

Sterile Barrier Systems: Managing Changes and Revalidations

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Abstract

The medical device package design and packaging process are critical steps for the production and distribution of terminally sterilized medical devices. Guidance on design validation and process validation is widely available, but guidance on changes that require revalidation activities is relatively limited. This paper reviews guidance from the harmonized medical packaging standard adopted by European Committee for Standardization (CEN) and International Organization for Standardization (ISO) EN ISO 11607, European Notified Bodies, and the US Food and Drug Administration's Center for Devices and Radiological Health (CDRH) on revalidation of packaging. Based upon these guidances, potential changes to the package and packaging process are categorized and reviewed.

Introduction

The key functionality of packaging for terminally sterilized medical devices is to allow for sterilization and to maintain sterility until the point of use in a healthcare setting. Package designs must be validated (qualified), and the packaging process must be validated and controlled. In 2006, EN ISO 11607 *Packaging for terminally sterilized medical devices* was published with Part 1 addressing materials and design while Part 2 is addressing packaging process validation (1, 2). These standards are recognized by FDA (3) and are harmonized with the essential requirements (ER) of the European medical device directives. The standards have been adopted by many countries around the world (e.g., Canada, Japan, Australia, South Korea, etc.).

In order to maintain the validated state for a sterile medical device packaging system, it is important to both conduct periodic system reviews and also to critically evaluate changes to the packaging system design and/or the process. This periodic review and change management process should be risk-based and focus on the impact of change inputs that could affect the system performance, efficacy, and safety of the packaged product. Periodic reviews are an important tool to assess the potential compound impact of numerous low risk changes that occurred over time and did not require action at the time of implementation. While much has been written about the requirements for validation, very little has been published on revalidation requirements driven by change. There are basic revalidation requirements covered in the standards and in various guidance documents, but due to the general nature, interpretation can be challenging. Validation of medical packaging can be a significant investment for medical device manufacturers. The fact that the standards provide a means to establish product families and to use worst-case considerations to create scenarios for validations can help leverage the cost by spreading them over an entire product range. It is important to build the revalidation on previously documented validation efforts. This approach can have a positive impact on cost or may be essential to avoid disruptions of supply in case of short-term changes that cannot be avoided. This paper provides an overview of the regulatory requirements for sterile packaging system revalidation and discusses points to consider when applying these requirements to various typical change scenarios.

Validation Requirements

Validating a sterile barrier system (SBS) is a process that involves four different types of validation activities which covers design, packaging process, sterilization, and test methods.

Design

Regarding design and development, EN ISO 11607 states the following key principle:

*6.1.1 The Packaging System shall be designed to **minimize the safety hazard** [emphasis added] to the user and patient under the intended specified conditions of use.*

This is accomplished by systemically applying risk analysis techniques throughout the entire system and process through the development and commercialization phases. Risks shall be analyzed, evaluated, and controlled by implementing appropriate mitigation measures so the product is not compromised by unacceptable risks. Validation is intended to provide objective evidence that the design outputs meet pre-determined requirements or design inputs.

Risk assessment and management are essential tools that support the development and commercialization of robust sterile packaging systems and processes. Among the outputs are meaningful component and process specifications, material science enhancements, improved process knowledge, qualification strategies, optimized validation strategies, etc. The completion and documentation of the risk analysis becomes the basis for establishing effective quality assurance and monitoring programs. It also provides a baseline for evaluating the effects of changes and for establishing any required mitigation measures.

Design Validation

Note: Package design validation may also be known as package design qualification; throughout this document the term "validation" will be used as defined under 3.18 in EN ISO 11607-1.

EN ISO 11607-1 provides the following definition, applicable to validation of test methods and design:

3.28 validation

<general> confirmation by examination and provision of objective evidence that the particular requirement for a specific intended use can be consistently fulfilled.

Under EN ISO 11607-1, package design validation consists of two elements, package performance testing and stability testing:

- **Packaging system performance testing** is a physical evaluation intended to demonstrate the packaging system provides adequate protection through the hazards of handling, distribution, and storage. According to EN ISO 11607-1 it "shall be conducted on the worst-case sterile barrier system produced *at the specified process limits of forming and sealing* [emphasis added] and after exposure to all specified sterilization." Often the worst-case packages are where

the process parameters yield the lowest seal strength. Additionally, SBS containing the worst-case device should be packaged in the worst-case SBS and tested. If the worst-case packages pass the tests, the system design is considered validated.

- **Stability testing** (aging), in contrast to performance testing, is a chemical *and* physical evaluation intended to demonstrate that the sterile barrier system maintains integrity over time. Stability testing is the basis for use-by-date or expiry claims of the packaged product.

Performance Testing

The objective of performance testing, as stated above, is to demonstrate the package system provides adequate protection to maintain a sterile barrier throughout the distribution and handling of a product. Performance testing is normally done by challenging a system through simulated distribution testing and then evaluating each package with physical package integrity testing. These tests or protocols typically are based on standardized test methods (e.g., EN ISO 11607 Annex B, ASTM D4169 [4], the ISTA series [5]). Depending on the defined distribution environment, packages are exposed to a series of drops, compression, vibration, and climate challenges intended to simulate what a package system (primary and secondary packaging) will experience in the “real” world. Again, the purpose of the testing is to demonstrate that the package system will adequately protect the product and the sterility of the product throughout distribution. A risk assessment of any changes to the distribution environment, packaging design, materials, process, or specifications may require performance testing to be redone in order to be compliant with the regulatory requirements.

It is well-accepted industry practice to conduct performance testing and stability testing as distinct or independent studies or protocols. While there are numerous reasons for this practice, primarily, there is the need to evaluate two very different failure modes independently. As discussed above, performance testing is a physical test intended to evaluate physical failures that might occur during distribution that in turn might affect the sterile barrier, and stability testing is intended to evaluate material chemical degradation over time and product package interaction over time (chemical and physical) to establish the shelf-life and sterility maintenance for this shelf-life. Stability testing is conducted under accelerated conditions and timeframes (elevated temperatures) and ambient, real-time conditions. This approach also enables efficient root cause analysis if failures should occur and provides better baseline data for risk assessments when changes to the system do arise.

Stability Testing

Flexible sterile barrier systems are comprised of several material substrates combinations; often referred to as a “top web” and “bottom web.” They can be made from flexible, semi-rigid, or rigid films; single or multi-layered films; and porous barrier materials that are all usually made from various organic substrates. Flexible barrier systems are popular because they are lightweight while still providing adequate physical protection and excellent barrier properties.

The stability of the substrate is generally a function of the type of polymer, whether it is a homo-polymer or copolymer, the type of polymerization process, the catalyst and additive system used, and the conditions to which the substrate is exposed. Processing the substrate has an immediate effect on the properties during initial manufacturing and also during subsequent conversion steps, high processing temperatures, applied coatings, or printing inks, which, especially if they are solvent based, may lead to deterioration. Among others, common conditions, or elements, to which a substrate is exposed that can cause chemical reactions that can impact stability are oxygen, sterilization processes, ultraviolet light, elevated temperatures, and humidity. The rate of deterioration can also be influenced by packaging material physical characteristics, such as thickness, number of film layers, whether coatings are present, etc. The chemical deterioration of the material’s mechanical properties, such as tensile strength or brittleness, is typically due to changes in the polymer microstructure (e.g., bonds, chain length, cross-linking, etc.) as a result of exposure to the elements discussed above. To counteract these effects, stabilizers and antioxidants are added to the organic substrate usually during the initial processing of the material.

Films or top web materials may be coated with an adhesive that can be activated thermally or by pressure for sealing, or bottom webs or forming webs may have a sealant layer that also can be activated thermally and facilitate the sealing process.

All components as well as the seals between the films and top web materials need to retain their properties within a given range during the shelf-life of the sterile barrier system. The objective is to maintain integrity and microbial barrier properties and to enable aseptic presentation at least until the stated use by date.

Stability has to be demonstrated with real-time aging, but accelerated aging is accepted as sufficient evidence for product

commercialization provided there is a program initiated in parallel to evaluate the packaging in real-time studies. Accelerated aging at elevated temperatures typically increases the velocity of the chemical reactions that lead to the deterioration of the properties of the different organic substrates. It is widely accepted in the industry to apply the Arrhenius equation, which correlates real-time aging with accelerated aging at elevated temperature based on the fact that rates of chemical reactions double with every temperature increase of 10°C as documented in ASTM F1980 (6).

Stability testing is a way to demonstrate that the specified sterile barrier system and its specified seals are chemically stable to retain their mechanical properties within a given range so that integrity and microbial barrier properties, and therefore also sterility, are maintained over the stated shelf-life. This is supported by EN ISO 11607 and by FDA guidance on integrity testing in lieu of sterility testing (7). Generally, processing steps that would cause enough chemical damage to a packaging substrate for it to fail during aging would also have been detected during the more rigorous performance testing. In that sense, while there is a clear requirement in the standard that performance testing shall be conducted on the worst-case sterile barrier system produced at the specified process limits of forming and sealing, there is no such requirement for stability testing.

Process Validation

The following definition is provided in EN ISO 11607 for process validation:

3.29 validation

<process> documented procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications.

The purpose of process validation is to provide documented, objective evidence that the packaging process is in statistical control, is repeatable, and makes product that meets pre-determined specifications. The process validation represents the combination of a successful installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). In this context, it is important to have pre-determined acceptance criteria for seal strength taking into consideration the sometimes conflicting requirements of maintaining the integrity of the package while providing the user a package that is easily opened in order to facilitate aseptic transfer when the device is used. In addition to seal strength, other important package attribute specifications must also be predetermined, such as material thickness, seal width, etc. It is also essential to have the sealing process window properly defined and verified, which is normally done during OQ. The process window is the range for the sealing process parameters, which are normally temperature, dwell time, and pressure. The established process window allows for the production of sterile barrier systems with seal characteristics within the established specification. Seals activated by heat are the most common. The process window is specific for every type of sealing equipment and material combination since it depends on numerous variables, such as where on the platen and how the sealing parameters are measured and how they are controlled. Assembly and forming processes are part of packaging process validation and can have a significant impact on the sterile barrier system and on the reliability of the entire production process. The process validation will be concluded with the demonstration of adequate process control and capability during PQ.

ISO 11607 and Revalidation

There is language on revalidation in EN ISO 11607 Part 1 that covers materials and design. EN ISO 11607 Part 2, however, addresses revalidation under 5.7.2:

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

And it specifies under 5.7.3:

“The need for revalidation shall be evaluated and documented. If the situation does not require that all aspects of the original validation be repeated, this revalidation does not have to be as extensive as the initial validation.”

In fact, EN ISO 11607 does not give extensive direct guidance on design revalidation.

The New Upcoming Guidance Document ISO TS 16775

Since the introduction of EN ISO 11607 Part 1 and 2, the application of the standard has been the subject of numerous

discussions. ISO TC198 WG7 is responsible for these standards and any forthcoming revisions. In 2010, the working group initiated development of an extensive guidance document on the application of EN ISO 11607. The document, DTS 16775, is currently in the final voting phase and is split into two sections, an industrial section with guidance for packaging development and validation activities addressing specific industry needs and a section addressing specific needs for the healthcare environment. Publication is expected for the end of 2013 or beginning of 2014.

In the industry section, the guidance states that revalidation is required when changes have been made to the medical device, packaging system, process, or equipment that will affect the original validation. Revalidation is often affiliated with design control and the associated change control procedure. The extent of the revalidation required will depend on the nature of the change and how it affects the process or medical device. In the healthcare section, the guidance document states that a documented rationale should be developed to support the decision of partial revalidation.

Regulatory Requirements

EN ISO 13485 (9) regarding medical device quality management systems requires the organization to establish arrangements for revalidation of processes and implement them as required to maintain the effectiveness of these processes. Every manufacturer obviously has to follow its own revalidation procedures as well as any regulatory requirements or guidance in the markets where the product is marketed. Further on, EN ISO 13485 states that “design changes shall be reviewed, verified and validated, as appropriate, and approved before implementation.”

FDA CDRH Guidance

CDRH provides significant guidance on process validation and packaging process validation (10-12). Additionally, EN ISO 11607-1 and 2 is on the list of recognized standards (3). Guidance is also given on the appropriate type of Premarket Approval (PMA) notices and supplements to file depending on the nature of the change (13).

CDRH states that “package validation involves two separate validations: 1) the design validation of the package as a component of the device and 2) the process validation of the packaging process.” (12). This includes establishing evidence the design and process will consistently produce packages that meet specifications. Included is routine monitoring of the process to demonstrate it is operating in a state of control. If changes or process deviations occur, these must be evaluated and revalidated as appropriate.

Notified Body (NB) Guidance in Europe

The NB-Med issued a guidance (14) on “Reporting of design changes and changes of the quality system.” This document makes it clear that when the NB has been involved in the device design/type, then they must be informed before implementing any substantial changes to the product-range or the device “which could affect compliance with the essential requirements of the respective Medical Device Directive or the intended use.” It is the responsibility of the manufacturer to establish a documented procedure for change management that includes criteria for deciding on the substantial or non-substantial nature of changes. The guidance provides complementary elements for those criteria as well as a number of examples.

Highlighted below are two examples that the guidance indicates for changes to EC-approved medical devices design/type (including software) (MDD Annexes II, 4.4 and III; IVDD Annexes VI-4.2 and V, respectively):

- *“Change in the packaging configuration that could potentially affect protection against transportation or maintenance of sterility during shelf life (ER 5, 8).”*
 - Classified as reportable change
 - It is evident that this change will require performance testing to be done as a minimum unless a rationale can be established (see the Table below).
- *“Changes in a manufacturing process that will need process validation, but does not affect the product specifications (including tolerances) do not necessarily affect performance (ER 7), so is not considered a significant change.”*
 - Classified as a non-reportable change
 - This guidance can be applied to packaging. The process validation makes sure that the manufacturing process (e.g., sealing machine) produces packages that consistently meet the established specifications (e.g., sealing width and strength). The design validation is based on the specified product utilizing the worst case and testing

at the minimum seal strength. Generally, as long as the seal strength specifications and equipment process capability are not changing, the basis is there to establish a rationale that the design validation is not affected. Further elements may have to be considered depending on the situation.

Further Elements that May Be Used When Developing a Rationale

The EN ISO 11607 standard has two key clauses that can be directly used for building a rationale for justifying the extent of revalidation studies after changes.

The first aspect is the basis for establishing packaging families, but it can also be used as a basis to decide on redoing validation studies after changes:

6.1.6 When similar devices use the same packaging system, a rationale for establishing similarities and identifying the worst-case configuration shall be documented. As a minimum, the worst-case configuration shall be used to determine compliance with this part of ISO 11607. NOTE For example, similarity could be established by different sizes of the same product.

This can be used to build a rationale if the new packaging or new respectively modified device stays within the limits of the predefined worst-case definition for the packaging and device combination previously validated.

Both EN ISO 11607 and FDA guidance establish the importance of understanding and applying concepts of worst-case concept during stability testing when establishing families. For stability testing families, in addition to size, worst-case clearly includes maximum sterilization method exposure. It can also include package headspace gas volume and concentration for sensitive devices, but generally does not include seal strength unless the gas volume or device itself is exerting forces on the seal during aging. In this instance, the worst case would again be the settings where the process parameters yield the lowest seal strength. The upper sealing process limit is generally not used as the worst case for stability testing.

The second aspect is part of the section on stability testing:

6.4.7 When it is demonstrated that the product does not interact with the specified sterile barrier system over time, previously documented data for stability testing shall be sufficient to be in accordance with 6.4.1.

In this clause, the term “interact” needs to be considered in a broad way; the interaction could be mechanically, for example, by introducing a device that applies more force to the seals, or it could be chemically, by leaching any components into the packaging that could have a negative impact on the stability.

Table: Revalidation Considerations for Four Key Change Areas (Material, Sealing Equipment, SBS Design, Device).

| | Design | | Packaging Process | Sterilization Process |
|---------------------------------|-------------|-----------|-------------------|-----------------------|
| | Performance | Stability | | |
| Material Change | Yes/No ? | Yes/No ? | Yes/No ? | Yes/No ? |
| Sealing Equipment Change | No ? | No ? | Yes ? | No ? |
| SBS Design Change | Yes/No ? | Yes/No ? | Yes ? | Yes/No ? |
| Device Change | Yes/No ? | Yes/No ? | Yes/No ? | Yes/No ? |

Table Footnotes

1. A change of material is to be considered as a change of the design of the package and would normally require performance testing to be redone. The extent of the change can vary significantly, however, as illustrated by the following cases:

- Transitioning to the same material from a new or different manufacturing line (or manufacturer) with identical specifications can hide risks, so that further analysis is required. Reviewing differences in the manufacturing process can be one option; however, this is usually not possible or only to a limited extent. If data is available indicating that the new material is performing in a similar way through the various processes of forming, sealing, sterilization, and generating packages fully within specifications, or in other words functionally equivalent, it could be the basis for a rationale to support the decision that previously documented performance testing data is sufficient to fulfill the requirement.
 - When introducing the “same” material from a different converter, like reels or lids for a packaging machine, while the original material manufacturer and/or product are not changing, the extent of the change is normally only related to the material converting process steps, and risks to be examined would only include those related to these steps. Examples of aspects to consider would be the precision of the required dimensions, cleanliness, reel-winding tension, or printing aspects if applicable.
 - Introducing a different type of film, different substrate, or different adhesive clearly requires a new design and process validation.
- See rationale under 1.
 - See rationale under 1.
 - The need for revalidation or verification of the sterilization process needs to be evaluated separately; key aspects to consider are significant changes of porosity, potential impact on radiation penetration, or any negative impacts on EO residuals.
 - Test methods are validated for the materials intended to be used. A revalidation has to be considered in case the new material is outside of the validated range of materials.
 - It is normally not necessary to redo performance testing if the sealing equipment uses similar sealing technology, is properly validated, and capable of consistently producing seals that meet the specifications of the packaging that was used for the previously documented performance testing. In other words, if there is no change of the packaging design.
 - No, same rationale as under 6.
 - Yes, new sealing equipment must be properly validated to demonstrate that it is capable of producing consistently seals that meet the specifications of the respective packaging. Depending on the case, this revalidation needs to be more or less extensive, focusing on the elements that are changing:
 - If a second sealing machine is introduced, or a portion of a machine such as the sealing platen is replaced the objective is usually to produce SBS that meets the same specifications than produced on the packaging machine that produced the validated packaging design. This is normally achieved by performing a process validation on the new packaging machine and by integrating measures into IQ to verify that the new packaging machine meets the established machine specifications and is properly calibrated. During OQ, it is essential to verify that the established process window is still valid for the new machine or if it requires adjustments to meet the specified sealing parameters.
 - If new sealing equipment representing a machine improvement is introduced, the objective should be to confirm that the produced SBS meets specifications and has test data exhibiting no more variability than the SBS previously produced.
 - No, assuming no change to the package seal specification and device position in the package.
 - Not applicable, unless there is a change of test method.
 - A change of packaging design will normally require performance testing to be redone. However, previously documented performance testing data may be reused if the new design is part of a previously validated packaging family and if the rationale that the device provides less stress to the packaging than the worst-case configuration already tested can be supported.
 - Normally yes unless it is possible to build a rationale on clause 6.4.7 of ISO 11607-1.
 - A change of packaging design would normally require a new validation unless it is part of a previously validated product family.
 - Same consideration as under 4.
 - Some test methods are established and validated for specific packaging designs, so that revalidation or changes to the test method might be required depending on the design.
 - Packaging a different product would normally require performance testing to be redone unless the new device is part of a previously validated product family and does not represent a new worst case. If the materials of construction for the device change, it is important to evaluate any risks from a device/package interaction.
 - Normally yes unless it is possible to build a rationale on clause 6.4.7 of ISO 11607-1. If the materials of construction for the device change, it is important to evaluate any risks from a device/package interaction.
 - The potential impact of the changed device on the assembly and sealing process needs to be evaluated; a partial revalidation

is usually necessary as a minimum unless the new device has similar characteristics.

- Normally validation or verification is required unless a rationale can be developed based on worst-case considerations for sterilization families.
- See 15.

Conclusion

In case of change, the efforts required for revalidation of terminally sterilized medical device packages are highly dependent upon the nature of the change and the potential impact on identified risks. Revalidations are often not avoidable; the efforts can be optimized, however, as the existing regulations allow for partial revalidations based on previous worst-case family window testing and valid rationale. This requires that the various validation efforts be structured in separate activities where clear failure mechanisms can be determined and reproduced. The scientific basis of these activities and the regulatory requirements must be well understood. The material and process knowledge must be available along with a consistent design and risk management file that follows the nature and impact of the change in detail.

Some changes are self-evident, such as purchasing identical material produced by the same material manufacturer from a different converter or distributor requiring a minimum of assessment and revalidation activities, documented in the rationale. Similarly, changes to the machinery that forms the heat seal would typically require IQ, OQ, and PQ activities. The new equipment may have a slightly different operating window than the original equipment used in the process validation. However, if the minimum seal strength and seal width as well as seal integrity meet the previously established specification for the SBS, shelf-life and performance testing would not be needed. There is no evidence in the literature that would suggest that heat seals produced by similar but different process conditions have different degradation chemistry kinetics and thus different physical performance characteristics.

It is important in revalidation that items addressed in the original validation be addressed with a rationale supporting the omission and documented in the revalidation plan.

Finally, regulatory requirements addressing packaging changes, revalidation, and subsequent submissions vary globally; it is important to understand these requirements for the markets where the device is available for sale.

Acronyms

| | |
|--------|--|
| ER | Essential Requirement for medical devices as listed in Annex I of the MDD |
| FDA | US Food and Drug Administration |
| MDD | Medical Device Directive (European Union) |
| N/A | Not Applicable |
| NB | Notified Body |
| NB-med | Medical Notified Body coordination group hosted at the European Commission |
| SBS | Sterile Barrier System |
| IQ | Installation Qualification |
| OQ | Operational Qualification |
| PQ | Performance Qualification |

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