling

Labelling can either be printed directly on the packaging materials or on label stock which is then affixed to the packaging materials. If using separate labels, specifications for label stock should be established, considering similar requirements to those for SBS materials, e.g. nontoxic, abrasion resistant, clean. Ink used should not bleed or leach onto contents.

5.10.2.2 Placement of labelling

Visual device recognition at point of use is critical. Therefore, it is important to place labelling in a position where it does not hinder device identification. For instance, many SBSs have a clear side to facilitate device identification. If this is the case, any labelling placed on that side should not impede that ability.

5.10.2.3 Ability to remain attached and intact

Labelling should remain adhered to the substrate complete and undamaged such that labelling content is not compromised following sterilization, and subsequent handling, distribution and storage. Labelling should be evaluated as part of performance testing/studies on the SBSs. Label printing and adhesion can also be evaluated during an aging study.

5.10.2.4 Legibility

In order to satisfy legibility requirements, the printing process should be designed properly, with consideration given to adhesion to the substrate and potential of damage to the print or label.

a) Print design: It is important to keep in mind the attributes of the packaging materials when designing the print. Printing in the seal area is discouraged, as it can affect the sealability of a material, as well as the sealing process can affect the ink and/or print legibility. Labelling should also not be placed in the seal area prior to sealing as it can impact the ability to seal consistently.

b) Print (or label) adhesion to substrate: New packaging materials to be printed should be subject to an evaluation for printability. The printability of a material is related to its wettability or surface tension. Surface tension measurement, whether utilizing contact angle equipment, or dyne solutions, can be used to determine the level of surface treatment and/or the printable side of a substrate. Some treated surfaces can degrade, which can affect their printability over time. 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 should to be agreed upon by user and producer of packaging material. See ASTM F2252[54]. The amount of ink coverage, top coating or label on a porous material can also affect material porosity and sterilization effectiveness which should be considered when designing print or label.

c) Potential for damage to print/label: In order to remain legible until the point of use through the hazards of sterilization, handling, distribution, storage and conditions of use labels should be designed to be indelible which is also a regulatory requirement in some jurisdictions (i.e. in Europe under the MDR). The ability to survive these hazards should be evaluated. These hazards can typically be divided into two categories, those posed by physical abrasion or rubbing and those posed by exposure to an agent that can smear or remove the ink.

   Abrasion of printed packaging material in the distribution environment can change the graphic appearance of an SBS 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 and distribution. For further guidance see ASTM D5264[55].

   The printed surface of SBS and/or packaging system materials can be exposed to chemicals during its life cycle. In thinking about "chemicals" it is important to consider environments of use where wet hands are anticipated as well as environments where fluids can be present. Exposure to chemicals can degrade, soften, smear, and remove printing, which affects its appearance and legibility. The relative resistance to known or expected chemicals should be evaluated. For further guidance see ASTM F2250[56].

5.10.2.5 Compatibility of labelling with sterilization process

a) Sterilization parameters: Sterilization process conditions such as temperature, humidity, chemicals used should not affect the legibility of print or adherence of labels.

b) Sterilization effectiveness: Labels should not be placed in an area where they will impact the sterilization process, without evaluating the impact. For instance, labels placed on the breathable area of an SBS when using a gas-based sterilization process can impede the flow of that sterilant. The effectiveness of the sterilization process should be evaluated to confirm this is acceptable.

5.10.2.6 Protection of sterile barrier system and contents

a) Application to SBS: When placing print or labelling on package care should be taken that this process does not damage the materials. This is especially important when this step occurs after inserting the content, as the shape or composition of components can affect the ability to apply the label consistently and without damage.

b) Hand-writing process: Ballpoint pens or any writing instrument or printing system with the potential for creating a hole or puncture in the SBS should not be used. Any handwriting on the package should be outside the area enclosed by the outside dimensions of the seals, not inside the seals where the sterile contents will be contained. Writing on SBSs known as wrappers should be on the closure tape, not on the wrapper itself. Writing on closure tapes or adhesive labels should be done before applying them. Only pens with non-toxic ink that is suitable for use with the chosen sterilization process should be used.

For further information on the process of labelling, see 6.11 of this document.

5.11 Storage and transport of materials and preformed sterile barrier systems (ISO 11607-1:2019, 5.5)

5.11.1 Intent

The intent of this subclause is to create requirements that materials and preformed SBSs are to be transported and stored so that there is no degradation of those attributes that allow sterile contents protection and preservation of sterility when formed into the fully assembled SBS.

5.11.2 Guidance

Considerations should be given to the various types of delivery and storage, and variations in environmental conditions which might be encountered when transporting and storing materials and preformed SBSs.

Manufacturers of materials and preformed SBSs should ensure their outer transport packaging provide adequate protection for storage and transport and advise purchasers on appropriate storage and transport conditions and of any known risks and ways to mitigate them. Environmental conditions (e.g. temperature variation, relative humidity, direct sunlight or ultraviolet light) or any other conditions occurring during storing and transportation can affect the properties and functionality of the materials and/or preformed SBSs.

Materials and preformed SBSs, for example, need to be protected against dust and any foreign matter that would alter their cleanliness levels, increase bioburden potentially leading to a compromise of the materials usability for an SBS application.

Materials may be sensitive to aspects of the storage use condition and should be stored or conditioned following the manufacturer's recommendations.

Protection will typically be accomplished by overwrapping/encasing in poly wrap, light-blocking or metallized wrap if light exposure is a potential risk, and /or cartons suitable for protecting the materials.

Suggested storage cautions to mitigate specific risks will typically be provided by the manufacturer. These can include statements such as do not store in direct sun light, keep dry, no excessive heat, do not stack, etc. Additionally, it can be required, depending on the conversion processes to condition materials or move them into the area in which they will be processed for at least 24 hours to allow them to reach equilibrium if they are being moved in from a less controlled environment.

During storage and transportation, it is recommended to keep original wrapping in place and minimize handling of materials (e.g. reels, trays, die cut lids, wrapping sheets) and preformed SBSs to protect them from contamination as well as from the effect of environmental conditions (e.g. relative humidity, direct sunlight or fluorescent light, temperature).

When selecting suitable storage facilities, one should consider not only environmental conditions (e.g. temperature and humidity) but also ways to minimize the risk of possible physical damage. It can be appropriate to check the product periodically in storage to detect possible deterioration. Consideration should be given to administrative procedures for use-by-dates, stock rotation and lot segregation.

Manufacturers of materials and preformed SBSs can provide data as part of their supplier documentation on retention of product attributes such as seal strength if applicable, material strength (e.g. tensile, tear, puncture), or performance characteristics (e.g. barrier properties, optical properties, sealing performance) for real time aged materials and preformed SBSs stored in specific storage conditions or after accelerated aging.

While the user of materials or preformed SBSs should consider this data in determining their own required storage conditions, it is important to realize that the conditions in these studies do not always exactly mirror the storage and transport conditions at the medical device manufacturer or in the healthcare facility. Deviations from the conditions utilized by the manufacturer should be evaluated by the user to determine that they will not cause degradation of the materials or SBSs.

The requirements of 5.5 of ISO 11607-1:2019 apply to materials and preformed SBSs. Once the SBS is filled and fully formed/sealed and placed into a packaging system, the storage and transport conditions are evaluated by the user (medical device manufacturer or healthcare facility) in accordance with Clause 8 of ISO 11607-1:2019 on packaging system performance and stability.

5.12 Design and development (ISO 11607-1:2019, 6.1.1)

5.12.1 Intent

The highest priority of the development of a medical device packaging system is to systematically minimize the risk to the healthcare user/patient.

5.12.2 Guidance

The intent of this subclause is to minimize the risk through appropriate design and development covering the fundamental functions of an SBS, i.e. allow for sterilization, protect the contents, maintain microbial barrier and allow for aseptic presentation.

Different jurisdictions can define the need to minimize risk slightly differently for example requiring minimizing the risk as far as possible or as low as reasonably possible which obviously changes the requirement. In some jurisdictions like the EU, it is required to minimize the risk for the specified intended use and/or the reasonably foreseeable misuse.

Guidance on risk management is provided in 4.4.2.2 and Annex C of this document.

As a minimum the following aspects that apply to all packaging systems, components and materials should be considered when assessing risks:

a) they should be made of known and traceable materials with processes capable of meeting the requirements of ISO 11607-1:2019 (see requirements in ISO 11607-1:2019, 5.1.3, 5.1.4 and 5.1.5);

b) they should be non-toxic (see requirements in ISO 11607-1:2019, 5.1.6; for guidance see 5.5.2.6);

NOTE If the SBS or associated components contain natural rubber latex, the SBS 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, and storage for sterility maintenance up to the point of use (see requirement in ISO 11607-1:2019, 5.1.6 and 5.2, 8);

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 11607-1:2019, 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 11607-1:2019, 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 11607-1:2019, 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 and distribution (see requirements in ISO 11607-1:2019, 5.5 and Clause 8);

h) they should allow aseptic presentation (see requirement of ISO 11607-1:2019, Clause 7).

5.13 Aseptic presentation (ISO 11607-1:2019, 6.1.2)

5.13.1 Intent

The contents of the SBS are to be dispensed without compromising sterility of the device.

5.13.2 Guidance

At the point of use, the user needs to be able to remove the contents from the SBS without compromising sterility.

Aseptic presentation is the transfer of sterile contents from its SBS using conditions and procedures that minimize the risk of microbial contamination.

To adequately minimize the risk of microbial contamination during aseptic presentation, the packaging system designer needs to focus on the opening features of the packaging system considering the specific application in the healthcare environment. Hence, 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.

An assessment of customer requirements should at a minimum include the following:

a) Customer: It is important to understand who will be using the packaging system. For a terminally sterilized implantable 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 SBS will be opened. For a terminally sterilized medical device this is usually an operating room or healthcare environment but can be a home care environment as well. 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.

NOTE The number of 'sterile barrier layers' can affect the ability to present a medical device aseptically. The selection of a single sterile barrier or a double sterile barrier can be based on the end user needs or the risk of the device. See 5.2.2 of this document. In some healthcare facilities, sterile goods are stored in location where SBSs and packaging systems can be exposed to dust. In such case, packaging systems should be designed to allow end users to remove the protective packaging before entering the sterile environment (i.e. operating room) to reduce risk of contamination at point of use (see also 5.17.2 in this document for additional guidance).

c) Ease of opening: The SBS 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 SBS is difficult to open, the likelihood of contamination increases. If applicable to the packaging design or type, the following hazardous situation should be considered:

— opening at the wrong end or taking the device from the wrong end;

— not having enough room to grab the opening notch for the lid;

— peel force too high or too low;

— tearing of top or bottom web;

— handling difficulties with large or small size packaging as well as large and/or heavy device;

— handling sharp devices;

— top or bottom web curling inwards so that the device is contaminated;

— opening too small;

- particulate or fiber release during opening;
- device not being secured and moving during opening so that the unsterile edge of the packaging is touched;
- difficulties of pulling device from its snap-fit feature of the packaging;
- not having enough room for the gloved fingers to grab the device;
- difficulties of holding the packaging during opening;
- not being able to recognize the sterile layer in case of multi-layer packaging (see also 5.17 of this document).

Depending on the packaging design or device, additional hazard or hazardous situation could be identified during the risk assessment.

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.

Clause 7 of ISO 11607-1:2019 provides step by step guidance on performing usability evaluation for aseptic presentation.

5.14 Physical protection (ISO 11607-1:2019, 6.1.3 and 6.1.4)

5.14.1 Intent

The intent of 6.1.3 and 6.1.4 of ISO 11607-1:2019 is to describe the main design input requirements for the packaging system and the protective packaging in order to protect the sterility of the contents inside the SBS until point of use.

5.14.2 Guidance

This standard uses three terms:

1. Sterile barrier system (SBS) — minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents at the point of use;
2. Protective packaging — configuration of materials designed to prevent damage to the SBS and its contents from the time of their assembly until the point of use;
3. Packaging system — combination of a SBS and protective packaging.

The packaging system is to be considered the combination of the SBS and the minimum necessary protective packaging for the product to be distributed safely to the end user until point of use. For example, cargo containers and pallets, or, transfer cabinet used in healthcare facilities (even though they can be considered protective packaging) are generally not to be regarded as part of this minimum level of protective packaging. They are considered transport accessories. The packaging system can have one, two or more layers of unit or user packaging.

The protective packaging is usually additional layers of packaging outside the SBS. Protective packaging can also be protective components or materials inside the SBS. For example, if the medical device is sharp or has sharp points or edges, these can be shielded with protective materials to keep them from puncturing or interfering directly with the SBS or help keep the device in a fixed safe location inside the SBS.

When designing the different components in the packaging system, consideration should be given to the conditions and environment throughout the packaging lifecycle (sterilization, thermal and mechanical hazards from handling, distribution, storage, etc.).

For detailed inputs to the design phase, see Annexes A and B of this document.

5.15 Sterilization compatibility (ISO 11607-1:2019, 6.1.5)

5.15.1 Intent

The SBS must be compatible with and allow for product sterilization. This encompasses the entire packaging system that is processed through sterilization.

5.15.2 Guidance

Annex F of this document discusses the details of selecting materials for compatibility with the sterilization process.

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 SBS. Additional information on sterilization process requirements and references can be found in Annex F of this document.

Subclause 5.9 of this document includes guidance on sterilization compatibility and contains more detail on material compatibility requirements detailed in ISO 11607-1:2019, 5.3.

5.16 Maintenance of Sterility (ISO 11607-1:2019, 6.1.6 and 6.1.7)

5.16.1 Intent

ISO 11607-1 requires the SBS to maintain sterility until the point of use or expiry.

5.16.2 Guidance

5.16.2.1 Handling, distribution, and storage guidance

The packaging system designer should understand the stresses imposed upon the packaging system through its total life cycle. These stresses include all factors of handling, distribution and storage. The requirements for these environments are determined largely by the type of medical device, type of packaging system, sterilization process and the type of distribution. A thorough understanding of these factors will help to address all pertinent medical device protection requirements. The sterility maintenance will help to define the appropriate sterile barrier and packaging system materials. Evidence that the ingress of microorganisms can be prevented is demonstrated under test conditions which consider sterilization process, handling, distribution and storage.

An assessment of handling, distribution and storage 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 of 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 healthcare facility, 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 consider any distribution by the customer. The methods of accomplishing these medical device

movements are critical design inputs. Product distribution could include multiple transportation episodes, such as the return of a partially utilized kit of devices to the manufacturer.

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 by 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.

When the use conditions are properly defined for the packaging system, these conditions should then be accurately accounted for in the performance and stability testing. Contents will be sterile as long as sterile barrier integrity is maintained. Clause 8 of ISO 11607-1:2019 (specifically, 8.2 and 8.3) contains requirements on the validation of packaging systems with consideration to the conditions of use.

5.17 Requirements for multi-layer packaging (ISO 11607-1:2019, 6.1.8)

5.17.1 Intent

The end user needs to be able to recognize the layer of packaging that is the sterile barrier in order to apply proper handling techniques when using the packaging system in particular during aseptic presentation.

5.17.2 Guidance

There can be circumstances where it is difficult to differentiate between a validated SBS (see ISO 11607-1:2019, 9.1) and protective packaging that looks like an SBS. In these circumstances the labelling should include an indication to identify the SBS(s). In instances where two layers of packaging appear similar, an indication to the end user if layers are an SBS can assist in determining the proper handling/dispensing techniques.

NOTE A set of SBS symbols have been validated by the Sterile Barrier Association (SBA). A summary of the validation report is available on the website of the SBA as well as guidance how to use the symbols. The validation demonstrated good comprehension, usability and memory for the symbols which means that healthcare users widely understand the symbols, take the correct actions and memorize the meaning. The symbols are included in ISO 7000[57] and are available via the ISO Online Browsing Platform. (example: Double SBS: https://www.iso.org/obp/ui/#iso:grs:7000:3704). ISO 15223-1[58] has been revised and published in July 2021 with new symbols that have been developed to deal with the labelling requirements of the medical device regulation (EU) 2017/745[59] including the new SBS symbols. The plan is that EN ISO 15223-1 will be harmonized with the MDR. Use of an indication to mark the SBS such that it can be recognized as such is now required by the MDR.

The use of symbols to recognize the SBS(s) should be considered when applying risk management for usability. The symbols help the user understand the packaging configuration at the point of use and as such control the risk of unintentional contamination of the sterile field. Risk management can be the basis to decide which layers are to be labelled and which not. The usability evaluation (see 5.22 of this document) should demonstrate that the labelling system is adequate and correctly interpreted.

For healthcare facilities, attention is drawn to protective packaging called “transportation wrap” only featuring mechanical protection without microbial barrier. To avoid any confusion or misuse, sheet colour coding can be an acceptable practice of recognition indication of a sterile barrier layer. An example of this is when packaging reusable medical devices, a double wrap package made of two layers of breathable webs is used. Each of these sheet layers can be of a different colour. The personnel in the healthcare facility are trained to know that the external one is always of a pre-set colour and is a “dust cover” to be removed prior entering the operating room.

5.18 Packaging families (ISO 11607-1:2019, 6.1.9)

5.18.1 Intent

It can be an efficient and cost-effective way to develop a packaging system family by using the worst-case device/packaging system combination to validate the design.

5.18.2 Guidance

5.18.2.1 General

When determining and assessing the packaging system, thought should be given to other packaging system designs and medical devices that require validation. Many times, similar medical devices, comprising a "product family," can be validated together, where package materials, packaging machinery, sterilization processes, and other aspects of the medical device use and life cycle are the same or similar. Choosing a device/packaging system combination that represents a "worst-case" example can be advisable, in order to ensure that less demanding variants of the SBS 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 can provide the basis for a valid rationale to limit the amount of testing required to establish efficacy of an SBS.

5.18.2.2 Packaging family considerations for healthcare facilities

A common SBS can be used to pack and protect a variety of tray families (i.e. trays composed by a set of similar reusable medical devices but not identical) used in the operating room. The worst-case is established by identifying the tray(s) that apply the most stress to the packaging system. The worst-case configuration can be the bulkiest, heaviest, the sharpest or the densest set of reusable items organized in a given size tray. Often, the determination of the worst-case configuration is clear. However, in some cases it can be necessary to test more than one operating room's tray to ensure that the packaging system has been fully challenged.

The determination of the worst-case scenario can also encompass the review of:

a) having the reusable medical devices oriented to facilitate aseptic presentation or not;

b) having the sharp items shielded (so that the healthcare user is protected from injury and the SBS and medical device is protected from damage) or not;

c) having associated components used inside the SBS in order to ease or facilitate the organization, drying or aseptic presentation (e.g. inner wrap, instrument organizer tray, absorbent tray liners or a containment device around the medical device) or not.

Properly characterizing and evaluating the worst-case configuration will ensure that the other trays in the same category will be appropriately protected by the packaging system. Often historical data exists for already selected material combinations. Therefore, capitalizing on this available information can be supportive of determining if it is an appropriate solution to be also used on additional configurations / sets of reusable medical devices of the same family.

ISO 11607-1:2019 addresses "worst-case" in three areas and in each case, it means something slightly different. In order to correctly interpret and apply these subclauses dealing with worst-case, it is important to understand the terms that are used.

5.18.2.3 Worst-case configuration — Medical devices

Within medical device product families (i.e. medical devices that are similar but not identical), a common SBS 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 can 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 can 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. This is especially important when device functionality is also tested with the packaging system. 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. Alternatively, a worst-case device which is not a commercial configuration but a combination of other worst-case device features, intended to present the maximum challenge to the packaging system, can be used.

Packaging systems can be designed to contain a range of product, SBS, and product literature configurations. Often this leads to dramatic differences in the weight, or the headspace present within a packaging family. For example, a lighter mass configuration can have more headspace present in the protective packaging, leading to damage to the SBS. Or, a heavy mass configuration can minimize headspace limiting movement but create different opportunities for SBS damage. In some cases, the idea of bracketing can be employed to test extreme ranges within a packaging system, such that all configurations that fit within that range can be included by equivalence.

Alternatively, for performance testing, a worst-case device which is not a sellable configuration but a combination of other worst-case device features, intended to present the maximum challenge to the packaging system, can be used.

5.18.2.4 Worst-case — Sterile barrier system

Additional direction regarding worst-case testing is provided in ISO 11607-1:2019, 8.2.2 on packaging system performance testing, "Performance testing shall be conducted on packaging systems comprised of the worst-case SBS as well as the worst-case protective packaging." Nominal sealing parameter settings are acceptable but should be justified for package performance testing. There are two predominant approaches to addressing the key issues of this subclause.

The first and most common approach utilizes sourcing preformed SBSs manufactured using a fully validated process. SBSs 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 normally 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 (see 4.5 of this document) 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 SBSs at the worst-case conditions of manufacture, generally the extremes of the validated window. In some cases, SBSs can be produced at the lowest validated temperature, the lowest validated pressure, and the shortest validated dwell to yield SBSs with the low-end worst-case seal quality. Typically, the parameters used to establish the Operational Qualification (OQ) are used to produce the SBSs needed to assess the packaging system performance. This approach should be used when there is documented data that supports the seals are a lower strength than the nominal condition.

The approach to achieving conformity to ISO 11607-1:2019 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.

5.19 Design process (ISO 11607-1:2019, 6.2.1)

5.19.1 Intent

Following a documented design process is intended to be part of the systematic approach to ensuring the safety of the packaging system.

5.19.2 Guidance

The procedures for the design and development process of packaging systems should consider the aspects described in 5.20 of this document.

NOTE This is applicable to medical device manufacturers, manufacturers of medical packaging and healthcare facilities.

Choosing an appropriate packaging material for a sterilizable medical device requires careful consideration. It is desirable to include packaging system development 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 resource in determining suitable options.

Medical device manufacturers are directed to Annex A of this document, which provides information on relevant processes and practices.

Healthcare users are directed to Annex B of this document, which provides information on relevant processes and practices.

The use of contract packagers if applicable should also be considered during design. More guidance is available in Annex G of this document.

5.20 Design inputs (ISO 11607-1:2019, 6.2.2 and 6.2.3)

5.20.1 Intent

These subclauses require the design owner to consider the physical characteristics of the product, design inputs related to the end user needs, the use conditions, and the use of materials meeting the prerequisites of ISO 11607-1:2019, Clause 5.

5.20.2 Guidance

5.20.2.1 General

A set of design inputs should be developed prior to considering materials and/or packaging system design. These will be used in assessing the materials and/or design. Design inputs are developed from end user needs and intended uses. This information will come from end users, engineering, manufacturing, marketing, regulatory, etc. Some examples of design inputs are medical device physical attributes, medical device protection requirements (e.g. barrier to light, oxygen, and contamination), sales unit configuration, sterilization process, distribution, handling, and use environment.

Healthcare users are directed to guidance provided in Annex B of this document.

5.20.2.2 Design inputs — medical device attributes

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. 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. They can be divided into several categories, like product protection requirements, manufacturing requirements, sterilization process requirements, handling, distribution and storage

requirements, marketing requirements, budget requirements, customer requirements and regulatory requirements.

Each of these categories are addressed in Annex A of this document to provide baseline guidance for gathering design inputs prior to designing a packaging system for a terminally sterilized medical device product.

5.20.2.3 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 and diameter 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 SBS. 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. This will guide the development in the planning/execution of stability testing of the packaging.

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.

5.20.2.4 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, 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 SBS 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 or moisture. If a device is sensitive to moisture, the packaging can provide a barrier or resistance to moisture ingress.

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 forces: Determining the amount of shock the medical device can handle in the absence of packaging will help determine the amount of shock protection required from the packaging system (e. g. force resulting from drop/impact). It is also important to understand if the medical device is more susceptible to shock forces in a particular orientation. Healthcare users should refer to instructions for use for more information on this topic.

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.

g) Duration: the amount of time the medical device needs to be protected by the SBS and/or packaging system.

See Annex C of this document for the use of FMEA (Failure Mode and Effect Analysis) or risk management techniques to address risk of the product and/or packaging system.

Healthcare users should refer to the handling, distribution and storage checklist in Annex H of this document.

5.21 Sterile fluid path (ISO 11607-1:2019, 6.2.4, 6.2.5)

5.21.1 Intent

When sterile fluid path assemblies are considered an SBS, they are to be identified as such and follow key requirements.

5.21.2 Guidance

Sterile fluid path packaging is defined as the system of protective port covers and/or packaging designed to maintain sterility of the portion of the medical device intended for contact with fluids.

NOTE For example, the interior of the tubing for administration of an intravenous fluid needs to be sterile while the sterility of the outer surfaces could not be required.

Sterile fluid path packaging is typically closed with tortuous path closures. Examples of closures are luer caps, spike caps, drip chamber caps, etc.

A sterile fluid path is a special case when it comes to an SBS, which is why there is a specific definition in ISO 11607-1. In a sterile fluid path system, fluids flow through a lumen. The critical characteristic is that the inside of the tube is sterile. This contrasts with a typical medical device, where is it critical that the outside of the instrument is sterile. The sterility of the sterile fluid path system is maintained by the closure system of the fluid path, and it should be demonstrated that the closure system maintains sterility until point of use. Sterility validation is usually conducted by exposure to an aerosol of spores followed by sterility testing of the lumen.

Simulated distribution (e. g. shock and vibration) should be done to assure that the integrity of the sterile fluid path remains intact, i.e. closures do not fall off or become loose. Acceptance criteria for the integrity of the sterile fluid path closures should be developed.

As many sterile fluid path systems are packaged in pouches, a common SBS, it is important to determine in each case what (e. g. the pouch or the closures such as luer cap, spike caps, etc.) is providing the sterile barrier and to make sure that the package is labelled accordingly. Without such labelling an end user could assume the pouch is providing the sterile barrier. If the sterile fluid pathway is labelled as such, then the pouch enclosing can be considered protective packaging and validated as part of the packaging system.

Figure 1 — Sterile fluid path symbol — ISO 7000-3084

The symbol in Figure 1, when placed on the medical device packaging, indicates the presence of a sterile fluid path within the medical device in cases when other parts of the medical device, including the exterior, might not be supplied sterile.

To make sure the end users understand the function of a pouch containing the sterile fluid path, it is recommended to use the symbols referred to use the symbols referred to under 5.17 of this document.

NOTE ISO 15223-1[58] includes symbols for SBSs (see also 5.17.2 of this document).

Some examples of sterile fluid path products include:

— Collection devices: drainage bags, vials, syringes.

— Administration devices: feeding bags, syringes.

5.22 Usability evaluation for aseptic presentation (ISO 11607-1:2019, 7.1, 7.2 and 7.3)

5.22.1 Intent

The intent of these subclauses is to describe specific requirements for a usability evaluation to demonstrate that an SBS allows for aseptic presentation.

5.22.2 Guidance

The SBS should facilitate an adequate opening performance in order to allow for the medical device to be dispensed aseptically to reduce the risk of microbial contamination of the contents. Usability evaluation is intended to address these risks and demonstrate effective risk control. This is fundamental for sterile medical device packaging. If the SBS is difficult to open, the likelihood of contamination can increase. When a sterile medical device is contaminated, it should not be used. Seal fiber tear is an example of an opening defect that could be considered a source of contamination by a healthcare user.

The usability evaluation may be conducted in real or simulated environments. ISO 11607-1:2019 requires that the study give consideration of the different end users, for example:

— Healthcare environment: trained personnel for opening SBS, trained in sterile field, experienced, accustomed to several different SBS forms. The study can consider a healthcare user with minimal training and/or experience.

— Home environment: lay person, no training, potentially no experience opening these sorts of packages. Patients could have limited strength and dexterity limiting their ability to easily open an SBS.

The following practices can be employed to create a robust usability evaluation:

a) The evaluation should address the hazardous situations that have been identified in the design process for aseptic presentation following the requirements under 5.13 c) of this document.

b) Evaluation participants should represent end users, and should wear appropriate surgical/clinical attire, as applicable.

c) Attributes of the use environment should be represented in the evaluation.

d) Observe and document participant behaviour to assess participants' adherence to the instructions and to identify errors/problems.

e) Afterwards, ask the participants about difficulties, problems or hesitations, and for feedback regarding unclear instructions (wording/symbols/graphics) in case instructions for use are being used. Validate significant changes to the instructions.

f) It is recommended to include potential use scenarios not aligned with the intended use by the designer/manufacturer (intentional or unintentional misuse of the SBS, abnormal use as defined in IEC 62366-1[60]). This could also be a regulatory requirement in some jurisdictions.

Usability evaluations for aseptic presentation can be done together with usability evaluations for the devices, and sample sizes can be aligned.

NOTE Reference IEC 62366-1[60] for further guidance.

5.23 Leveraging usability evaluations (ISO 11607-1:2019, 7.4)

5.23.1 Intent

It can be an efficient and cost-effective way to evaluate the usability of SBS families by using the worst-case configuration to evaluate the design.

5.23.2 Guidance

It is common for both manufacturers and healthcare facilities to utilize similar SBS configurations for families of products that are similar. In these situations, organizations can embark on an efficient approach by grouping SBSs that can be considered equivalent based on a number of factors. Such factors could include:

a) multiple sizes of preformed SBSs that are common to industry (e.g. chevron opening, corner-peel, etc.);

b) multiple sizes of rigid SBS (tray/lid) in which the means of opening and dispensing of the contents present an equivalent risk of contamination (e.g. same clearance for a gloved hand to pick contents).

For legacy SBSs that have been in the market, historical data can be leveraged to document the evaluation of the usability for aseptic presentation.

Manufacturers should review the impact on aseptic presentation in case of design changes to the device. Post market surveillance can be a data source for understanding the usability of the marketed SBS. Historical data can often be leveraged when adopting a new but similar product into an established/validated SBS. Leveraging historical data is applicable to both healthcare facilities and medical device manufacturers.

5.24 Usability evaluation failures (ISO 11607-1:2019, 7.5)

5.24.1 Intent

When the steps for the usability evaluation are conducted and the requirement is not met, additional information can be provided to the end user or the SBS could be redesigned to achieve the objective. If a redesign is made or additional information is provided, ISO 11607-1:2019 requires that a subsequent usability evaluation is conducted.

5.24.2 Guidance

In the event, that the usability evaluation fails to demonstrate the steps outlined in ISO 11607-1:2019, 7.2, risk management is deployed to resolve this issue as described below.

If the steps outlined in ISO 11607-1:2019, 7.2 are not initially met:

a) Investigate:

   — Document the failure(s) and determine any primary and contributing root causes. It is very important to understand if the cause of a failure can be attributed to the design of the SBS or to the end user's comprehension of how to use the SBS.

b) Correct:

   — Based on the results of the investigation and the documented root cause, perform corrective actions.

   — If the root cause was the design of the SBS, a design change or redesign should be performed.

   — If the root cause was end user comprehension, additional information can be provided to the end user to aid the usability of the SBS.

c) Re-evaluate usability:

   — If the SBS design is changed based on the results of a usability evaluation, ISO 11607-1:2019, 7.2 requires that the redesigned SBS demonstrate that the steps can be met. If the design change addresses only one design feature, then the subsequent usability evaluation can focus on usability of that specific feature.

   — If additional information is to be provided to the end user, ISO 11607-1:2019, 7.2 requires that the usability evaluation include an assessment of the ability for an end user to follow that information and subsequently perform the steps successfully.

5.24.3 Guidance on formative and summative studies

Usability testing is a methodology for assessing whether a design is meeting its intended use (or ease of use) when an end user is interacting with the design. This methodology can be approached by formative studies gaining insights of end user's acceptance of the design, which can then be demonstrated with a summative study confirming design acceptance by end users.

5.24.3.1 Formative studies

The following questions can be useful in a formative study for usability:

a) Initial evaluation of the design usability. A formative study can indicate how intuitive a design is for the end user to interpret how to use the SBS. The formative study is an optional study; one can proceed directly to a summative study.

   — Is labelling sufficient?

   — Is opening location understood?

   — Is the opening technique and dispensing method understood?

   NOTE Usability evaluation can also be an opportunity to verify if disposal is understood, if applicable and required by regional regulations.

b) Outcome of the formative study can be a refinement in the design or labelling, or it can confirm readiness for a summative evaluation.

5.24.3.2 Summative studies

a) Final confirmation of the usability requirement.

b) The outcome of the summative study is the demonstration that an end user can aseptically open and dispense the contents of the SBS by meeting the steps in ISO 11607-1:2019, 7.2.

NOTE The IEC 62366-1[60] standard and US FDA guidance "Applying Human Factors and Usability Engineering to Medical Devices[61] contain significantly more detail on performing usability evaluations and can be a valuable resource when evaluating the usability of an SBS.

5.25 Packaging system performance and stability (ISO 11607-1:2019, 8.1)

5.25.1 Intent

The intent of ISO 11607-1:2019, 8.1 is to set performance and stability testing requirements to the final design, and to describe the purpose and importance of integrity testing and also the difference between performance and stability testing as outlined in ISO 11607-1:2019, 8.2 and 8.3.

5.25.2 Guidance

5.25.2.1 Significance of integrity testing

After sterility is achieved in a validated sterilization process, the most important acceptance criterion of the packaging system design is retaining/maintaining this sterility. This can be confirmed by testing the integrity of the SBS. Testing for sterility is often considered a less effective method for several reasons:

— risk of false negatives and false positives;

— impossibility of demonstrating the presence of one viable microorganism in one million sterilized products by testing (need to test minimum 1 million negatives);

— sterility result is only the status at a single point in time and depends on several aspects, e.g. if exposure to dry conditions or high temperature was conducted just before testing for sterility, then SBSs could be broken but sterile contents could likely pass sterility testing as typical bacteria would likely not survive the exposures.

Thus, SBS integrity becomes an essential element for a medical device that is supplied in the sterile state. The SBS integrity 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. ISO 11607-1:2019 regards the loss of sterility as event related rather than time related. Such events occur during the handling, distribution and storage of medical device products and are usually catastrophic in nature, i.e. occurs in conjunction with a physical breach of the SBS. Exposures to excessive and frequent temperature and pressure variations during storage and transport or wetting of SBSs are also considered as events.

Test methods associated with package integrity can be used to discover possible physical breaches in the SBS, which jeopardize the microbial barrier.

5.25.2.2 Before testing

SBSs submitted for the packaging system design validation should be manufactured under standard operating procedures. Packaging systems need to be sterilized using a validated sterilization process. The sterilization challenge should be elevated by considering worst-case, multiple sterilization cycles and/or sterilizer process tolerances, as applicable. If a manufacturer decides to validate multiple sterilizations to be able to resterilize a load, then this needs to be applied to the packaging system as well. The packaging systems for performance testing should contain the actual medical device or a surrogate of the medical device (which is suitable in terms of mass and surface geometry), appropriate labelling, and IFUs expected to be included in the final market packaging system.

If sufficient stability or performance data of similar SBS design exists, it should not be necessary to redo testing unless it is evident that the contents inside the system could pose a risk to the SBS or materials. An example could be a new size of a plastic syringe in the same sterile pouch used for other sizes. The effects of physical interaction by a heavier syringe would be shown in performance testing and not in stability studies.

5.25.2.3 Separation of performance and stability testing

ISO 11607-1:2019 is clear regarding the separation of SBS 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.

— 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 SBS samples to continuously elevated temperatures (e.g. 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.

— If a failure occurs during performance testing of aged packaging systems or SBS, 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)?

Users should also refer to Annex I of this document for guidance on failure investigations.

5.25.2.4 Different methods for integrity testing

SBS integrity can be measured in different ways. Annex B of ISO 11607-1:2019 lists several applicable tests for sterile barrier integrity, including:

— Visual inspection: Channel defects in SBS seals can be detected with good probability by applying ASTM F1886/F1886M[62]. Despite certain material limitations, for example pinholes and minute tears, it is a valuable method for monitoring of 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 SBSs are evaluated during initial SBS and/or packaging system, but frequently serve as an in-process check during regular SBS and/or packaging system production.

— Dye penetration: ASTM F1929[63] involves the wicking of a dye solution through a seal channel defect with porous materials and ASTM F3039[64] involves the wicking of a dye solution through a material defect or a seal channel defect on nonporous materials. This is a common test for seal validation if seal quality has not yet been correlated with visual inspection. Dye tests can be affected by the materials used, and operator training and experience. Depending on the nature of the materials and particularly if they are porous, it is essential to perform the dye test following the recommendations of ASTM F1929[63] in terms of timing to avoid the dye from wicking into the structure of these material. 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.

— Bubble testing: ASTM D3078[65] and ASTM F2096[66] involve submersion of a package (SBS) in a fluid and the application of a pressure differential. An evolution of gas can 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 (SBS) integrity.

— 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.

NOTE See also the note under 5.8.2 of this document regarding whole package test methods.

5.26 Packaging system performance testing (ISO 11607-1:2019, 8.2)

5.26.1 Intent

The intent of ISO 11607-1:2019, 8.2 is to establish testing requirements related to the risks occurring through the hazards of handling, distribution and storage to the representative packaging system configuration.

5.26.2 Guidance

In the packaging system design validation context, the term performance means performance in withstanding the hazards of handling, distribution and storage.

5.26.2.1 Establishing a performance test plan

Establishing a test plan for the risks occurring through the hazards of handling, distribution and storage should consist of six general steps:

a) Specify the packaging system/content. If applicable make a rationale for worst case/ family if the performance testing should cover more than one product (for packaging family worst case guidance see 5.18 of this document). Specify the acceptance criteria.

b) Specify the anticipated shipping environments that can occur during packaging/repackaging, transportation, warehouse storage, and handling as applicable.

c) Specify testing conditions that simulate the anticipated shipping environments, e.g. temperature, humidity, shock, vibration, compression, pressure changes (use standardised laboratory simulations where possible).

d) Expose the sterilized packaging system to the defined/selected testing conditions.

e) Test the SBS for integrity (sterile contents and packaging can be tested for additional quality/ performance attributes in the same testing sequence if appropriate or beneficial).

f) Conclude on the test results and investigate any failures. Document according to ISO 11607-1:2019, 4.5.

5.26.2.2 Define the distribution environment

Based on the design inputs regarding the logistics and distribution anticipated for the medical device, shipping and handling tests should be defined. These tests can be designed by several means:

— actual shipment;

— standardized laboratory simulations;

— laboratory simulations based on measured data;

— environmental challenging (if appropriate).

NOTE For guidance on choosing an appropriate distribution challenge method see Annex B of ISO 11607-1:2019 (performance testing section). For further information on environmental challenging see 5.26.2.3 of this document.

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. Actual shipment is not a repeatable method. For healthcare facilities, which control the distribution environment from end to end, actual shipments using the worst-case conditions can be an acceptable performance test.

5.26.2.3 Environmental challenging

Another aspect of SBS testing relates to environmental challenging or conditioning the SBS at various temperatures and humidity extremes in order to simulate exposure to various conditions from shipping to different climates. The temperature and humidity levels should be chosen carefully based on an understanding of the product distribution and use conditions.

Hot/cold cycling can be used to mimic day/night or seasonal extremes to which packaged medical devices can be subjected. However. attention should be paid to the rate of change since rapid changes can be stressful for the integrity of the SBS. The rate of change should be aligned with real conditions encountered.

NOTE 1 For guidance on choosing an appropriate environmental challenge method see Annex B of ISO 11607-1:2019. One approach for a commonly used distribution system can be found in ASTM F2825[67] and ISTA series[68].

NOTE 2 As per ASTM F17[69], environmental challenging is defined as 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.

Healthcare users should also refer to Annex B as well as Annexes J, K, L, M and N of this document.

5.27 Stability testing (ISO 11607-1:2019, 8.3)

5.27.1 Intent

The intent of ISO 11607-1:2019, 8.3 is to set testing requirements related to the risks occurring through the aging of materials throughout the claimed shelf life, on a final representative SBS configuration.

5.27.2 Guidance

5.27.2.1 Aging time practicalities and requirements

The requirement of ISO 11607-1 is that stability testing be performed using real-time aging. 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 SBS or packaging system shelf life is commonly accepted as valid for new medical device introductions, provided that real time aging is started to confirm accelerated aging test results. The same sampling plan and testing requirements should be applied for accelerated and real-time aging to support the claimed shelf life.

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 test data for other properties than integrity should be considered in order to capture the effects of the sterilization process prior to beginning the aging process on the SBS materials and seals.

The user can look for trends that indicate that the materials and seals could be changing in a manner that could affect sterile barrier integrity over time. For example, if the trend in seal strength is significantly negative, the materials could not be suitable for use. The decision to use the candidate materials and SBS is based on risk level and the criticality of the attribute (i.e. functional versus cosmetic attributes such as colour changes and print fading) to the function of the SBS.

Healthcare users should refer to Annex B of this document.

5.27.2.2 Establishing a stability test plan

One important aspect of a validation protocol is the rationale and test parameters for establishing medical device shelf life. Setting up a test plan for the risks occurring through the hazards of aging should have the following general steps:

a) Specify the SBS. If applicable make a rationale for worst case/ family if the stability should cover more than one product (see family worst case guidance in 5.18 of this document).

b) Specify the desired SBS shelf life.

c) Specify aging testing plan.

d) Expose the SBS to the defined aging conditions.

e) Test the SBS for integrity (sterile content and packaging can be tested for important quality/ performance attributes in the same testing sequence if appropriate or beneficial).

f) Review the accelerated aging test results and apply the documented acceptance criteria. Investigate any deviations and failures and conduct a root cause analysis. Determine if the failure is due to a stability or other issue. Decide if the product can go to market.

g) Continue to monitor real time aging test results until the claimed shelf life is reached. Apply the documented acceptance criteria. Decide follow-up actions based on results.

h) Document according to ISO 11607-1:2019, 4.5.

NOTE 1 Real time aging is usually combined with accelerated aging plans. Aged samples are often tested at intervals shorter than the end date indicated on the SBS labelling, especially when evaluating new materials where limited or no stability data are available.

NOTE 2 Aging studies can be performed on empty SBSs 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.

5.27.2.3 Accelerated aging

Accelerated aging temperatures can create an extreme challenge condition to a material and SBS that would not be found in real world situations, and thereby create false interpretations of the failure mode. When choosing the temperature to conduct the accelerated aging, care should be taken to select temperatures which do not cause any material transitions or SBS and/or packaging system distortion, or induce nonlinear changes such as crystallinity, generation of free radicals, or other material degradation.

When considering the role of humidity in accelerated aging, it is important to realize that relative humidity 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.

ASTM F1980[70] provides valuable guidance regarding the development of accelerated aging, and discusses the importance of selecting aging temperatures and humidity that do not exceed the limitations of the SBS materials.

AAMI TIR17[53] defines accelerated aging as 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.

5.28 Packaging system validation and changes (ISO 11607-1:2019, 9.1)

5.28.1 Intent

ISO 11607-1:2019, 9.1 establishes the criteria to identify a packaging system as validated when meeting the requirements of design, usability, performance testing and stability testing as well as conforming with ISO 11607-2.

5.28.2 Guidance

The presence of this clause clarifies the status of a validated packaging system based on objective evidence. This subclause also assists users of ISO 11607-1:2019 when distinguishing between specific verification activities, and an overall packaging system validation. This also assists the users of ISO 11607-1:2019 in determining the impact to a packaging system validation when changes are made.

For healthcare users a set of annexes (J, K, L, M and N) in this document are available for documentation of validation steps including related changes and end user feedback.

5.29 Change control (ISO 11607-1:2019, 9.2)

5.29.1 Intent

This subclause defines the need for a change control procedure for packaging system designs.

5.29.2 Guidance

Change control is an element in a quality management system. See also guidance for ISO 11607-1:2019, 4.1.

NOTE 1 Examples of change control requirements can be found in ISO 13485:2016, 7.3.9[2]; and ISO 9001:2015, 8.3.6[3].

Validation reports and related records (i.e. reports, data) should be maintained in accordance with the documented requirements. The last step is the formal approval of the final report. See also guidance for ISO 11607-1:2019, 4.5.

The change-control procedure applies to both initial validation and subsequent revalidation.

NOTE 2 The MDR requires manufacturers to maintain these records in the technical documentation.

5.30 Revalidations (ISO 11607-1:2019, 9.3, 9.4, and 9.5)

5.30.1 Intent

The intent of these clauses is to identify conditions that could require revalidation of packaging systems.

5.30.2 Guidance

Revalidation is required when changes have been made to the medical device, packaging system, process, or equipment that will affect the original validation. Changes made to the design should be evaluated to determine if the original validation is impacted by the change. Some examples are changes in physical characteristics of medical device contained in the SBS, process relocations, changes of formulation or equipment, changes at component manufacturer, and changes of raw materials used (ISO 11607-2:2019, 5.7).

Revalidation is often affiliated with design control and the associated change control procedure. The extent of the revalidation and the rationale chosen will depend on the nature of the change and how it affects the process or medical device.

Revalidation can be less extensive than the initial validation of a new packaging system. For example, if a new device using an existing packaging system is larger than the predicate device, performance testing can be completed but the existing stability data could still be applied[71].

Review of the process, medical device, and packaging system should be considered periodically to ensure that the combined impact of multiple minor changes, which did not require revalidation, have not affected the packaging system (ISO 11607-2:2019, 5.7.4).

5.31 Inspection immediately prior to aseptic presentation (ISO 11607-1:2019, Clause 10)

5.31.1 Intent

Intent is to perform a visual inspection immediately prior to use to ensure end users of the medical device package and SBS do not use sterile contents with potential breaches of the sterile barrier.

5.31.2 Guidance

Medical device manufacturers and healthcare systems validate to a high level of confidence that packaging for terminally sterilized medical devices will maintain sterility of contents to the point of use. Despite the robustness of the validation activities, there is always the possibility that unforeseen events can occur in the lifecycle of the packaging system. As a conservative measure, it is considered best practice for end users of medical device packaging to visually assess the condition of an SBS to ensure integrity is not compromised. The "damaged package" symbol on the SBS (ISO 15223-1:2016, 5.2.8[58]) can remind end users not to use the contents in case of integrity issues, ISO 11607-1:2019, Clause 10 requires that instructions for use (IFU) contain direction to visually inspect the SBS.

It should be clearly evident to the end user which layer of packaging is the sterile barrier in order to facilitate an inspection. A label with the symbol for the number of barriers (ISO 11607-1: 2019, Annex E) can support the end user with this inspection. See 5.17 of this document for guidance pertaining to ISO 11607-1:2019, 6.1.8.

5.32 Information to be provided (ISO 11607-1:2019, Clause 11)

5.32.1 Intent

This clause is meant to provide general guidance on common information that is possibly required for material, preformed SBS or SBSs placed into a given healthcare market.

5.32.2 Guidance

The listed items of information to be provided are self-explanatory. This list is not meant to be exhaustive therefore, when entering a specific market, it should be reviewed that the information accompanying the product are also meeting any other national or regional applicable requirements.

For the information provided across a labelling system, when designing the print, it is important to keep in mind the attributes of the printed substrate as well the selected printing technology capabilities, including the ones used for printing variable information such as lot or serial number, manufacturing date, and expiry date.

Printing intended to convey information should have no missing print, smears, smudges, or offset that renders it incorrect or illegible. Font sizes or styles could be inappropriate for specific substrates or label dimensions or printing technologies. Print colour(s), artwork placement and copy should also be considered. Printed ink properties need to ensure physical and chemical resistance to degradation.

One way to reduce the amount of space needed on the labels is to use symbols. This also avoids having to provide the information in multiple languages. The regulations allow that information can be provided as internationally recognized symbols. Symbols from standards such as ISO 15223-1[58] can be used

or, if a suitable symbol is not included, the symbol used needs be described in the instructions for use (IFU).

NOTE For information, in relationship with medical device regulation (EU) 2017/745[59], it has to be pointed out that the SBS has to be clearly identified as such and be labelled with an instruction to consult the IFU if the SBS is damaged or unintentionally opened before use. An appropriate symbol can be used. For healthcare facilities, application of a label to indicate the SBS can be an appropriate solution. The EU Medical Device Regulations (MDR[59] and IVDR[72]) use the term *Sterile Packaging* which can be considered equal to the term *Packaging System* as used at the point of use.

All labelling and information requirements that are given in regulations are often too extensive to be printed on the SBS on many of the smaller single use medical devices such as needles, small filters, contact lenses, syringes, etc. These products need to address the information somewhere else on the unit or in the packaging protective packaging.

6 Guidance on Clauses 5-8 of ISO 11607-2:2019

6.1 General Clauses 1-4 of ISO 11607-2:2019

See Clause 4 of this document.

6.2 Validation of packaging processes – general requirements (ISO 11607-2:2019, 5.1.1 and 5.1.2)

6.2.1 Intent

The purpose of these subclauses is to provide the framework for packaging process validation to produce objective evidence that the process is capable to consistently manufacture SBSs meeting all predetermined requirements and specifications.

6.2.2 Guidance

ISO 11607-2 provides examples of processes that must be validated. The commonality of these processes is that they include a closure or sealing operation with the objective of achieving closure or seal integrity.

The document introduces the process validation steps to be included: an installation qualification (IQ), an operational qualification (OQ), and a performance qualification (PQ).

There are slight differences in the definitions compared with the previous edition of ISO 11607-2. In an effort to align definitions with those for sterilization standards, the definitions have been adapted, but this has no impact on the actual activities performed under IQ, OQ and PQ.

Process validations should be performed to a predefined validation plan, protocols, and/ or standard operating procedures.

Historical data can be used after it has been determined that this data is suitable for use. A rationale should be documented.

NOTE The 2004 guidance document on process validations from the International Medical Device Regulators Forum (Global Harmonization Task Force archival) [73] provides guidance on statistical methods and an example of a sealing process validation.

6.3 Process specification (ISO 11607-2:2019, 5.1.3)

6.3.1 Intent

The process specification is a living document that includes all equipment, process variables and parameters, monitors and materials required to manufacture a product that consistently meets requirements (see also ISO 11607-2:2019, the definition under 3.15 for process specification). The process specification is an output of process development and it is traceable to the predetermined packaging design specification; it is the basis for process validation.

6.3.2 Guidance

The process specification is a new concept first introduced in ISO 11607-2:2019. The process specification is a document (or series of documents) that describes all of the equipment, fixtures, variables, parameters, process steps, controls, monitors and procedures required to complete the SBS. Process validation begins with identification of variables and when complete results in confirmed process parameters for those variables.

It is important to note also the difference between a *process parameter* and a *process variable*, terminology that is used more consistently in the document than in the previous version. In the 2019 edition, the concept of *critical* process parameters is discontinued and replaced by the *process specification* that includes all variables and parameters that have an impact on the process output. The degree of control and required monitoring should be a risk-based decision, depending on the role that a variable or a process parameter plays in the process and the impact they could have on the process output. For example, sealing variables like temperature, pressure and dwell time have a direct impact on the sealing quality and lack of control to the specified parameters poses an immediate and high risk for the integrity of the seals. These should be included in every sealing process specification. Depending on the complexity of the process, further parameters need to be considered. For example, low film tension in a form-fill-seal machine can increase the risk of folds if the film is not held tightly which could result in seal integrity issues. Attention is drawn in particular to the definitions of *control*, *monitoring*, *process parameter* and *process variable* in ISO 11607-2:2019.

NOTE "Risk based decisions" are a key element of ISO 13485:2016[2], the quality management system implemented by the majority of medical device manufacturers, but also of ISO 9001:2015[3]. See also ISO 11607-2:2019, 4.2.

6.4 Process validation of packaging families (ISO 11607-2:2019, 5.1.4)

6.4.1 Intent

The purpose of this subclause is to provide permission to leverage validation activities over families of similar SBSs or preformed SBSs based on worst case considerations regarding their manufacturing process to reduce the overall validation efforts.

6.4.2 Guidance

Validations can be performed for individual products/processes or for product/process families that are defined based on established similarities. A rationale for the validation of a family of products or processes and the related worst-case considerations should be documented.

Based on similarities between SBS materials, process, products; etc the SBSs may be grouped into families of SBSs or preformed SBSs for example chevron pouches or reels using the same top and bottom materials but of different sizes. Leveraging of validation activities should be based on worst case considerations and is done in an effort to reduce the overall validation activities. In this case, worst-case configuration applies to the SBS manufacturing processes not to the medical device itself. When validating a manufacturing processes, it can then be based on the worst-case SBS and contents.

To ensure that the validation is meaningful for the entire SBS family, the worst-case configuration(s) for the (preformed) sterile barrier family need to be identified based on risk. When heat sealing, it is important to look at the extremes of seal area. For example, both small and large seal areas on pouches and blister packs present unique challenges and should be assessed. For preformed sealed trays and form fill seal blisters, the total square centimetres in the sealing area (i.e. total square centimetres of seal under the sealing platen) could be considered. This approach allows the impact of over-sealing and undersealing as well as temperature and pressure distribution to be assessed.

It is also recommended to assess the different devices within a proposed product family and assess how the device could impact the sealing process. In preformed SBSs such as a pouch or header-bag a large or bulky product can create challenges in sealing operation versus a small and low-profile device. In form fill seal applications, a heavy product can pull on the bottom web more than a lighter product thus causing distortion of the seal flange and should be assessed.

6.4.2.1 Example No. 1

A manufacturer has a family of pouches (preformed SBS or PSBS) with many different sizes from the same supplier with the same top and bottom web materials. It should be possible to seal all these PSBS with the same process and leverage the validation efforts. The manufacturer performs a risk analysis and concludes that there is a risk that larger seal areas could be exposed to colder sealing temperatures at the edge of the sealing platen while the smallest seals could be over-sealed in the middle of the sealing equipment. As there could also be risk that the pressure control will react differently with different sealing areas, the largest and smallest seal areas are included in the validation. Some of the pouches are very long, whereas others are short. The risk of misalignment is greatest for the longer pouches as they are difficult for the operators to handle. This is also the case for the heaviest and bulkiest product. The bulkiest product also represents the greatest risk of creating folds in the seal. Based on these considerations, the manufacturer defines the bracketing to include the largest and smallest seal area as well as the longest, heaviest and bulkiest product.

6.4.2.2 Example No. 2

The same manufacturer decides to validate a second identical machine. A new machine always requires a new validation. IQ is specific to machine No. 2 to make sure that everything is properly installed, calibrated and the documentation is complete. For OQ, process development can be leveraged from the previous validation. The bracketing can be simplified, since the manufacturer comes to the conclusion that the configuration is identical and the risks regarding handling of long pouches by operators are well understood and under control. Although alignment of the machine has been properly checked during IQ, the manufacturer decides to challenge machine No. 2 with the bulkiest product to prove that it can seal without folds similar to machine No 1. Machine No 2 is further challenged with pouches that have the smallest and largest seals to make sure that the machine produces packaging that meets the predetermined specification. During PQ, three lots will be run to confirm that the process on machine No 2 is capable and reproducible meeting specifications. Each situation is unique, and manufacturers should carefully perform their own risk analysis.

The same concept can be applied to other packaging types like reusable healthcare containers or sterilization wrap, for example based on the dimensions, or the weight of the packages or other relevant variables.

A rational for the validation of a family of products and their processes and the related worst-case considerations should be documented.

6.5 Installation qualification (ISO 11607-2:2019, 5.2)

6.5.1 Intent

The purpose of installation qualification is to establish by objective evidence that all key aspects of the process equipment and ancillary systems adhere to the manufacturer's and/or user's approved specifications and the equipment is correctly installed, calibrated and working properly.

6.5.2 Guidance

During the IQ it is verified that all equipment used in the manufacturing process meets specified requirements and is appropriately designed, constructed, placed and installed to facilitate maintenance, adjustments, cleaning and operations.

Examples of typical IQ activities / checks (as appropriate) include:

— availability of the process specification (used as a basis for checking the process);

— verification of installation status compared to installation drawings and instructions (facilities, utilities, space, hook-ups, etc);

— availability of up-to-date equipment documentation (drawings, schematics, spare parts list, manuals, etc.);

— software documentation (i.e. type, version, etc.);

— critical equipment features (i.e. materials of construction, process range, fixtures, ancillary equipment, etc.);

— environmental conditions (i.e. clean room requirements, temperature, humidity, lighting);

— preventive maintenance requirements and schedule;

— calibration requirements and frequency;

— identification of changes/repairs that require re-qualification;

— safety features and requirements;

— system start-up, operation and shut down (including use of software);

— confirm alarms, warning systems, and machine stops operate when equipment process variables are run outside pre-set limits.

Calibration of equipment should be conducted as part of IQ, to ensure equipment has been installed correctly. A calibration and preventative maintenance program/schedule should be established to ensure that they continue to meet the set requirements. Software embedded in the machine or equipment requires a separate validation. Because the details of imbedded software are typically unknown, the validation is usually limited to checking the input and output after installation of the equipment (black box testing). Test documentation or certificates from the supplier can support the validation process.

The validation of custom-made software (developed in-house or outsourced) is usually based on testing all critical functions listed in the user requirement specification (URS).

NOTE For additional guidance on software validation see References [2] and [18].

Healthcare users should see also Annex B of this document.

6.6 Operational qualification (ISO 11607-2:2019, 5.3)

6.6.1 Intent

The purpose of operational qualification (OQ) is to obtain and document evidence that installed equipment produces outputs that meet specification when run at the limits of the operating window and in accordance with its operational procedures.

6.6.2 Guidance

During OQ the process limits will be defined and qualified to ensure that the output of the process meets the process specification, even under conditions of manufacturing that are extremes of the established process window. The upper and lower process extremes are determined by the right combination of high and low settings of the individual parameters for a given material combination. A rationale should be documented for the chosen combination.

This confirms that the process window is appropriate over its entire range. Refer to Annex E of this document for the development of process parameters.

Examples of typical OQ activities (as appropriate):

— perform engineering studies to establish a worst-case operating window by determining impact of process variables listed in the process specification on the closure;

— establish process limits (process parameters) for process variables defined in the process specification (examples: time, temperature, pressure, line speed, etc.);

— determine appropriate sampling plans. Guidance for sampling can be found in 4.5 of this document (ISO 11607-1:2019, 4.3);

— produce a statistical valid number of samples on the extremes of the process limits (e.g. lowest and highest temperature, lowest and highest pressure, and shortest and longest dwell time);

— verify that the SBS produced at operating extremes will reliably meet the acceptance criteria defined in the protocol;

— verify that all control measures defined in the risk management process are in place and operate effectively;

— document all results and conclusions.

Samples for performance testing according to ISO 11607-1:2019, 8.2.2 can be built during the OQ. In this case, these samples would be produced under conditions that can be defined as the worst-case according to ISO 11607-1:2019, 8.2.3.

This approach can also apply to fluid path packaging, variables in that case can be torque to apply a closure, for example.

Healthcare users should see also Annex B of this document.

6.7 Performance qualification (ISO 11607-2:2019, 5.4)

6.7.1 Intent

The purpose of performance qualification (PQ) is to establish by objective evidence that the process, under anticipated conditions, consistently produces a product which meets all predetermined requirements.

6.7.2 Guidance

During PQ, it is examined and shown that the process is under control and capable of consistently producing products which meet the requirements. It is important to include all-natural variation that also occurs in practice in the PQ. Consideration should be given to different operators, process start-ups and stops, raw material batches, maintenance, time factors like morning and afternoon or summer and winter, wear and tear, etc.

The PQ study can be based on a required number of dedicated PQ runs with all necessary variation included. Alternatively, it can be based on the required number of real manufacturing runs with

material on hold until data is considered sufficient. In both situations, the size of the PQ runs should be sufficient to be statistically valid.

Examples of typical PQ activities (as appropriate):

— running at nominal conditions using typical manufacturing environments and including typical variation;

— running a statistically valid number of units /lots / batches (across shifts, operators, time, etc.);

— verify that the produced SBS meets the acceptance criteria defined in the protocol and assess process capability;

— documentation of deviations from the protocol;

— documentation of the conclusion: is the process considered validated?

Three successful production runs are typically evaluated under PQ, however it is possible that more production runs are necessary to successfully complete the validation. These runs are produced at normal operating conditions and the runs can be interrupted by other manufacturing processes on the equipment. Considerations should be given to sufficient run time, warm up time after start-up and the effects of transitions to different products, breaks, and multiple shifts.

6.8 Formal approval of the process validation (ISO 11607-2:2019, 5.5)

6.8.1 Intent

The purpose of this subclause is to make sure that all validation data and results are documented, reviewed and approved including all related conclusions.

6.8.2 Guidance

The documentation should include the development of a written process validation protocol before starting any validation activities. This can be one document covering the entire validation or a separate document covering IQ, OQ and PQ.

Validation protocols may be written for SBS families. The rationale for determining the SBS families to evaluate should be documented.

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

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.

For OQ and PQ, the acceptance criteria need to be detailed. These predefined requirements typically include dimensions of the SBS(s), seal strength, seal integrity, opening features, and material integrity depending on the equipment and the type of SBS.

The process validation protocol should be reviewed and approved by appropriate personnel prior to any activities taking place.

Assess validation results and the activities performed to verify that they meet the established acceptance criteria. Any deviations from the protocol should be documented and reviewed and assessed to determine if the intent of the validation protocol has been met.

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

6.9 Process control and monitoring (ISO 11607-2:2019, 5.6)

6.9.1 Intent

The purpose of this subclause is to make sure all necessary controls and monitoring activities are in place to maintain the process in a state of control and capability.

6.9.2 Guidance

Ongoing process control and monitoring typically includes

a) monitoring and recording process parameters and variables;

b) in-process testing of SBSs in accordance to the quality system.

NOTE Selected monitors should 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.

Recommended tests are integrity, seal strength, peeling behaviour, and visual inspection.

Peeling should be continuous and homogeneous, without delamination or tearing of the material (see ISO 11607-1: 2019, 5.1.9 d)).

NOTE For applicable test methods refer also to ISO 11607-1:2019, Annex B.

6.10 Process changes and revalidation (ISO 11607-2:2019, 5.7)

6.10.1 Intent

ISO 11607-2:2019, 5.7 introduces the requirement to manage changes and revalidations based on a review of the impact of the change so that the validation status is maintained after implementation.

6.10.2 Guidance

6.10.2.1 General

Change control is a fundamental element of state-of-the-art quality systems. A formal change control procedure is required for conformance with ISO 11607-2:2019, 5.7. Since the 2019 edition, the change control requirement is also included in ISO 11607-1 to cover design changes while this subclause covers the changes that affect the process validation status (see ISO 11607-1:2019, Clause 9). If packaging specification is met after a process change, there is no need to consider revalidation of the packaging design.

Keeping design and process validations separate is recommended for two reasons:

a) in case of failure, it will be much easier to perform root cause analysis, the source of issues can be easier identified and corrected;

b) in case of revalidation, it is easier to revalidate those elements that are really affected.

6.10.2.2 Process change examples: new sealing heating element in a sealing equipment

In case of a replacement of part of sealing equipment, with potential impact on variables that have high influence on the process output, it is obvious that at least a confirmation study should be considered to show that the package design specifications are being met.

If the sealing heating element is replaced with the same original equipment part, then the following targeted activities should be considered:

— IQ can be reduced in scope to focus only on the replaced part to make sure that it meets the specifications and that it is properly installed and connected.

— OQ needs to focus on the areas that can be influenced by the new heating element or by the installation process: SBSs should be produced again at both the upper and lower process limits to reconfirm those limits and to make sure that they meet predefined specifications.

— PQ should demonstrate that the equipment with the new heating element will consistently produce SBSs that meet predefined requirements. The focus needs to be on the variability that could be introduced by the new part, while other sources of variability have already been considered during the initial validation.

This way of proceeding assumes that the previous validation has been performed properly, still represents the state of the art and there are no issues for which a complete revalidation should be considered.

NOTE It is not recommended to validate the process with different elements or modules available as spares and to take them into service at a later date without considering a revalidation at that time. Over time other subtle changes could have occurred that could impact the results and the installation of the new element or module is a source of variability in itself.

If a sealing element is replaced with a similar but different part (e.g. a different type of material, a different PTFE layer, different pressure rolls, etc.) then it will be necessary to review this modification for the risks of potential impacts on the SBS or on the process. Most of the time the modifications are designed to improve the long-term reliability of the process, but some can have an impact on the process sealing window. For instance, different PTFE layers can reduce the heat transfer. It could be necessary to increase the heat-sealing temperature to compensate for the lower heat transfer. Coating thickness variability over the heating element surface could lead to sealing uniformity issues. This needs to be investigated and confirmed during OQ. The long-term process reliability can be confirmed during PQ and by putting in place additional controls during normal operation. Coating adhesion needs to be inspected as well as any wear that could lead to contamination or changed seal properties.

6.11 Assembly (ISO 11607-2:2019, Clause 6)

6.11.1 Intent

The purpose of this clause is to define basic requirements regarding appropriate environmental conditions during assembly, to assemble following established instructions based on a validated process and to control labelling to prevent mislabelling.

6.11.2 Guidance

6.11.2.1 General

The clause referred to above highlights three key risks that need to be controlled:

a) risk of contaminants due to lack of controls of the work environment;

b) risk of mislabelling due lack of controls in the assembly process;

c) risk of sterilization issues due to packaging configurations that diverge from those that were at the basis of the validation of the sterilization process.

6.11.2.2 Environmental conditions for forming, sealing and assembly processes

ISO 11607-2:2019, 6.1 requires minimizing the risk posed by contaminants to the medical device. It is obvious that the focus is on the device, however, as packaging materials are or can be in contact

with the device or as contaminants can be transferred to the device through other mechanisms than direct contact, this should be applied also to materials. A good practice is to establish a risk analysis of contamination risks in the defined work environment and to define measures to mitigate those risks appropriately so that the work environment becomes a controlled environment. This risk analysis should consider personnel (work attire, hygiene, drinking and eating, access control), pest control, heating and ventilation, moving materials into and out of the production environment, process equipment including its maintenance, transitions to different products, product mix ups, cleaning activities, waste handling, etc. and cover all stages of the manufacturing process.

NOTE 1 For companies that have implemented ISO 13485:2016[2], this is done during the product realization planning activities to define the infrastructure, the work environment and the contamination control measures and it will become part of the quality management system documentation. See 6.3 and 6.4 of ISO 13485:2016[2].

NOTE 2 Further information on classified environments can be found in ISO 14644-1[74].

Users should also refer to 5.2 of this document on conditions for production and handling and ISO 11607-1:2019, 5.1.3.

6.11.2.3 Labelling and processing procedures

Labelling systems can take several forms, including printing directly on the material and /or SBS, or labels consisting of another layer of material attached to the surface of the material and/or system by adhesion, fusion or other means.

Typical process steps:

a) Process steps for labelling generally include printing and inspecting the information to be conveyed, as well as affixing labelling to the package when not printed directly on package. In case of information by handwriting on the package, consult 5.10.2.6 b) of this document.

b) In some cases, SBS materials or preformed SBSs can be received pre-printed by the medical device packager, and additional information can be added at the time of closure.

c) The steps in the process should be documented and operating procedures developed for each step.

These procedures typically include but would not be limited to acceptance criteria for legibility, direction on placement, verification of adhesion, verification of information and be developed with specific safeguards to prevent mislabelling. Risk management principles should be applied to the process.

6.11.2.4 Assembly instructions

The way packages, unit boxes and larger unit box are assembled, can have an impact on the sterilization process. The packaging density and orientation of products will impact the radiation dose delivered to the product, and shadowing effects need to be considered. For gaseous sterilization processes, gas or steam needs to penetrate the package and residuals need to be evacuated which is considered when designing the packaging configuration. It is therefore important to clearly define the packaging configurations that were at the basis of the sterilization validation so that these configurations can be reproduced during assembly. Deviations from the defined configuration can negatively impact the validation status of a sterilization process. Deviations can also lead to packaging performance issues (i.e. sterile barrier integrity issues) during handling, distribution and storage.

See Annex F of this document for more details on sterilization methods and aspects to consider. MDMs should refer to Annex A of this document and integrate these requirements into their design process. Healthcare users should refer to Annex B of this document.

6.12 Use of reusable sterile barrier systems (ISO 11607-2:2019, Clause 7)

6.12.1 Intent

This clause requires users to consider requirements provided in ISO 11607-1:2019 when using reusable SBSs.

6.12.2 Guidance

When performing operations for reusable SBSs, the reader is referred to ISO 11607-1:2019, 5.1.10, 5.1.11 and 5.1.12. The reason for referring to the standard is that the requirements listed in those subclauses are very prescriptive in terms of activities to be performed during the cleaning, filling, assembly and closing of reusable SBSs. This guidance is inclusive of both reusable containers and textile wrap SBSs, as the subclauses in the standard are referencing both types.

See also B.4.4 of this document on reusable container design and use for further guidance.

6.13 Sterile fluid path packaging (ISO 11607-2:2019, Clause 8)

6.13.1 Intent

The purpose of this clause is to make sure that the assembly process of sterile fluid path components is validated in order to achieve the same outcome as for other SBSs.

6.13.2 Guidance

See 5.21 of this document on sterile fluid path packaging.

The process specification needs to include all the variables and parameters as well as any controls and monitoring activities to maintain the sterile fluid path assembly and closure process in a state of control and capability.

NOTE Some examples of variable and parameters can include torque, pull force, dimensional tolerances including tolerance stack up analysis.

Annex A
(informative)

Design and development for packaging systems – guidance for industry

A.1 Design inputs

A.1.1 General

In addition to the guidance given in the body of this document for ISO 11607-1:2019 6.2.2 and 6.2.3, this annex provides further guidance on effectively developing a packaging system. For guidance on design inputs see also 5.20 of this document.

A.1.2 Manufacturing guidance

Prior to initiating 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, and use a risk-based approach to the analysis.

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.

   NOTE For medical device manufacturers that use contract manufacturers for packaging operations, it is important to verify the contract manufacturer has the minimum manufacturing requirements implemented in their quality system.

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 a packaging system that is 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 SBSs is SBS process validation. The time and cost of validation activities for sterile barrier forming, sealing and assembly should be addressed prior to SBS 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.

A.1.3 Marketing guidance

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 plan for the medical device. This information will be used to drive several key decisions regarding the packaging system design.

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, as for example intended use of the SBS, conditions of use and opening 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.

A.1.4 Budget guidance

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.

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.

d) Resources: Determine human resources and external competence resources needed.

e) Deadline: Determine time needed and deadline for the project.

Though an important factor in business decisions, a budget does not influence conformance with either part of ISO 11607-1:2019 and ISO 11607-2:2019.

A.1.5 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.

A.2 Sterile barrier system and protective packaging design (packaging system development)

A.2.1 Key elements in the design

A key component of the packaging system design process is gathering and assessing the design inputs (ISO 11607-1:2019, Clause 6). 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.

SBS and protective packaging (i.e. packaging system) design can be performed in conjunction with a contract packager. Guidance on the use of contract packagers is available in Annex G of this document.

A.2.2 Selection and evaluation of materials

A.2.2.1 General

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. When selecting appropriate materials, environmental aspects should also be considered, see Annex D of ISO 11607-1:2019.

A.2.2.2 Guidance on sterilization requirements (ISO 11607-1:2019, 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 F of this document.

A.2.2.3 Material physical properties

ISO 11607-1:2019, 6.2.2 requires for the selection and qualification of appropriate materials and preformed SBS to consider at a minimum the properties evaluated under ISO 11607-1:2019, Clause 5. Some typical material physical properties that can be considered are listed in this section. Additional properties are listed in 5.5.2.5 of this document.

The shape and mass of the medical device, the type of protective packaging (if applicable), and the transport and storage systems will all play an important role in defining the SBS and/or packaging system as well as its materials. While the only definitive means of establishing the appropriateness of a packaging system is through actual use with the medical device, a number of standard physical properties provide a base for evaluating potential materials for use in a given application. 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 selection of these physical properties is included in Table A.1.

Table A.1 — Typical material properties

Property	Description
Puncture resistance	The puncture resistance of a material could be important to consider if the medical device contains sharp edges or protrusions that may penetrate the packaging material, destroying its integrity.
Abrasion resistance	Abrasion resistance is the ability of a surface to withstand the effects of repeated rubbing, scuffing, and scratching. During distribution this can occur between: — the medical device and the SBS; — the SBS and 2nd SBS; — the SBS and the protective packaging.
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.
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.

Table A.1 *(continued)*

Property	Description
Bond strength	The bond strength is the amount of force needed to separate interlaminate plies of a material.
Wet strength	The wet strength could be important to consider if the packaging is sterilized in wet conditions as moist heat and EO.
Permeation Properties	The permeation properties of a material may be important to consider if a medical device is sensitive to the ingress or egress of moisture, oxygen, carbon dioxide, or other gas.

A.2.2.4 Guidance on optical requirements of materials

There are several standard test methods which can be used to test optical properties of packaging materials to assess if they meet 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[75]. Gloss, which is the reflectance or surface sheen of a substrate, can be determined with ASTM D2457[76]. Opacity is the ability of a material to stop the transmission of light, more information on which can be found in ISO 2471[77].

Visibility and appearance requirements, if applicable, will be determined by the desired aesthetics (for example an SBS with high gloss versus one with a matte finish), labelling approach (for example, a label insert could require an SBS with good clarity), and the desire to see (or mask) the device. Areas to consider are haze, gloss, opacity, and clarity. Some examples of material properties for these attributes are also included in Table A.1.

For test methods for the above-mentioned properties, refer to Annex B of ISO 11607-1:2019.

A.2.2.5 Material processing guidance

Many SBS 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[78] for linear measurement guidance.

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 SBS and/or packaging system processing. See ASTM D1894[79] for further guidance.

SBS formation and sterility maintenance are dependent on sealability. Packaging materials can seal at a variety of conditions. Therefore, the characterization of the sealability of a packaging material can 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 can vary from one piece of equipment to another. See ASTM F2029[80].

Porosity, stretch (elongation) and printability are also important considerations. Excessively porous materials can lead to issues with vacuum operated automatic handling equipment, whilst material with too low porosity may give issues with the carton packing of product. Stretch (elongation) can be an important factor since too much stretch can lead to problems maintaining print registration on automatic packaging lines. Packaging materials with comparatively stable stretch (elongation), and smooth and flat surfaces will give significantly improved reproduction of fine type and machine-readable codes.

A.2.3 Steps in packaging system design

A.2.3.1 Design the sterile barrier system

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

a) preformed tray and lid;

b) preformed pouch;

c) preformed sterilization bag;

d) preformed header bag;

e) reusable containers;

f) self-contained products with tortuous path closures;

g) those requiring fabricating of SBS and making all seals – form/fill/seal and four-side-sealing.

Specify and document the materials, dimensions, tolerances, geometry, and physical characteristics of the SBS, based on the design inputs and in accordance with the procedures outlined in the quality system.

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

A.2.3.2 Design the protective packaging

Specify and document the materials, dimensions, geometry, and physical characteristics of the protective packaging, in accordance with the procedures for the design and development.

A.2.3.3 Prototype the packaging system

a) Produce a prototype of the packaging system to determine if it is physically as intended by the designer. If the 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 can be found in A.4.

A.2.3.4 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.

a) 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 usability of the packaging system.

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

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

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

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

f) 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.

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

h) Procedures should to be developed to maintain labelling processes under control to prevent mix-up of labels and to prevent devices from being mislabelled (see also 6.11.2.3 of this document). It is also important to examine labels for accuracy in correct expiration date, control number, storage and handling instructions or other relevant information.

A.3 Packaging process feasibility evaluation

A.3.1 General

This clause proposes a process to assess the feasibility of the packaging process.

NOTE Conducting a packaging process feasibility evaluation is not a requirement of ISO 11607-1:2019 or ISO 11607-2:2019.

A.3.2 Sterile barrier system manufacturing process

Define the manufacturing process for the chosen SBS. 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 SBS 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 C of this document). Indicate packaging system material and medical device movement. For guidance on determining process parameters, see Annex E of this document.

A.3.3 Equipment installation qualification guidance

Determine equipment IQ requirements for each stage/piece of equipment defined in the process map or flowchart. See 6.5 of this document for IQ guidance.

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.

A.3.4 Trial run with Prototypes

During process development produce prototype packaging system for initial testing. This is recommended as it reduces the risk for failure during validation of the packaging process.

Prototype SBSs should be produced using process parameters that are to be used for SBS testing.

A.4 Packaging system design feasibility evaluation

A.4.1 General considerations

This is an engineering evaluation in which the 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.

This testing typically assesses:

a) the condition of the post stress effects on the packaging system, labels and labelling;

b) whether the packaging system containing the medical device and managed to protect it from being physically damaged;

c) possible physical interactions between SBS and contents (e.g. protrusions, breaches, etc.);

d) SBS integrity.

Root cause analysis should be performed in case of identified issues.

NOTE Conducting a design feasibility evaluation is not a requirement of ISO 11607-1:2019 or ISO 11607-2:2019.

A.4.2 Packaging system design feasibility plan

Use a documented test plan employing validated test methods.

This test plan should include pass-fail criteria.

SBS tests should be conducted on samples that have been constructed considering the worst-case elements (ISO 11607-1:2019, 8.2.2) and manufacturing of samples should be as much as possible within a standard manufacturing processes flow.

A.4.3 Worst-case feasibility condition

To properly determine feasibility, determine worst-case conditions and configurations to be tested, 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) SBS manufacturing (sealing parameters, etc.);

b) sterilization process (parameters, number of cycles, etc.): it could 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 could be sold in many packaging system configurations. As an example, it could be sold as a single medical device in an SBS with protective packaging in a box with the necessary labels and labelling. It could also be sold as a box of 12, 12 SBSs with protective packaging in a single box with the required labels and labelling. It could also be sold as 50 SBSs with protective packaging in a single box with all the required labels and labelling. There could be pallet size units of sale as well.

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

e) distribution environment: this requires an understanding of the conditions under which the medical device will be shipped to the customer;

f) 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 11607-1:2019, Annex B.

A.4.4 Pass/fail status of packaging system

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

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.

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 could include redesigning the concept and repeating feasibility. Guidance on determining failure mode and appropriate corrective action is available in Annex I of this document.

Annex B
(informative)

Guidance on the application of the ISO 11607 series in healthcare facilities

B.1 Introduction

Packaging is a vital step in reprocessing. The user requires knowledge of the quality and type of packaging required to maintain the sterility of medical devices. Packaging is available in many types and this annex will address the types, quality and techniques used in healthcare settings.

This annex is intended to provide comprehensive guidance for safe and reliable packaging of reusable medical devices.

This annex provides guidance on essential elements for the evaluation, selection, inspection, and proper use of preformed SBSs, SBSs, and packaging systems. The selection criteria are based on the requirements of ISO 11607-1:2019 and ISO 11607-2:2019 to help healthcare settings choose packaging systems that are appropriate for their intended use.

This annex applies to the following:

1) sealable sterilization pouches and reels;

2) sterilization wraps including

— reusable sterilization wrap;

— disposable sterilization wrap;

3) reusable sterilization container systems including trays and cassettes intended for use in sterilization processes that do not rely on wrapping.

In addition, this annex addresses items intended to facilitate aseptic presentation such as protective organizing cases or trays that require additional wrapping or an additional method of containment for sterilization and maintenance of sterility.

This annex provides guidance in the following areas:

a) policies and procedures related to the use of packaging;

b) general characteristics, selection, and purchasing of packaging;

c) evaluation of the design, performance, and labelling of packaging;

d) matching of packaging to appropriate sterilization methods and cycles;

e) testing and validation prior to use for

— processes of preparation, assembly and sealing or closing of packaging including wrapping methods;

— packaging performance and stability;

— aseptic presentation and use;

f) quality assurance.

B.2 General requirements

The healthcare facility should follow a documented plan for evaluating the choice of SBSs. 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 policy of the facility. In ISO 11607-1:2019, Clause 11 provides a list of information to be provided that can 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.

In healthcare facilities, the design and selection of appropriate SBSs and/or packaging systems should be based on risk management. Each healthcare facility could have multiple and different aspects to consider, such as but not limited to equipment, staff, transport and storage constraints.

Therefore, individual risk management typically includes:

a) identification of potential failure mode(s) in the packaging process, transport, storage and associated risk (i.e. for loss of sterility);

b) determination of process failure modes that require mitigation;

c) selection and implementation of action plan(s) to ensure that those packaging process failure modes are controlled and monitored.

B.3 Design and development guidance for packaging systems (ISO 11607-1:2019, Clause 6)

B.3.1 Design and development planning

When planning for the most appropriate packaging solution for sterile devices, it is important to focus on the priorities, which are the ability to effectively sterilize, physical protection of the medical device, the maintenance of sterile barrier integrity (i.e. sterility) to the point of use and the ability to aseptically transfer the content to the sterile field without contaminating or damaging it.

B.3.2 Design and development inputs

The following are typical inputs to be considered.

— type of devices, specific requirements;

— sterilization volumes to be handled;

— methods of sterilization;

— packaging methods, sealing equipment;

— labelling requirements;

— CSSD controlled environment requirements;

— transport from CSSD to points of use or storage;

— storage environment;

— operating room: controlled environment requirements;

— types of surgeries practiced;

— end user requirements;

— personnel handling packaging

— applicable standards, best practices, local recommendations and regulatory requirements;

— packaging waste handling requirements.

B.3.3 Packaging design and selection considerations

When a healthcare facility determines which packaging system to use, the design and development guidance for those packaging systems should be considered (see requirements in ISO 11607-1:2019, Clause 6). When a healthcare facility uses a contract packager or sterilizer additional considerations are necessary (see Annex G of this document).

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;

NOTE 1 In some parts of the world, EN 868 series[21-26] are used to support specific requirements of ISO 11607-1

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

NOTE 2 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 F of this document.

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

f) allow for aseptic presentation at the point of use;

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

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 SBS or packaging system conforms with ISO 11607-1, that requirements concerning product compatibility are met and that processes for packaging, sterilization, storage and distribution are validated and controlled.

The selection process at the healthcare facility should include an evaluation of the ability of both the SBS and protective packaging (if required) utilized to maintain the integrity of that SBS 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 healthcare procedures practiced at the facility. These risks should be analysed by the healthcare facility and procedures put in place to mitigate/control those risks (see Annex C of this document).

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

1) Duration and conditions of storage can affect the type of SBS or packaging system needed. Some items may be stored for some time before use and may require a more durable SBS and/or the

addition of protective packaging. The more the SBS or packaging system is handled the greater the probability that cracks, lid deformation, gasket damage, tears, holes or material separation could occur.

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

3) 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. Examples of packaging components are pouches within pouches, trays within pouches, inserts inside of pouches or trays, other packaging accessories, etc.

4) 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 could significantly increase the risk of loss of integrity of the package, compromise aseptic opening or contaminate the contents.

5) The need for single-layer or multi-layer packaging should be considered according to the risk analysis and national requirements, best practices or recommendations. Refer also to ISO 11607-1:2019, 6.1.8, or 5.17 of this document, on requirements for multi-layer packaging to make sure that protective packaging and SBS are properly identified.

B.3.4 Sealing Equipment Considerations

It is recommended to use only sealing equipment manufactured and intended for preformed SBSs.

NOTE 1 Sealing equipment without a reproducible process cannot be validated. E.g. simple bar sealers without fixed settings for process variables are not suitable for sealing of SBSs in healthcare facilities because they cannot be validated.

The sealing equipment should be capable of monitoring the following sealing process variables:

— temperature;

— pressure;

— dwell time/speed.

The sealing equipment should be equipped with a temperature controller. The sealing temperature tolerance typically should not deviate by more than ± 5 °C from the specified target temperature. Tolerances for pressure and dwell time are typically determined by the manufacturer of the sealing equipment.

NOTE 2 For sensitive SBSs (e.g. made from polyolefin nonwovens) it could be necessary that the sealing equipment allows for flexible adjustment of alarm-levels within a tighter temperature band.

The optimum sealing temperature is established and confirmed during process validation. After defining the temperature (process variable), it should be ensured that only trained personnel (administrator) can change the parameter. Operators should have been suitably trained, fully comply with appropriate operating procedures and stay within the validated process limits.

It is best practice that the sealing equipment stops the sealing process and/or alarms the user to ensure that the packaging process is under control and within the established parameters (see ISO 11607-2: 2019, 5.6: process control and monitoring).

A total seal width of at least 6 mm is considered best practice for healthcare pouches. In the case of ribbed seals, the sum of the rib widths would be at least 6 mm following this recommendation. For all

seals the peelability and aseptic presentation should be assessed. A seal width larger than 12-15 mm is generally not considered good practice as it will be difficult to peel open.

NOTE 3 This best practice is based on EN 868-5[47]. As this is a minimum requirement it can be necessary to use sealing equipment that produce larger sealing seams. This recommendation does not apply to SBSs for supplied single use medical devices.

The sealing equipment should be equipped with calibrated sensors for the process variables and these should be recalibrated on a regular basis.

NOTE 4 A calibration on-site could avoid transportation influences.

B.3.5 Assembly considerations

The sealing equipment should be maintained following the recommendations provided by the manufacturer. 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 end user is protected from injury and the SBS and medical device is protected from damage.

c) Associated components can be used inside the SBS 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 or associated components should:

   — be non-toxic;

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

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

   — allow for and be compatible with the intended sterilization process;

   — have the ability to withstand conditions of the 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 F of this document.

   — not undergo chemical or physical change after sterilization or within specified shelf-life to such an extent that the performance or safety is impaired or the medical device that they contact is adversely affected;

   — not compromise aseptic presentation;

   — allow for easy identification of contents;

   — 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.

B.4 Common choices for sterile barrier systems

B.4.1 General

Healthcare facilities are using mainly, but not limited to, the following packaging types:

— sealable pouches and reels;

— sterilization wrap;

— reusable container.

Preformed SBSs should be evaluated before purchase and use. It is useful to have a provided statement of conformance to the applicable clauses of ISO 11607-1: 2019 for the materials and/or preformed SBSs to be purchased. Before introducing associated components (e.g. labels, tapes, tray liners) into production, users should confirm that they will be suitable and validate them for use in their specific applications and conditions of use.

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 an SBS.

B.4.2 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 reel 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 can cause rupture. There should be enough space to make seal closure possible. Too many small items in the SBS can cause the items to move around, rupture the seal, penetrate or abrade the package materials. Thin or fragile materials can be damaged during handling, distribution and storage.

b) If not specified otherwise by the manufacturer the preformed SBS 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 SBS. 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 could 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 SBS integrity. Special attention should be paid to proper method of closure to ensure package integrity.

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[81].

i) The pouch should be opened according to the manufacturer instructions. If a specific peel direction is needed to prevent delamination or shedding of fibres during opening, then that peel direction 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 are used for the packaging of medical devices of diverse dimensions that do not easily fit standard preformed pouch sizes. 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. For pouches formed from reels, to reduce the risk of fibre release in the seal area at opening and support aseptic opening it is important utilize validated conditions that permit peelability.

k) Attention should be paid to the importance of conducting scheduled maintenance and calibration of the sealing equipment and periodic validation of the sealing process.

B.4.3 SBS sterilization wrap

B.4.3.1 General

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 healthcare 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 could impede sterilant penetration.

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

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, various strengths of tapes are also available. 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 11607-1:2019, 5.1.12).

— Manufacturer should provide instructions for use, cleaning/laundering, and storage so that barrier qualities are not compromised by improper handling or use of wrappers. The healthcare facility should establish procedure based on those instruction to conform with ISO 11607-1:2019, 5.1.12 b).

— The continued acceptability of each type of wrapping material should be monitored and maintained by means of a quality assurance system that includes an inspection of all wrappers before using them for packaging. ISO 11607-1:2019, 5.1.10 requires that manufacturer provide guidance on inspection technique. Possible inspection techniques are by means of a light table and by doing a water resistance test. In case of integrity issues, the material should not be used anymore.

NOTE Annex B of ISO 11607-1: 2019 includes a list of appropriate tests, for example ISO 811[82].

— It is important that the manufacturer provides information about microbial barrier and maintenance of integrity over time in relation to the repeated use. Instruction for use should also include information on how the end of service life can be recognized by users.

— The components of a wrapper (e.g. glues, threads, bias binding, any mending or repair materials) should be compatible with the base material and should not compromise the microbial barrier of the completed product.

B.4.3.2 General information about wrapping methods

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 can be performed sequentially or simultaneously.

Different methods can be used for the different layers, however for any wrapping method, it should be ensured that the end users opening the package

— understand how the wrapping is performed;

— understand the configuration of the wrapping in terms of SBS and protective packaging (see 5.17 of this document on double entry packages);

— can aseptically present the sterile contents (see usability evaluation in B.7).

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.

B.4.3.3 Envelope method

B.4.3.3.1 Simultaneous double envelope method

The wrapping and unwrapping steps are illustrated in Figures B.1 to B.4.

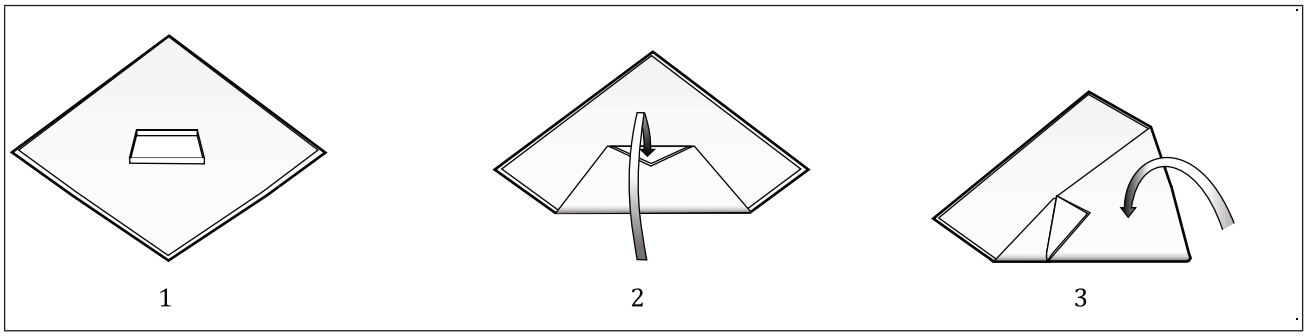


Figure B.1 — Simultaneous double envelope method steps 1 to 3

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.

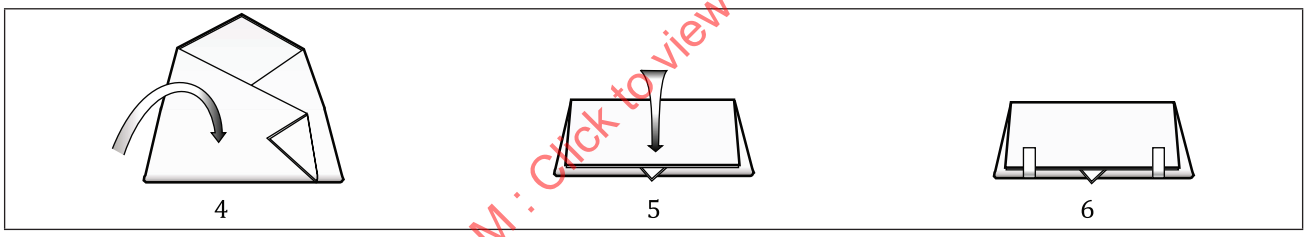


Figure B.2 — Simultaneous double envelope method steps 4 to 6

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.

The unwrapping steps for aseptic presentation are illustrated in Figure B.3. This figure illustrates the simultaneous double wrapping, but the single wrapping works in the same way. A usability evaluation (see 5.22 of this document) should be performed considering the actual use conditions and environment.

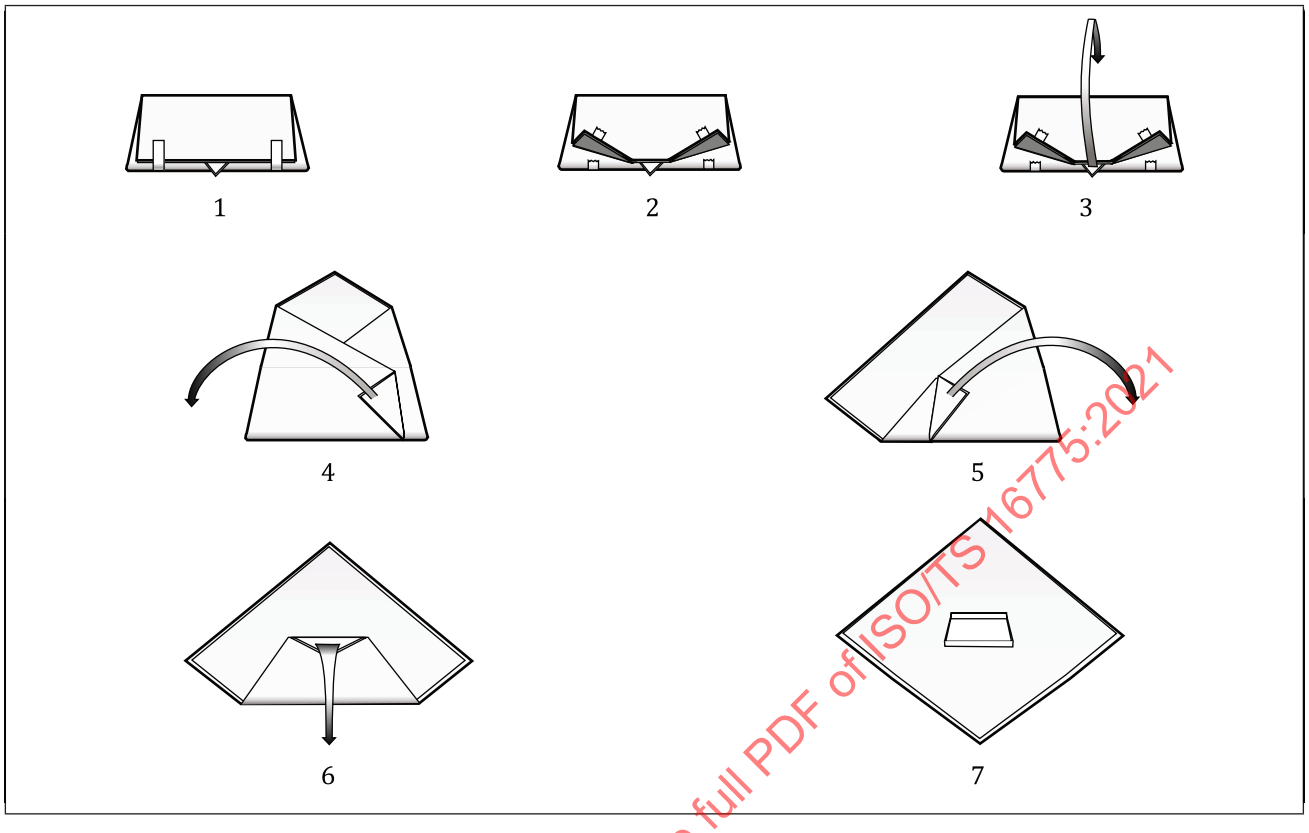
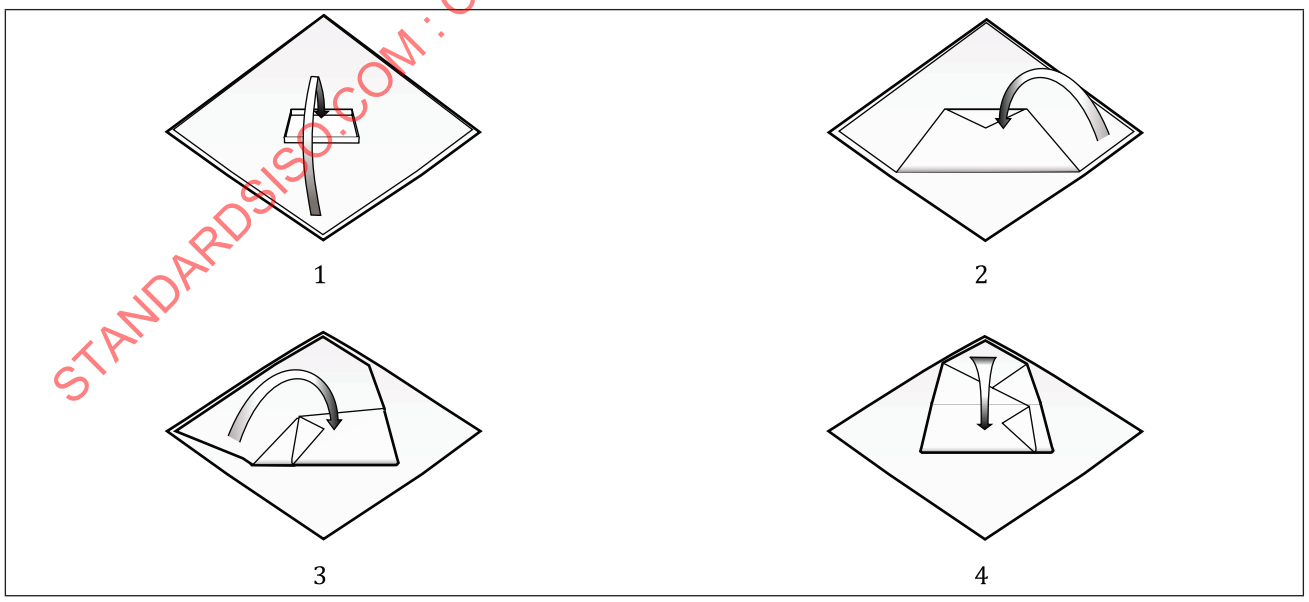


Figure B.3 — Aseptic opening of simultaneous double envelop wrapping

B.4.3.3.2 Sequential double envelope method

Figure B.4 illustrates the sequential double envelope method.



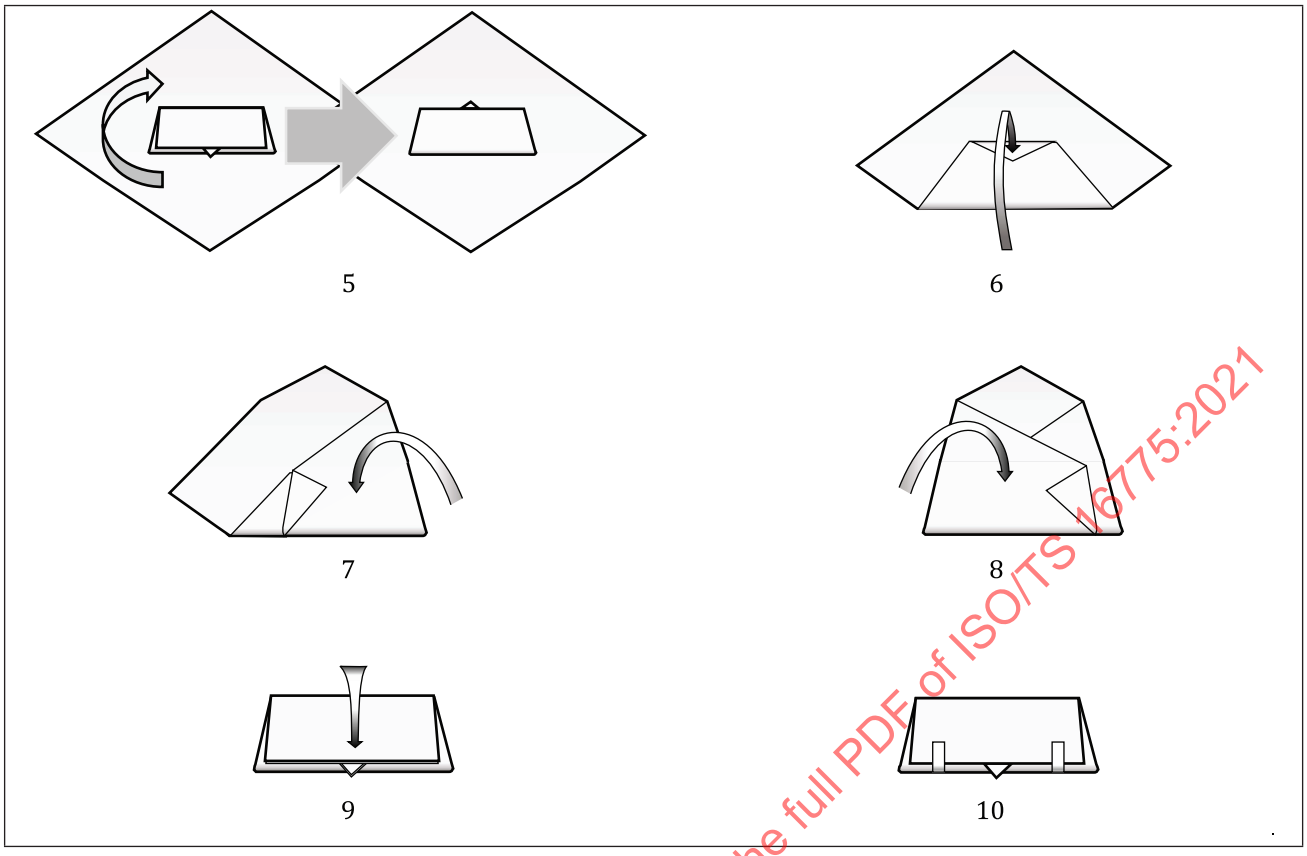


Figure B.4 — Sequential double wrapping envelope method

The unwrapping steps for aseptic presentation are illustrated in Figures B.5 and B.6. These figures illustrate the unwrapping sequential double envelope. A usability evaluation (see 5.22 of this document) should be performed considering the actual use conditions and environment.

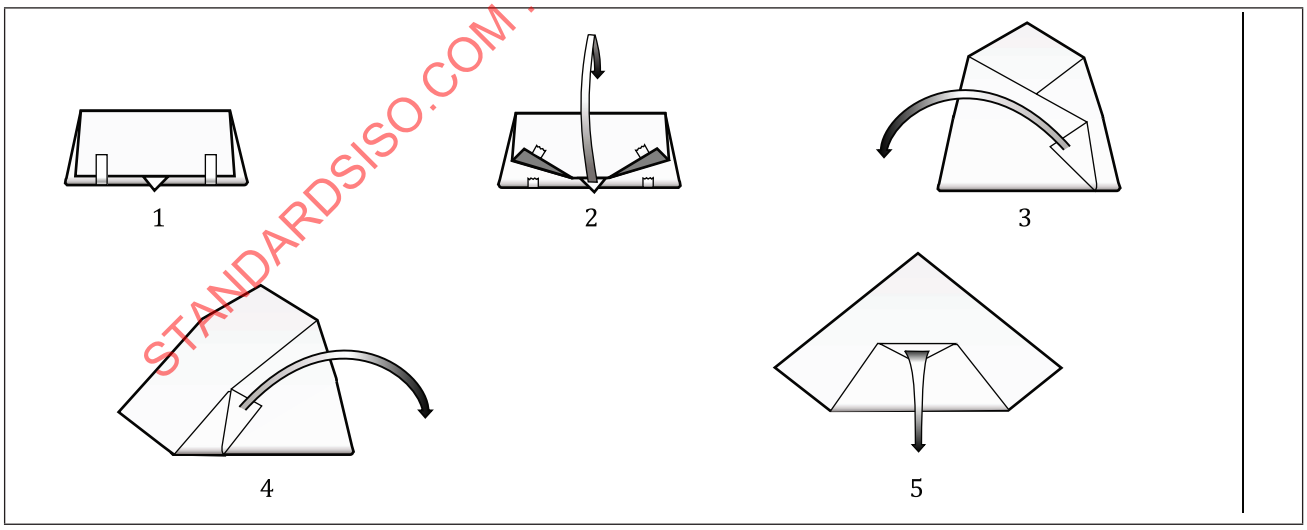


Figure B.5 — Aseptic opening of sequential double envelope wrapping by the non-sterile nurse

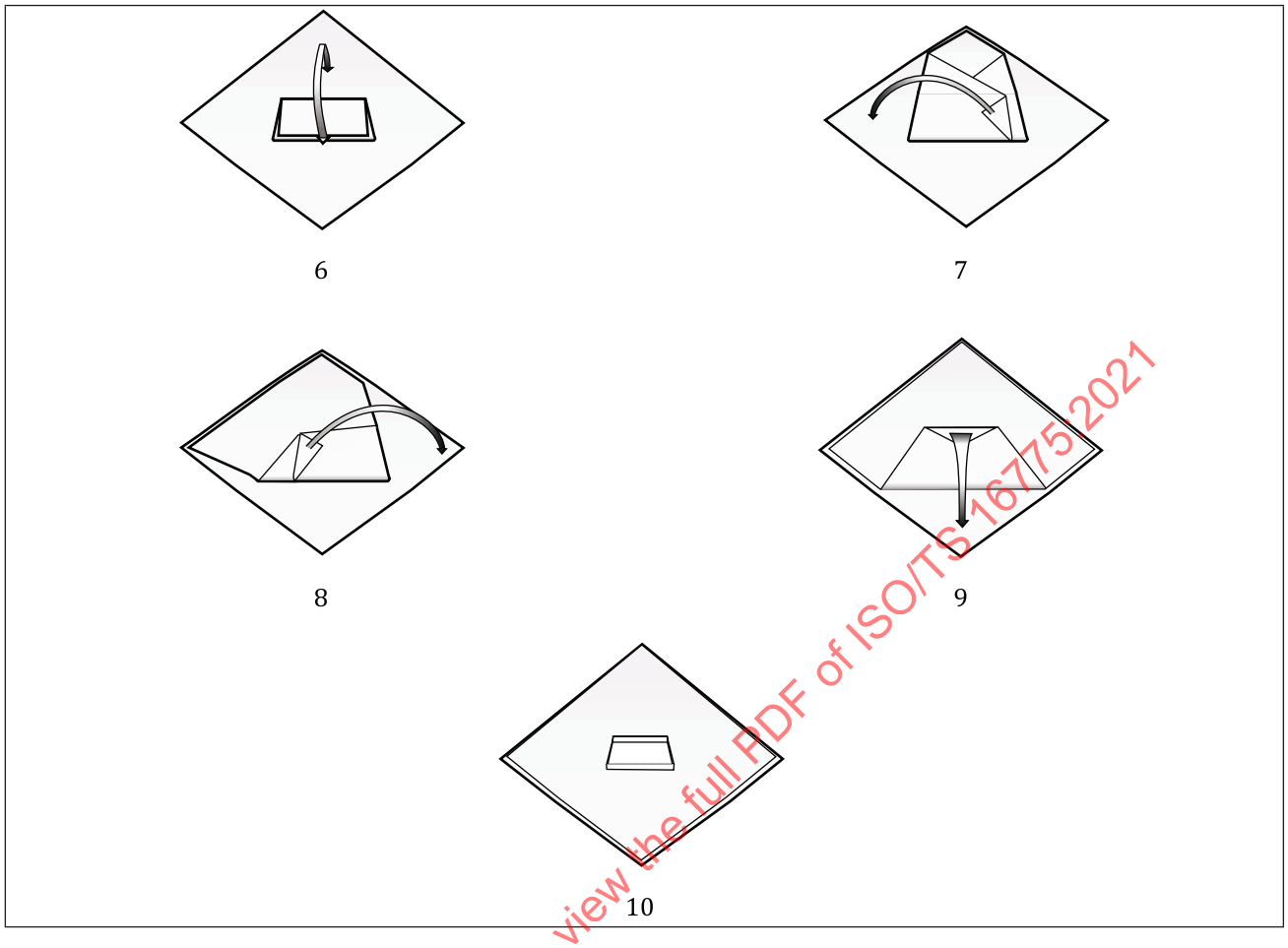


Figure B.6 — Aseptic opening of simultaneous double envelop wrapping by the sterile scrub nurse

B.4.3.4 Square fold / parallel wrapping method

B.4.3.4.1 Simultaneous double square fold / parallel wrapping method

The steps for simultaneous square fold / parallel wrapping are illustrated in Figures B.7 to B.9.

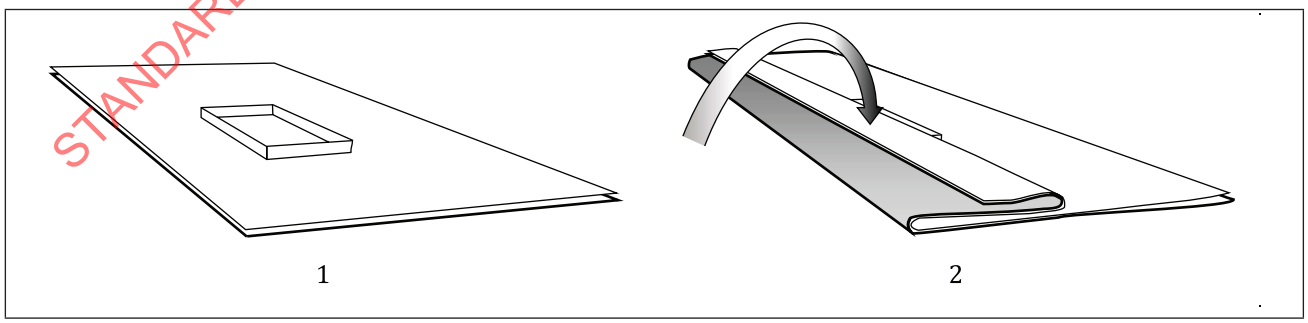


Figure B.7 — Simultaneous square fold / parallel wrapping steps 1 to 2

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

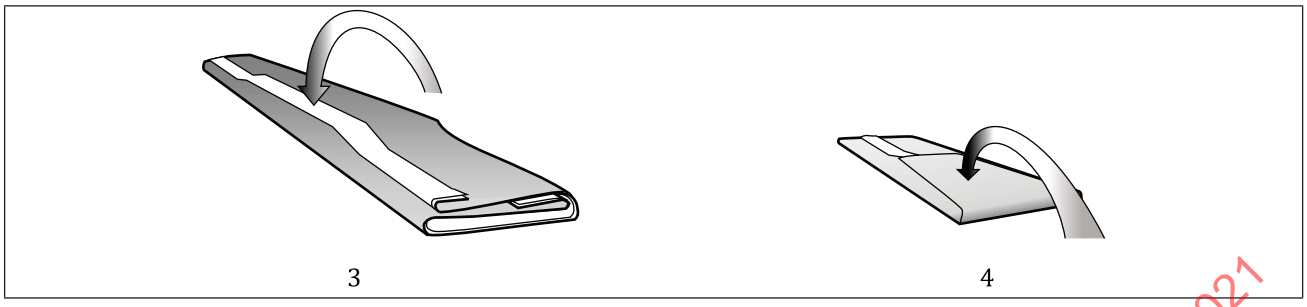


Figure B.8 — Simultaneous square fold / parallel wrapping steps 3 to 4

Step 3:

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

Steps 4 and 5:

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

Step 6:

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

Figure B.9 — Simultaneous square fold / parallel wrapping steps 5 and 6

The unwrapping steps for aseptic presentation are illustrated in Figure B.10. This figure illustrates the unwrapping of the square fold simultaneous double wrapping. A usability evaluation (see 5.22 of this document) should be performed considering the actual use conditions and environment.

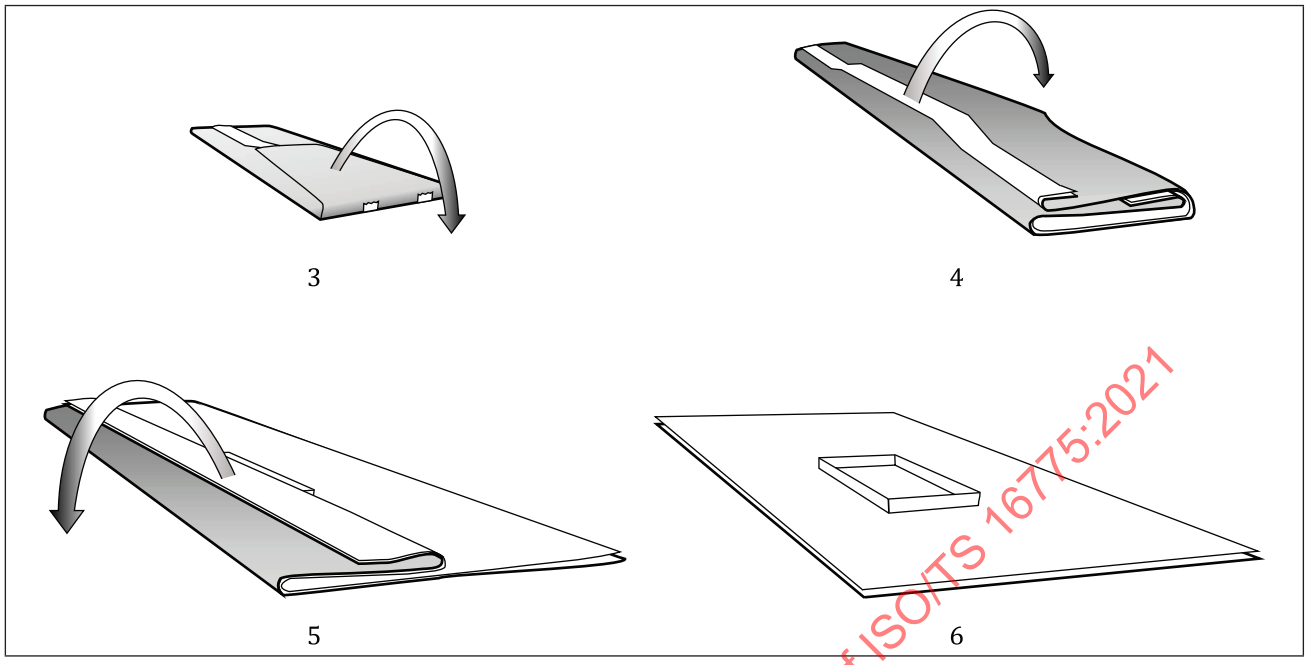


Figure B.10 — Aseptic opening of square fold simultaneous double wrapping by the non-sterile nurse

B.4.3.4.2 Sequential double square fold / parallel wrapping method

Figure B.11 illustrates the sequential double square fold or parallel wrapping method.

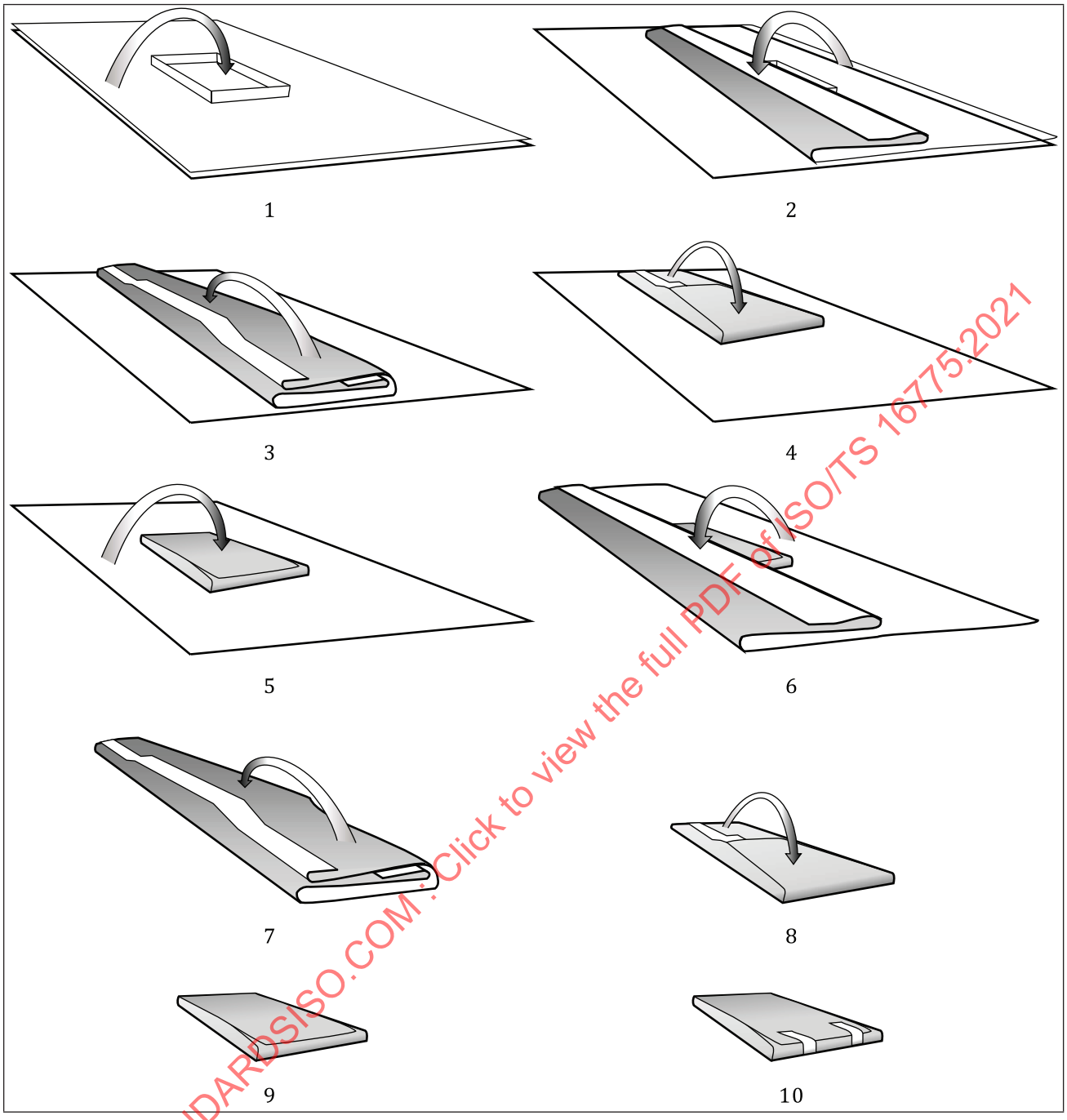


Figure B.11 — Square fold sequential double wrapping

The unwrapping steps for aseptic presentation are illustrated in Figures B.12 and B.13. These figures illustrate the square fold sequential double wrapping. A usability evaluation (see 5.22 of this document) should be performed considering the actual use conditions and environment.

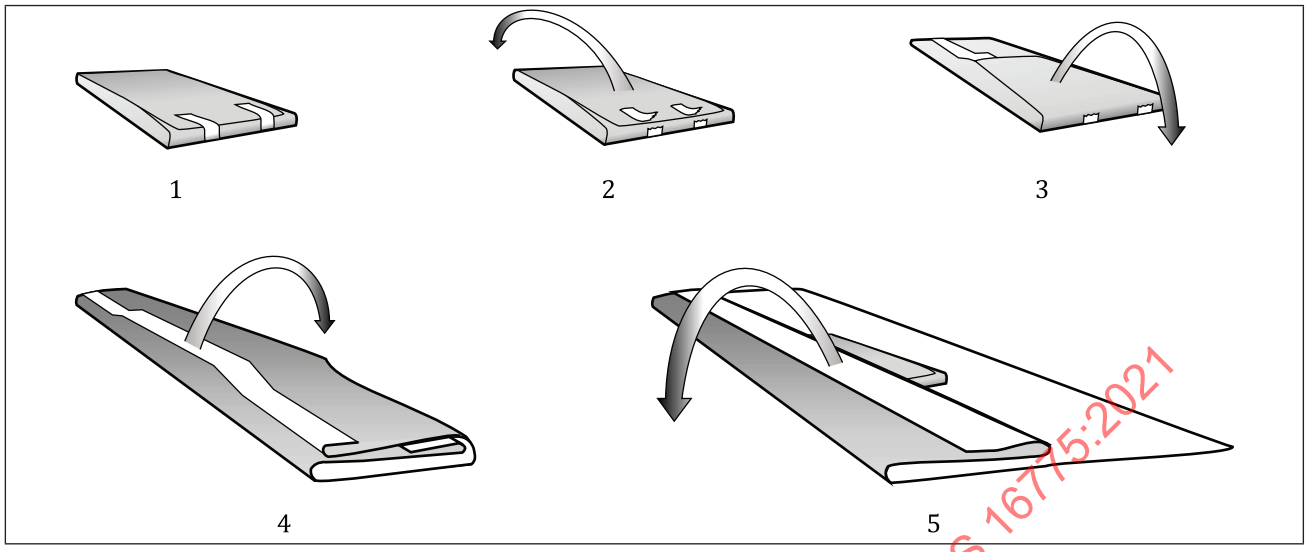


Figure B.12 — Aseptic opening of square fold sequential double wrapping by non-sterile nurse

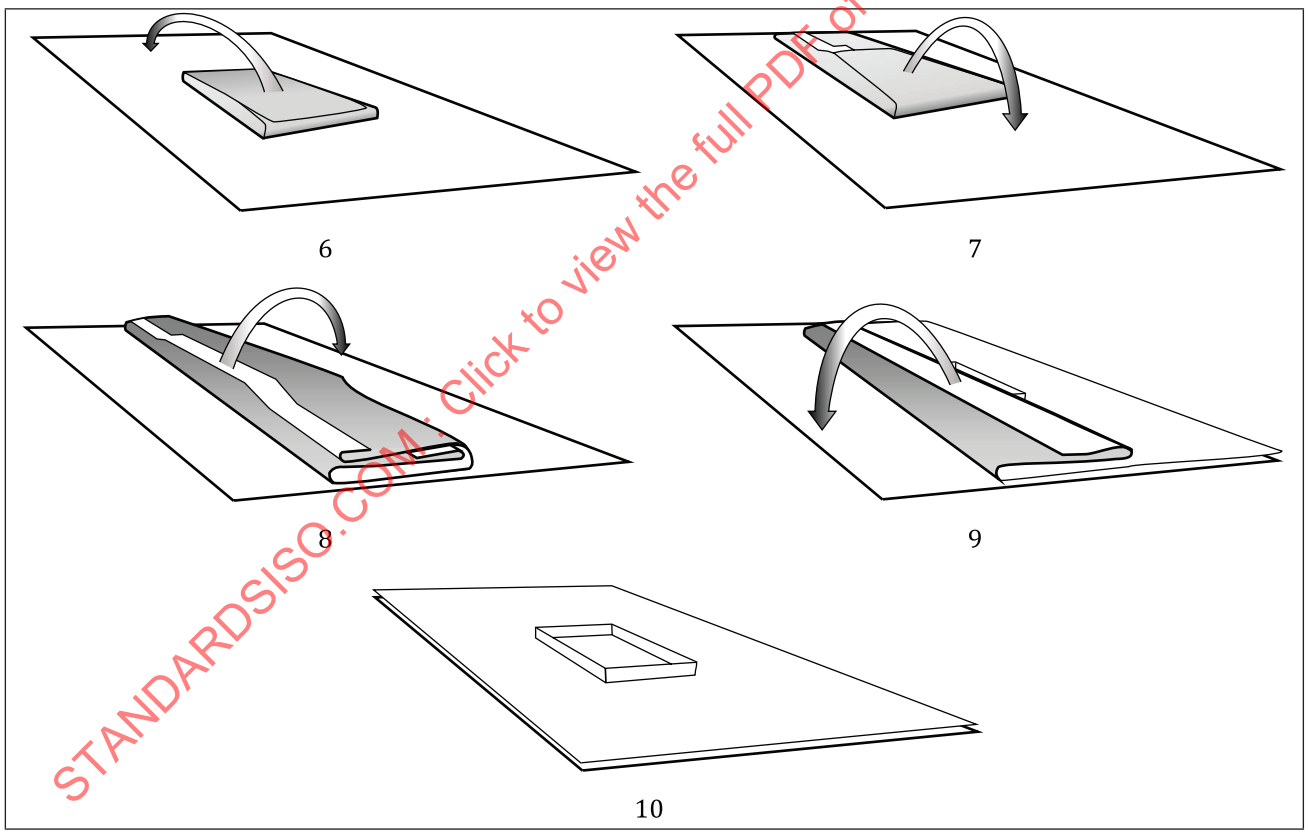


Figure B.13 — Aseptic opening of square fold sequential double wrapping by sterile scrub nurse

B.4.4 Reusable containers

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

Instrument cases, cassettes or organizing trays are containment devices but not SBSs. They should be contained in an SBS.

When using rigid reusable containers, the following should be considered (see requirements in ISO 11607-1:2019, 5.1.10):

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

b) Reusable 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 reusable container manufacturer's instructions and indicate that the SBS has not been opened and therefore the contents exposed to potential contamination before intended use.

d) Each reusable container should have a visible identification label and/or information card. 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 reusable container.

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

g) Procedures should be in place for the cleaning, disinfecting and maintenance processes for reusable containers after each use. These processes should be validated. Reusable containers should not be used beyond the manufacturer's stated usable life (see requirements in ISO 11607-1:2019, 5.1.12). Procedures should be in place to ensure that the manufacturer's stated usable life is not exceeded (see requirements in ISO 11607-1:2019, 5.1.12).

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

B.4.5 Protective packaging

Protective packaging can 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 SBS in particular could require protective packaging to be applied to ensure that distribution and handling does not affect the SBS. Sterilized packages should be handled as little as possible. Loss of SBS integrity is regarded as event related rather than time related, therefore it is so crucial to guard against damage to the SBS.

When protective packaging is used, the SBS should be clearly identifiable. Protective packaging is designed to provide additional protection against damage and outside elements or against damage from the device itself. In this sense protective packaging can be outside of the SBS or inside, but in both cases the objective is to protect the SBS against loss of integrity (e.g. trays, baskets, etc.). Some devices come with a protection (e.g. a tip protector) that is an accessory of the device and it can be used to protect the SBS and the end user. The IFU should be consulted to see if it is appropriate to leave these protectors on the devices during sterilization as some protectors might adversely affect the sterilization process. If protective packaging is to be applied after steam sterilization, it should be applied once the items are thoroughly cool and dry.

To facilitate aseptic presentation, trays can be wrapped with sterilization wrap prior to placement in an SBS (see figures B.14 and B.15).

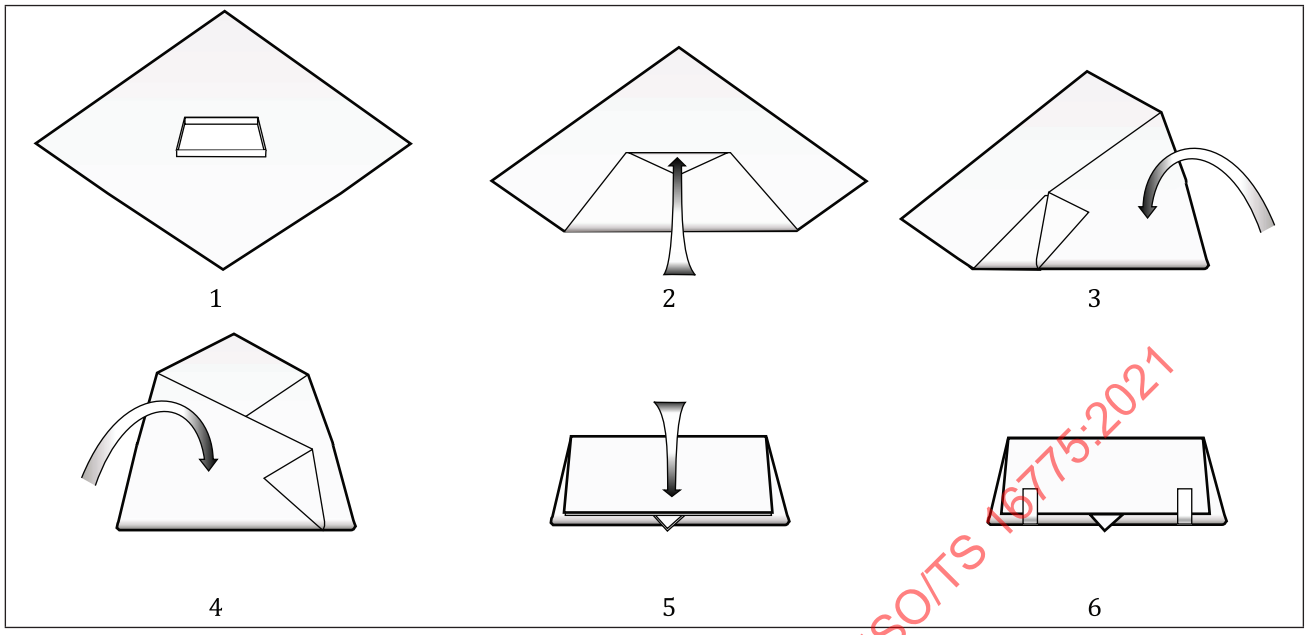


Figure B.14 — Single Envelop Method for inner wrap – wrapping

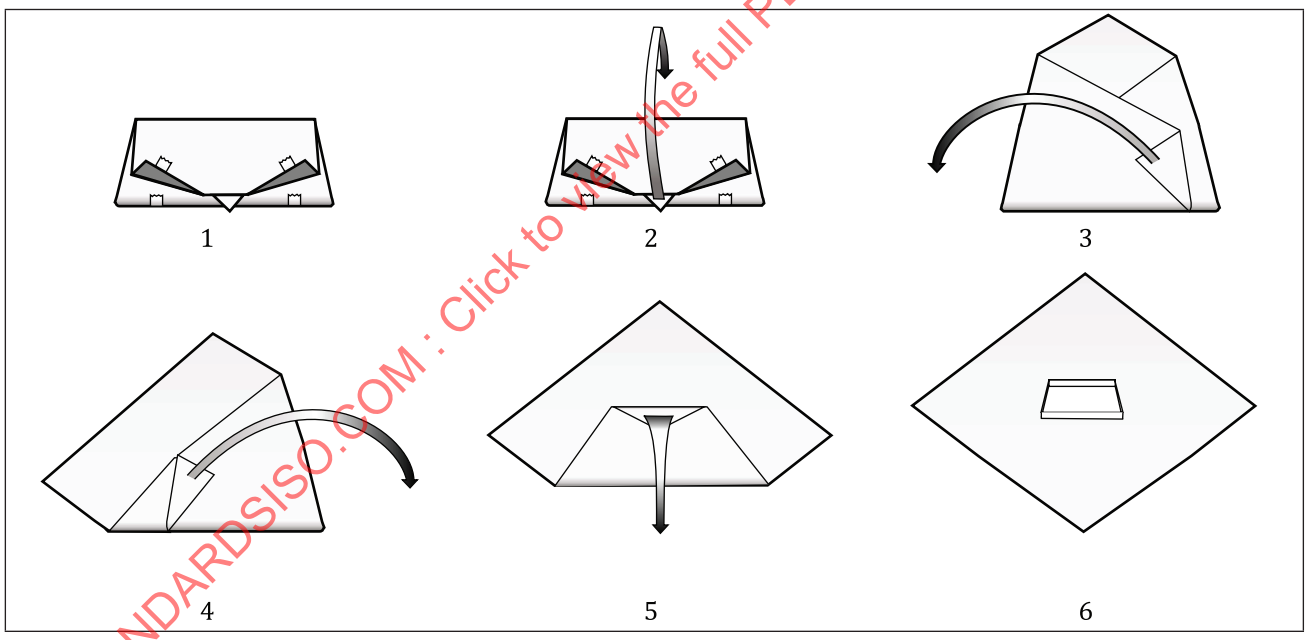


Figure B.15 — Single Envelop Method for inner wrap –Aseptic opening

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

B.5 Packaging system performance testing (ISO 11607-1:2019, 8.2)

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 SBS or packaging system holds up to the rigours of anticipated conditions of handling, distribution and storage, before and after sterilization. The SBS needs to maintain its integrity without any holes, tears or seal/closure rupture that can 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:

   — Assembly of SBSs which contain the medical device configuration which presents the greatest challenge to the SBS (e.g. biggest, heaviest, most dense, sharpest items see ISO 11607-1:2019, 8.2.2).

   — 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 can 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 SBS.

   — Sterilization of the SBS in the intended sterilization process, considering mixed loads or fully loaded sterilizer chambers.

   — Handling / distribution / storage / opening of the SBS.

Consideration should be given to the environment and other conditions in which the SBS or packaging system will be stored. Packaged products 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, healthcare facilities should visually inspect the sample SBSs 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 can be found in ISO 11607-1:2019, Annex B.

If an SBS is designed to be reusable and a degradation of performance characteristics is predicted by the manufacturer (see ISO 11607-1:2019, 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.

B.6 Sterile barrier system stability evaluation (shelf life) (ISO 11607-1:2019, 8.3)

Evaluation on the ability of the SBS materials or preformed SBSs to maintain their performance characteristics and seal integrity over time is normally performed by the manufacturer of the preformed SBS (see also requirements in ISO 11607-1:2019, 8.3.6).

NOTE 1 Suggested storage conditions and shelf life can be provided by the material or preformed SBS manufacturer. If anticipated or actual storage is outside these conditions the manufacturer should be consulted.

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

Loss of SBS integrity is regarded as event related rather than time related and is dependent on the performance of the SBS or packaging system, as well as the possible interaction between the medical device and the selected SBS, 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, limiting exposure to dust and sunlight, keeping 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 SBS can be greatly influenced by adequate inventory control and management systems.

NOTE 2 National or regional guidance can 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.

B.7 Allowing for aseptic presentation

The opening of the sterile packaging and the transfer of the device(s) into the sterile field while maintaining sterility is an essential and critical last step to provide sterile devices for a clinical procedure. The packaging needs to allow for easy opening without contaminating or damaging the device such that it supports aseptic presentation techniques to minimize the risk of microbial contamination. See also 5.13 of this document for further guidance on aseptic presentation as part of the design input for sterile packaging systems. When healthcare facilities implement their packaging solutions for the various device families based on standard packaging configurations, the following should be considered for aseptic presentation:

a) The end user requirements and the specific clinical procedure requirements including the requirements of any controlled environments.

b) The device requirements, size, weight, risk, etc.

c) The specific requirements and potential hazards of the standard packaging configurations based on the supplier's information. See also B.4 of this annex with guidance on specific packaging configurations.

NOTE The opening of large pouches can be more difficult if the enclosed content does not stabilize the package. Opening of large packs can be improved by using a table if this is possible. Transfer of the device can be difficult if the packaging is too small compared to the device.

d) The assembly requirements of the device(s) and its packaging to support transfer of the device (see also B.3.5 in this annex on assembly considerations).

e) The specification of sealing and closures to support easy opening.

f) When defining adequate protective packaging, this should include when such packaging should be removed and what protective packaging should be opened at the point of use.

g) Providing required labelling, easily readable in an appropriate location with an indication of the SBS(s) if the packaging to be opened at the point of use consists of more than one packaging layer (see also 5.17 of this document on requirements for multilayer packaging).

h) Establishing specific instructions for end users for aseptic presentation if required.

The recent version of ISO 11607-1:2019 introduces a new requirement to conduct a usability evaluation to demonstrate that an SBS or packaging system meets the requirements and allows for aseptic presentation. See 5.22 and 5.23 of this document on evaluation of aseptic presentation and on leveraging this for device families as well as how to deal with usability evaluation failures. For healthcare facilities the following can be considered for such usability evaluations:

1) Device and packaging families should be defined to leverage the effort. A family could be defined for example for all reusable containers with baskets, for sterilization wrap with internal baskets, for pouches with individual devices, etc. For the pouches, the evaluation could then focus on the worst-case devices, the largest, the heaviest or the smallest.

2) The evaluation should ideally be conducted with the end users, normally available more easily in a healthcare facility. This allows also to assess the status of training and to define any training needs.

3) Usability evaluation observations should be noted. These observations could result in actions to deal with failure or to further optimize the packaging or training of personnel. In case of failure a re-evaluation will be necessary after any changes have been made or if instructions for use are required, see also 5.24 of this document.

NOTE Most medical device manufacturers will be conducting their packaging usability evaluations as part of their overall device usability studies following US FDA guidance[61] or IEC 62366-1[60].

B.8 Validation requirements for forming, sealing and assembly processes

B.8.1 General

ISO 11607-2:2019 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;

— reusable 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 healthcare 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 11607-2:2019 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 can 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.

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 B.8.2);

b) implementation of validation (see B.8.3) consisting of:

— IQ (see ISO 11607-2:2019, 5.2);

— OQ (see ISO 11607-2:2019, 5.3);

— PQ (see ISO 11607-2:2019, 5.4);

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

d) validation approval (see B.8.4);

e) process control and routine monitoring (see B.8.5);

f) process/packaging changes and revalidation (see B.10).

B.8.2 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 SBS, loading and closure of reusable container);

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

d) description of SBS contents utilized. SBSs should be assembled as for normal use, see B.3.5 and B.4 of this annex;

e) description of the sterilization process (e.g. moist heat sterilization at 134 °C and 121 °C, Ethylene oxide (EO), vaporized hydrogen peroxide (VH2O2), low temperature steam formaldehyde (LTSF)), including the process parameters and loading configuration used;

f) description of transport, distribution and storage of the respective SBSs;

g) qualification steps (IQ, OQ and PQ), (see ISO 11607-2:2019, 5.2, 5.3 and 5.4) for further explanations for each process see B.9.1, B.9.2, B.9.3 and B.9.4 of this annex;

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

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) establishing and confirming procedures for process control and monitoring to maintain an effective process;

k) validation approval.

The validation plan checklists in Annexes K, L and M of this document can be used. A separate validation plan should be used for each different combination of sterilization procedure and SBS and/or packaging system (manufacturer, type, etc.), Table J.1 shown in Annex J of this document can be used for organizational purposes.

B.8.3 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 B.9 of this annex please refer to the following sections: sealing process (B.9.1), wrapping process (B.9.3), and reusable container process (B.9.4).

B.8.4 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 Annex J of this document).

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.

B.8.5 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.

Process parameters should be routinely monitored and documented based on the requirements established in the process specification.

B.9 Validation of common sterile barrier systems use in healthcare facilities

B.9.1 Validation of the sealing process (pouch, reel or bag forming and sealing) of preformed sterile barrier systems

Information on the validation of the sealing process of the preformed seals should be available from the preformed SBS manufacturer, this process validation pertains to the closure seal(s) made at the site of the healthcare facility.

B.9.1.1 Installation Qualification

This means that the sealing equipment 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 operators should be trained on how to correctly operate the sealing equipment.

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) Is the process specification with process variables and parameters defined (e.g. the process parameters should be defined for 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) Does the sealing equipment include systems to control, set or monitor process variables?

NOTE 2 In most cases, temperature is controlled by the equipment while pressure and dwell time or speed are set and monitored.

c) Does the sealing equipment include an alarm, warning system or machine stop in the event that a process variable exceeds the limits?

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

e) Are documented plans for preventative maintenance and cleaning available to the operators?

f) Have all operators been trained how to operate the sealing equipment and has this been documented?

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

The IQ checklist in Annex M of this document can be used for documentation purposes.

B.9.1.2 Operational Qualification

The sealing temperature range to be used in a healthcare facility should be determined by that facility using information provided by the preformed SBS manufacturer and the sealing equipment manufacturer.

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

The sealing equipment manufacturer typically provides information on how process variables are monitored/controlled based on established process parameters.

Contact pressure and seal/dwell time are generally preset 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 SBS manufacturer. In conditions of use different SBSs could require different sealing temperatures.

Using the information provided the operator should seal SBSs 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 5.18 of this document).

Samples should be sealed and evaluated at each adjustable upper and lower parameter limit. For a limit to be considered successfully established, all samples should pass the acceptance criteria. The acceptance criteria for sealed SBSs 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 tearing upon peel opening that would interfere with the aseptic presentation;

f) recommended to check that minimum seal strength is met.

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

In order to achieve the above acceptance criteria after sterilization a minimum seal strength is normally necessary. If the measurement of seal strength is not performed during OQ, there could be a higher risk of not meeting the acceptance criteria during PQ, which would require performing the OQ again.

NOTE 1 EN 868-5[47] 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. In EN 868-5, the seal strength value is determined as the average over the seal width curve excluding 10 % on either end.

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

Seal integrity indicator should consist of the same material as the porous material of the pouch or reel (e.g. EN 868–3[22]). 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).

The OQ checklist in Annex M of this document can be used to define the sealing temperature.

B.9.1.3 Performance qualification

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

The following should be considered:

a) Evaluation of the SBS should be performed after the SBS 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:

   — operator;

   — time and date;

   — sterilization process, parameters and cycle number;

   — SBS materials used;

   — contents of SBS;

   — 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 as specified in the validation plan, see B.8.2.

   In order to achieve the acceptance criteria after sterilization a minimum seal strength is normally necessary.

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

e) Three batches or sets of sealed SBSs should be made; these batches should encompass the potential significant sources of variation such as operator, time of day, material (size, source, lot), SBS contents. Package contents that present the greatest challenge (worst-case) should be included.

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

g) The SBSs 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 B.5 and ISO 11607-1:2019, 8.2.

The checklist for the PQ in Annex M of this document can be used for documentation purposes.

B.9.1.4 Routine monitoring

Optimal process parameters (e.g. sealing temperature) are established and confirmed during process validation. In addition, routine controls have to be defined to ensure that the process stays under control and that process deviations are detected. For example, process deviations could be due to mechanical wear, raw material variations or changes as well as process control issues.

Healthcare facilities should develop a rigorous plan for routine monitoring (e.g. daily verification).

For routine monitoring of the sealing process the following methods are recommended:

Test method:	Specification
Peel Test (EN 868-5[47], Annex E)	Verification of the peelability and fibre tear
Dye penetration test (ASTM F1929[63])	Verification of the integrity of the seal
Seal strengths test (ASTM F88[46]/ EN 868-5[47], Annex D)	Verification of the strength of the seal

NOTE 1 Seal indicators or seal check strips allow visual verification that the sealing instrument is free from scratches, cavities, deposits or folds in the film that could lead to sealing issues.

NOTE 2 A combined application of the test methods is recommended.

The healthcare facility should consider regular monitoring by a separate person observing operators performing the tasks and comparing with expectations defined in the procedures. Deviations should be recorded and reviewed.

B.9.2 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 11607-2:2019, 5.1.1). All appropriate elements and steps of validation detailed in ISO 11607-2:2019, Clause 5 should be addressed.

B.9.3 Validation of the wrapping process (folding and closing of sterilization wraps)

B.9.3.1 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.

B.9.3.2 Operational qualification

There should be a documented procedure for assembly of packages. This method should consider B.3.5 and B.4.3. 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 B.4.3.2).

Packages should be assembled in accordance with a documented procedure. In assembling these packages, the worst-case configuration should be included, see Annex G of this document. Samples should be closed/sealed and evaluated. All samples should pass the acceptance criteria. For guidance on sample size see B.8.2 h) and Annex D of this document.

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

SBSs are evaluated for SBS 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 failure (such as delamination or separation) upon opening;

e) unwrapping or opening should demonstrate that the SBS 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 SBSs the package should be opened and assessed for conformance to the documented assembly procedure.

The OQ checklist in Annex K of this document can be used.

B.9.3.3 Performance Qualification

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

a) Evaluation of the SBS should be performed after the SBS 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:

   — operator;

   — time and date;

   — sterilization process, parameters and cycle number;

   — SBS materials used;

   — closure tape used;

   — contents of SBS.

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 SBSs should be assembled in accordance with the documented procedures of the facility. These three batches should encompass the potential significant sources of variation such as operator, time of day, material (size, source, lot), SBS contents. The contents that present the greatest challenge (worst-case) should be included. If a reusable SBS 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 SBSs 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 B.8.2 h).

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

g) The SBSs 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 Annex K of this document can be used for documentation purposes.

B.9.3.4 Routine monitoring

Inspection steps defined under B.9.3.2 (OQ) above are critical and ongoing vigilance is required during wrapping processes. Any material that does not meet the requirements should be excluded for disposal.

For all grades of wrapping materials used for SBS and/or packaging system, the adhesive performance of closure tape is a critical point to ensure packaging integrity.

Depending on the type of sterilization process, vacuum can provide stress on the packaging and represent a significant challenge for closure tape performance.

Before sterilization, closure tape should be applied and positioned according to initial validation including OQ, PQ as per specified in B.9.3.2 and B.9.3.3.

After sterilization, operators should visually check individual packs and ensure that each piece of closure tape is still properly positioned on the wrapping material.

The healthcare facility should consider regular monitoring by a separate person observing operators performing the tasks and comparing with expectations defined in the procedures. Deviations should be recorded and reviewed.

B.9.4 Validation of the reusable container process (filling, closing and processing of reusable containers before use)

ISO 11607-2 and this guidance addresses filling and closing of reusable containers, but they do not address processing of these reusable containers prior to their reuse. In healthcare application, reusable containers should however be subjected to a defined validated process for washing, disinfection and controls prior to reuse.

When performing process validations using reusable containers, it is important to make sure that the manufacturer's instructions for use (of the reusable container and the washing/disinfecting/sterilizing equipment) are met for each type of reusable container system used. Best practice is for the reusable containers to go through the same decontamination process as the medical devices since reusable containers and medical devices later are to be combined.

B.9.4.1 Installation qualification

Although filling and closing of reusable containers is typically a manual process, the following IQ aspects should be considered:

a) environmental conditions such as cleanliness, temperature, humidity;

b) documented/operated training;

c) operating manual or procedure.

If machine equipment is used, then IQ should be performed in accordance with ISO 11607-2:2019, 5.2.

B.9.4.2 Operational qualification

There should be documented procedures for assessment for damage, filling and closing of the reusable containers. These procedures should consider B.3.5 and B.4.4.

Operators should be trained and assessed for competency. The (standard) operating procedure has to be documented and approved prior to beginning the process qualification.

Reusable containers should be cleaned, checked, loaded and closed with a tamper evident system in accordance with the manufacturer's instructions for use and documented procedure of the healthcare facility. In defining the load of these reusable containers, the worst-case configuration of content should be included, (e.g. reusable container loading with respect to weight, volume, size and material). The validation should also include typical routine activities such as filter changes made by operators. All

samples inspected should pass the acceptance criteria. For guidance on sample size see Annex D of this document. For this qualification the reusable containers can be loaded and assembled at one time or over time using the same reusable container(s), depending on the conditions of use.

Assembled and loaded reusable containers should be evaluated for SBS integrity and proper closure. Acceptance criteria should include, but are not limited to checking:

a) the sealing, mating surfaces of the reusable container bottom 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 closing mechanisms are functioning properly;

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

e) that gaskets are not brittle, securely fastened, and without breaks, cuts or other imperfections;

f) that valve-systems work freely;

g) closure continuity and integrity;

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

i) ability to open the reusable container without damage to contents;

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

k) tamper evident mechanism is effective and intact.

The OQ checklist in Annex L can be used.

B.9.4.3 Performance Qualification

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

Evaluation of the SBS should be performed after the SBS 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:

   — operator identification;

   — time and date;

   — sterilization process, parameters and cycle number;

   — SBS materials used;

   — any tamper evident closure used;

   — contents of SBS.

b) Three batches or sets of closed SBS(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), SBS contents. The contents that present the greatest challenge (worst-case) should be included into the validation. If the same SBS 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 B.8.2 h).

d) The SBSs 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 Annex L of this document can be used for documentation purposes.

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

B.9.4.4 Routine monitoring of reusable container processes

Inspection steps defined under B.9.4.2 (OQ) above are critical and ongoing vigilance and verification of functions is required during cleaning, disinfection, assembly and closing of reusable containers. The requirements of the manufacturer in the instructions for use of the reusable sterilization container must be followed. Reusable containers that do not meet the requirements should be excluded and send for repair or disposal according to the recommendation of the manufacturer.

The healthcare facility should consider regular monitoring by an authorized person observing operators performing the tasks and comparing with expectations defined in the procedures. Deviations should be recorded and reviewed.

Reusable containers should be inspected after sterilization and any visible deformation or damage to the filter should lead to questioning the load and to do a thorough investigation.

Before opening and unloading a reusable sterilization container, it should be confirmed that all locking parts are in place and not broken and the tamper evident system is intact.

NOTE In some countries, reusable container integrity test guidance[83] has been or is under development. There are no global consensus integrity test methods available at this stage and there is no requirement for water tightness of reusable containers in ISO 11607-1:2019.

B.10 Process/packaging changes and revalidation

Packaging designs and 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 1 See 5.28 of this document on packaging system validation and changes as well as 6.10 of this document on process changes and revalidation.

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

— SBS material changes;

— new or modified 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 SBS 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 could involve significantly changed challenges to the package);

— exchanging or changing critical parts or modules of a sealing equipment with potential influence on established parameters;

— changes in storage environment, such as high relative humidity, poor storage possibilities, etc.

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.

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).

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.

Annex C
(informative)

Risk analysis tools — Guidance for industry and healthcare facilities

C.1 Applications

There are a multitude of applications for risk analysis.

NOTE For more information on risk management refer to ISO 14971[8], ISO TR 24971[84].

C.1.1 Use/applications/system

This analysis looks at the packaged medical device from the user's perspective once the medical device is shipped to understand:

a) end user requirements and hazards;

b) ease of use, i.e. opening/presentation;

c) medical device application and hazards;

d) medical device identification, and sequence of use in case of multiple parts.

C.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).

C.1.3 Process

The manufacturing process could 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).

C.2 Risk analysis tools

C.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 risk priority number (RPN);

g) rank RPNs (Pareto format) and determine recommended action;

h) record action taken and determine the resulting RPN;

i) follow-up.

C.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 hazardous situations or possible harm;

b) determine failures, or combination of failures, that will lead to the named hazardous situations or harm;

c) prepare a diagram of a fault tree;

d) use the fault tree to intercept or design out unacceptable consequences.

C.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 D
(informative)

Considerations for sampling plans – Guidance for healthcare facilities

Sampling plans is a complex topic. The following information is intended to provide an overview of sampling plan considerations.

ISO 11607-1:2019 and ISO 11607-2:2019 both state in 4.3, "The sampling plans used for testing of materials, SBSs or packaging systems shall be applicable to materials, SBSs or packaging systems being evaluated. Sampling plans shall be based upon statistically valid rationale."

NOTE 1 Examples of suitable sampling plans are given in ISO 2859-1[9] or ISO 186[85]. Additional sampling plans can be specified by countries or regions.

There are ongoing questions in healthcare facilities about the requirements for a statistically valid sampling plan. This annex outlines guidance on how to answer that question for single use or reusable SBS. 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. There are also excellent programs available that will calculate the 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.

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 healthcare facility. The healthcare 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 2 ISO 2859-1[9] is primarily used in case of continuing series of lots (see ISO 2859-1:1999, 1.2). healthcare facilities, however, do not typically produce continuing series of lots of identical packages.

NOTE 3 Healthcare facilities 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[86] addresses variable (continuous) data, and ANSI/ASQ Z1.4[87] 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 precision and bias 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 clear acceptance criteria for every attribute tested. Visual inspection of SBSs is easy to define. This can 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 could not be maintained. If it is too high, opening the package could 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 can 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[88,89].

Annex E
(informative)

Guidance on establishing process parameters – guidance for industry

E.1 General

This annex is applicable to industrial manufacturers of both preformed SBSs and SBSs.

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.

E.2 Example of forming and lidding a tray

E.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 C 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 equation E.1:

RPN = Severity Number x Frequency Number x Ease of Detection Number (E.1)

— recommending actions to reduce the RPN.

An example for failure modes and effects analysis is given in Table E.1.

Table E.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	

E.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 SBS.

For example, the process conditions necessary to ensure an acceptable seal strength when heat sealing the lid should be:

— sufficiently removed from those process conditions which will result in failure of the seal;

— produce a seal according to specifications;

— 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;

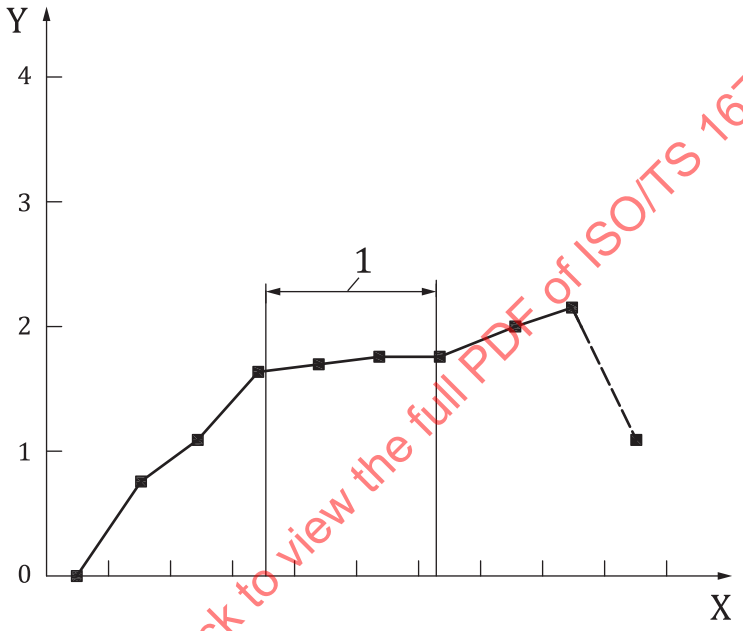
— a combination of the heat seal curve analysis and visual assessment;

— determination of process capability;

— seal integrity.

E.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. SBSs with seals just beyond these limits should still maintain integrity but the seals are likely to show slight visual defects (see Figure E.1).



Key

X temperature

Y seal strength

1 proposed process limits

Figure E.1 — Heat seal curve for optimum process parameters

E.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 (see Table E.2)

Table E.2 — 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

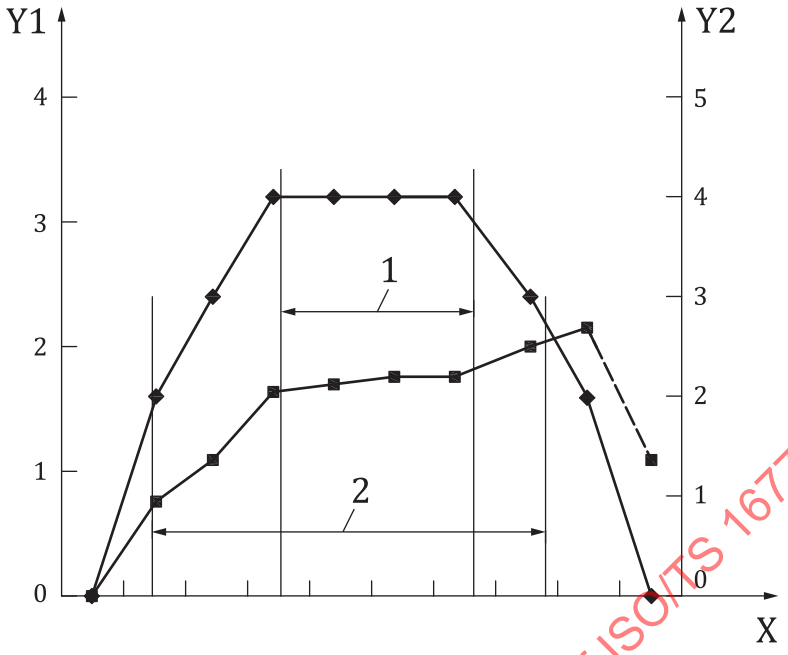
b) Upper end of sealing range

Table E.3 — 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

E.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 E.2.



Key

X temperature
Y1 seal strength
Y2 visual seal quality
1 proposed process limits
2 proposed specification limits

Figure E.2 — Seal strength and visual seal quality vs. temperature

E.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 (E.1):

$$Cp = \frac{USL - LSL}{6\sigma} \tag{E.1}$$

where

σ sample standard deviation

USL upper specification limit

LSL lower specification limit

If the process is not centred, Formula (E.2):

$$Cpk = \frac{CSL - X}{3\sigma} \tag{E.2}$$

where

CSL closest specification limit

X process average

Guidelines for Cp/Cpk values are given in Table E.4.

Table E.4 — CpK value example

	Cpk	Sigma level (σ)	Process yield	Process defects (PPM)
	0,33	1	68,27 %	317 311
	0,67	2	95,45 %	45 500
	1,00	3	99,73 %	2 700
Target	1,33	4	99,99 %	63
Better	1,67	5	99,9 999 %	1
Best	2,00	6	99,9 999 998 %	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 into more formal validation activities.

Annex F
(informative)

Sterilization considerations – Guidance for industry and healthcare facilities

F.1 Overview

F.1.1 Full consideration of the sterilization process for a terminally sterilized medical device needs to be included during medical device and SBS and/or packaging system design and verification to determine compatibility (ISO 11607-1:2019, 5.3). Very often, the sterilization method will dictate aspects of material selection, SBS and/or packaging system configuration, size, and medical device logistics.

Some aspects to be considered are:

a) compatibility — ability to withstand the process:

   Consider the medical device and SBS 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) could change with a given material undergoing irradiation and that the differences between e-beam and gamma sterilization methods and or dosage could have different degrees of effect on materials.

b) porous or impermeable; Gaseous sterilization methods typically require porous SBSs, while irradiation sterilization methods can use impermeable or porous SBSs. Porous SBSs can be used to enable abatement of odours that can develop during irradiation.

c) density/orientation:

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

d) special totes or carriers/conveyor limitations:

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

e) pallet configurations:

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

F.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.

F.2 Ethylene oxide

F.2.1 Process summary: Sterilization by ethylene oxide gas with moisture and heat.

F.2.2 Medical device/SBS considerations:

a) The medical device, SBS, 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 SBS 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 SBS integrity during the vacuum and/or fill process. Care should be taken to ensure that the configuration of individual SBSs contained in an SBS and/or packaging system does not impede their permeability. Avoid close contact of the permeable material with a non-permeable one as this could prevent the gas from penetrating.

F.2.3 Process considerations:

a) Timing: the process can 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.

f) Exposing product to two sterilization cycles, when resterilization is being considered.

For further information on EO sterilization see:

— ISO 11135[90];

— ISO 10993-7[91];

— AAMI TIR15[92];

— AAMI TIR16[93];

— AAMI TIR20[94];

— AAMI TIR28[95].

F.3 Gamma irradiation

F.3.1 Process summary: The packaged medical device is subjected to ionizing radiation in the form of high energy gamma photons released from a radioactive source such as cobalt-60.

F.3.2 Medical device/ SBS and/or packaging system considerations include:

a) The medical device SBS 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.

b) Elevated temperatures could 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 inaccessible in areas that cannot be sterilized with a gas or a non-porous SBS and/or packaging system is needed.

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

f) It is recommended to irradiate at or above the maximum dose in order to evaluate the effects to packaging materials.

F.3.3 Process considerations:

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

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

F.3.4 For further information on radiation sterilization see:

— ISO 11137-1[96];

— ISO 11137-2[97];

— ISO 11137-3[98];

— AAMI TIR17[53];

— AAMI TIR29[99];

— AAMI TIR35[100].

F.4 Electron beam sterilization (E-beam)

F.4.1 Process summary: An accelerator-based system sterilizes medical devices by directing a concentrated stream of electrons at SBS and/or packaging systems containing medical devices. Beta particles, free electrons, are transmitted through a high-voltage electron beam from a linear accelerator. These high-energy free electrons will penetrate into matter before being stopped by collisions with other atoms. Thus, their usefulness in sterilising an object is limited by density and thickness of the object. Death of a microorganism occurs by cumulative damage to the cellular machinery, particularly the DNA molecule, thus preventing cellular division and propagation of biologic life.

F.4.2 Medical device/ SBS and/or packaging system considerations:

a) The materials of the medical device, SBS, and inks should be carefully selected to withstand E-beam radiation. The effects on materials can 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 can be a good choice for medical devices that have closed in areas that cannot be sterilized with a gas.

F.4.3 Process considerations:

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

b) Orientation of medical device/SBS 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.

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

a) ISO/ASTM 51649[101];

b) standards in gamma irradiation (see B.3.4 in Annex B of this document).

F.5 X-ray sterilization

F.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.

F.5.2 Medical device/SBS and/or packaging system considerations:

a) The medical device or SBS 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) SBS 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 SBS seals because cycle does not 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 SBS and/or packaging system design to reduce dead space in the sterilization cycle.

F.5.3 Process considerations:

a) Efficiency will also depend on SBS 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.

F.6 Moist heat (steam) sterilization

F.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 SBS and/or packaging system in order to contact the medical device. Moist heat is more effective than dry heat as it speeds up heat penetration. The ultimate cause of microorganism death for moist sterilization is protein denaturation and causes death of microorganisms by a slow burning process coagulating the cell proteins.

Due to its temperature, high moisture and rates of changes in pressure steam sterilization can have some deleterious effects on some materials, including corrosion, mechanical stress and also certain effects on supporting materials. The chosen materials should be compatible with steam sterilization and thus only packaging materials that have been designed and qualified for these applications should be used.

F.6.2 Medical device/SBS and/or packaging system considerations:

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

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

F.6.3 Process considerations:

a) Timing: the process usually takes less than 2 h with no aeration required. Unless parametric release is used to release sterilized products, 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.

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

— ISO 17665-1[102];

— ISO/TS 17665-2[103].

F.7 Sterilization using moist heat and non-porous plastic bags

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

NOTE Examples can include IV bags, blood bags, etc.

F.7.2 Medical device/ SBS and/or packaging system considerations:

a) The medical device, SBS 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 SBS in order to create the steam and pressure that will sterilize the medical device.

F.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 products, 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 SBSs.

F.7.4 For further information on steam sterilization, see ISO 17665-1[102].

F.8 Dry heat

F.8.1 Process summary: the packaged medical device is subjected to high temperatures for an extended period of time. Dry heat in the form of hot air is used primarily to sterilize hydrophilic materials or materials that steam and ethylene oxide gas cannot penetrate, such as anhydrous oils, petroleum products, and bulk powders. The ultimate cause of microorganism death is protein denaturation through primarily an oxidative process. In the absence of moisture, higher temperatures are required than when moisture is present. However, moist heat cannot be used for hydrophilic materials.

F.8.2 Medical device/SBS and/or packaging system considerations:

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

F.8.3 Process considerations:

a) Timing: the process takes only a few hours, with no aeration required. Unless parametric release is used to release the 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.

F.8.4 For further information on dry heat sterilization, see ISO 20857[104].

F.9 Vaporized hydrogen peroxide sterilization (VH_2O_2)

F.9.1 The vaporized hydrogen peroxide sterilization process can use different methods of removing hydrogen peroxide residues after the sterilization phase. These can include:

a) use of a platinum catalyst and vacuum;

b) use of a gas plasma;

c) use of other gases, such as ozone.

F.9.2 Process summary: the packaged medical device is placed in a sterilizer chamber and subjected to vaporized hydrogen peroxide at approximately 50 °C. Hydrogen peroxide is used to sterilize heat or temperature sensitive articles and materials. It is a strong oxidant and these oxidising properties allow it to destroy a wide range of pathogens.

F.9.3 Medical device and SBS and/or packaging system considerations:

a) The medical device, SBS and/or packaging system, and ink to withstand temperature up to 55 °C and the moisture that is a by-product of the process for the duration of the validated cycle.

b) The medical device, SBS and/or packaging system, and ink should be compatible with deep vacuum or hydrogen peroxide.

c) The medical device, SBS and/or packaging system needs to be capable of withstanding the rates of pressure change allowed by the equipment.

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

e) Cellulosic materials cannot be used for the process.

F.9.4 Process considerations:

a) Timing: typical processes range from 15 min up to over one hour.

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

F.10 Chlorine dioxide (ClO_2 or CD)

F.11.1 Process summary: sterilization with chlorine dioxide gas is a low temperature 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 vaporized hydrogen peroxide (VH_2O_2) and low temperature steam formaldehyde (LTSF).

F.11.2 Medical device/SBS and/or packaging system considerations:

a) Nonwoven polyolefin as well as many transparent films, foil composites and rigid plastics are compatible with chlorine dioxide. Standard medical papers can be compatible. Unbleached, corrugated paper cartons can be affected by oxidation reaction of the sterilization medium.

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

F.11.3 Process considerations:

a) Timing: The process steps typically include

   — preconditioning or humidification;

   — CD charge;

   — exposure; and

   — CD removal and medical device aeration.

   The total process can 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 G
(informative)

Use of contract packagers – Guidance for industry and healthcare facilities

G.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 could wish to outsource the packaging for economic reasons.

G.2 Functions performed by contract packagers

The contractor can perform one, or any combination, of the following functions:

a) full final packaging system design, development, and validation;

b) packaging of the provided medical device in its SBS with 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) terminal sterilization or sterilization subcontracting of the packaged medical device.

G.3 Responsibilities

Contractors should comply with the same current good manufacturing practices (cGMPs) and regulatory and quality systems requirements to include ISO 11607-1:2019 and ISO 11607-2:2019 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 H
(informative)

Example of a handling, distribution and storage checklist – Guidance for healthcare facilities for selecting a sterile barrier system

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

Anticipated challenges that effect integrity of SBS

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

— 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 SBSs? ☐ yes ☐ no
if yes describe

Is there a hand hygiene protocol? ☐ yes ☐ no
if yes describe

Is there a dress code? ☐ yes ☐ no
if yes describe

Is the number of times an SBS is handled from point of sterilization to point of use known? ☐ yes ☐ no
if yes describe

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 SBSs? ☐ yes ☐no

Storage aspects

Are there dedicated storage areas for SBSs? ☐ 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 ☐ no
If yes, how often?

Is the shelving made of non-porous material? ☐ yes ☐ no

Is there a routine for regularly cleaning of shelf/basket? ☐ yes ☐ no
If yes how often

Can storage on shelf/ basket be without any risk of damage? ☐ yes ☐ no

Is there enough space between floor and sterile items? ☐ yes ☐no
cm/inch

Is there enough space between ceiling and sterile items? ☐ yes ☐ no
cm/inch

Is direct sunlight able to be avoided? ☐ yes ☐ no

Are the manufacturer's requirements of humidity being followed? ☐ yes ☐ no
Result %

Are the manufacturer's requirements of temperature being followed? ☐ yes ☐ no
Result °C/ °F

Is the air filtered?	☐ yes ☐ no State %
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 I
(informative)

Investigating failure – Guidance for industry and healthcare facilities

I.1 Evaluating failure

I.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 can include:

a) microscopic analysis

b) polymeric analysis;

c) manipulation of the package/device with visual inspection.

I.1.2 If these approaches prove unfruitful, several problem-solving approaches can 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.

I.2 Determining the source of the defect

I.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.

I.2.2 Medical device induced defects can be related to the weight or sharpness of the medical device. Firstly, perform visual control of the defective SBS and medical device, before reassembling, to observe if some part of the medical device is sharp, sticking out, create friction or is somehow related to the defect. The defective SBS and medical device should be reassembled, taking care to align in the same manner, so that any correlations to shape or rubbing pattern can be determined. It is important to reassemble the complete packaging system configuration, including the SBS and protective packaging. Often, an individual SBS or packaging system will not clearly show the source of the defect, but when packaged medical devices are stacked, it allows visual identification of the source.

I.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 SBS 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 SBS or packaging system back to the packaging process and retracing the production steps, important correlations could be discovered.

I.2.4 Defects that are not traceable to medical device or process can 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 5.5 of this document. 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.

I.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.

I.2.6 Environmentally induced failures can come from many different sources. Changes to air flow around equipment that requires temperature control sometimes can 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 can 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.

I.3 Chemical and mechanical causes

I.3.1 While researching the SBS or packaging system defect cause, it is important to try to differentiate between chemical and mechanical causes.

I.3.2 Chemical causes should be thought of in three 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 SBS or packaging system damaging the other);

c) chemical interaction between the protective packaging and SBSs (e.g. yellowing of the SBS 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.

I.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 can lead to a fruitful path of problem solving.