Strategies for packaging validation in medical devices according to ISO 11607

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The Various Types of Packaging

According to the World Health Organization (WHO), Healthcare-Associated Infections (HAIs) are the most frequent adverse event in the delivery of healthcare services worldwide, affecting hundreds of millions of patients each year. Ensuring the sterility of medical devices is an important tactic in the overall effort to reduce the rate of infections in hospitals and other healthcare settings.

Effective packaging and packaging materials are essential to help preserve the sterility of medical devices. However, the integrity of packaging material can degrade over time due to environmental exposure or be compromised through normal handling encountered during storage and transportation. As a result, rigorous testing of packaging systems used with medical devices is mandatory in most major jurisdictions around the world.

This UL white paper discusses the requirements and validation testing methods applicable to packaging systems and/or materials used in conjunction with sterile medical devices. Beginning with a review of the importance of packaging validation for medical devices, the white paper then presents a summary of ISO 11607, the standard for packaging materials used for sterilized medical devices and provides details on validation testing as prescribed in the standard. The paper concludes with some recommendations for manufacturers on the selection and evaluation of suitable packaging and packaging materials for medical devices.

Extract from the introduction of ISO 11607-1: 2006

The objective of a packaging system for terminally sterilized medical devices is to enable the sterilization, physical protection and preservation of sterility up to the point of use and to provide an aseptic presentation.

The sterile barrier system is essential for the safety of terminally sterilized medical devices.

Components

Several types of packaging components can be used for holding medical devices so that the integrity of the sterile barrier is preserved and they can be easily handled in the operation room. Single or double packaging can be used, depending on the type and shape of the products and the geometry of the packaging. Some examples are:

- The packaging can be presented as pouches or blister packs.
- All the packaging components for the device must be non-reusable.
- The device's packaging guarantees sterility throughout the storage life specified on the labelling under normal conditions of storage and transport.
- Validation for the devices should be performed.

Materials

There are two types of packaging materials:

- Gas-porous materials (e.g.: Tyvek®). For these materials, the micro-organism barrier properties shall be validated
- Waterproof materials plastic (e.g.: Blister)

Sealing

The packaging components are sealed. The sealing parameters to be tested are usually:

- Sealing temperature
- Sealing time sealing pressure

Standards and Regulations

ISO 11607-1 (2006) - Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems

ISO 11607-2 (2006) - Packaging for terminally sterilized medical devices - Part 2: Validation requirements for forming, sealing and assembly processes

Test methods standards listed in ISO 11607-1: 2006 – Annex B

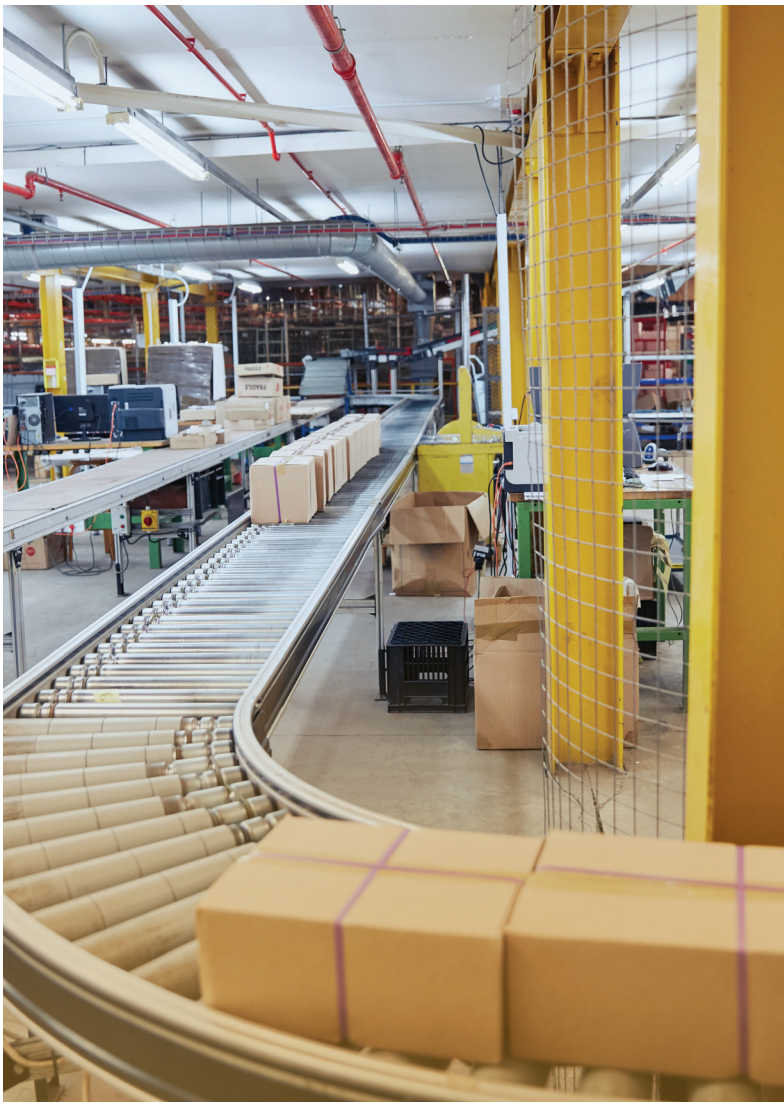
The Importance of Packaging Validation for Medical Devices

Despite the clear imperative to control sources of infections in hospital settings, inadequate or ineffective medical device packaging and packaging materials remains a key challenge.

The U.S. Food and Drug Administration (FDA) reports that packaging-related issues accounted for nearly 380 Class 2 medical device product recalls during a recent 10-year period, with packaging and labeling issues constituting 13 percent of all medical device recalls.

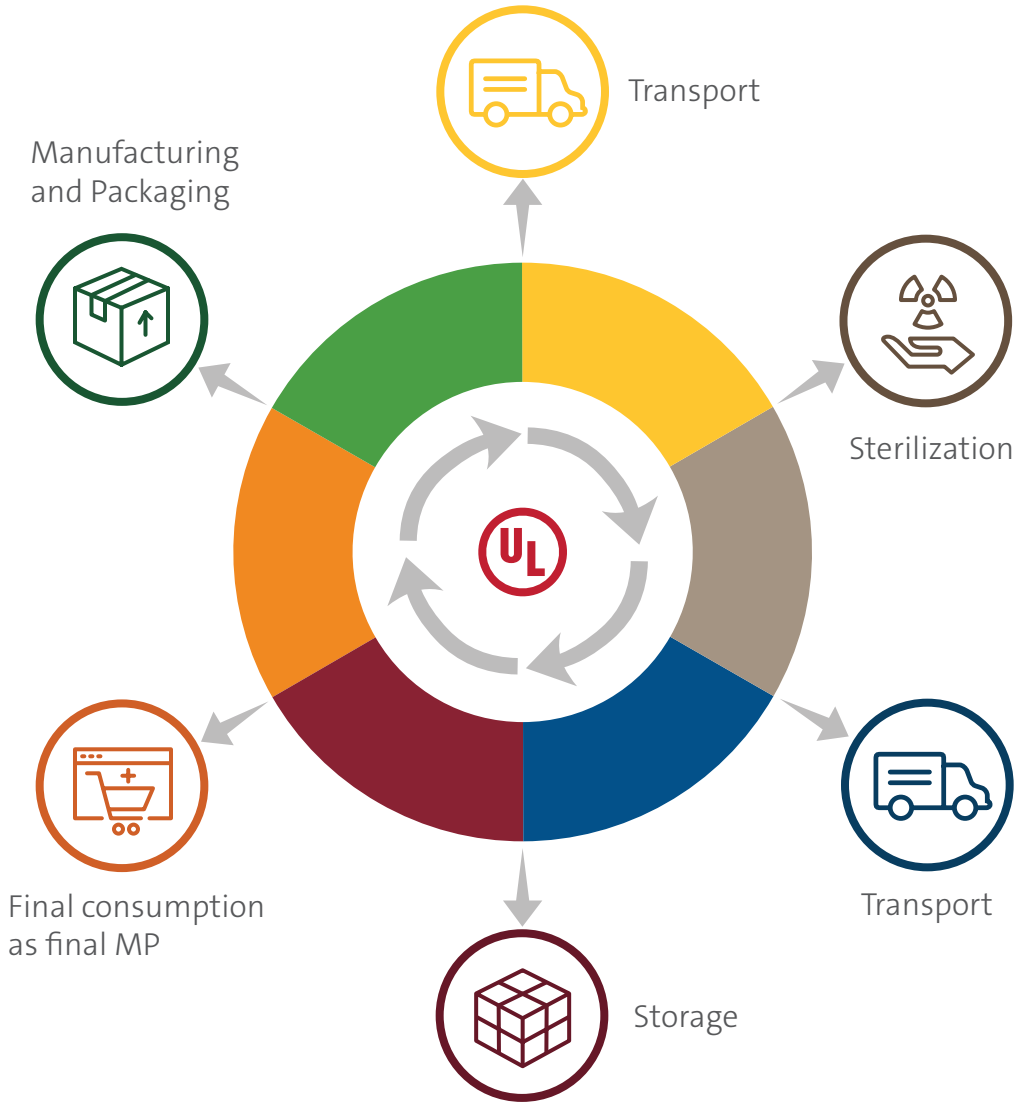
In one such instance in 2015, a medical device manufacturer was forced to recall nearly 17,000 units of five different orthopedic arm implant devices due to concerns regarding the integrity of the products' packaging and the risk of damage to the devices during transit. The action was designated a Class 2 recall by the FDA, its second highest recall classification. In a separate action in August 2014, the FDA recorded 233 separate Class I recalls (the highest recall classification) related to defective packaging in several hundred thousand medical devices from a single manufacturer based in Puerto Rico. This unprecedented recall action was the largest ever recorded by the FDA in a single day, regardless of the cause.

While no deaths or injuries were directly attributed to the medical devices affected by these recalls, defective packaging materials can still impose significant financial costs on medical device manufacturers. Depending on the number of devices with inadequate packaging systems and materials and the scope of their geographic distribution, the cost of initiating a product recall can run into the millions of dollars. In some cases, the marketing of defective medical devices can



lead to regulatory fines or penalties as well as civil litigation that can incur considerable costs and result in sizeable settlements. Finally, recalling defective products can do significant harm to a device manufacturer's reputation in the healthcare market, impacting both current and future revenue.

Simulation of life cycle of a medical device



ISO 11607 Series of Standards, Packaging for Terminally Sterilized Medical Devices

For these reasons, regulators in the EU, the U.S. and other major healthcare markets have implemented strict requirements for packaging systems and packaging materials used to preserve the sterility of medical devices, protect their functionality, and retain their biological safety. In the EU, medical device directives and regulations mandate that medical device packaging materials and systems conform to the requirements of the ISO 11607 series of standards, packaging for terminally sterilized medical devices. In the U.S., the FDA accepts evidence of compliance with ISO 11607 in support of 510(k) applications for the approval and registration of medical devices.

Originally published in 2006 and amended in 2015, ISO 11607 series is today the internationally accepted standard series for packaging and packaging materials used in conjunction with medical devices and consists of two separate parts.

- **ISO 11607-1**: Requirements for materials, sterile barrier systems and packaging systems, establishes requirements for device packaging and packaging materials.
- **ISO 11607-2**: Validation requirements for forming, sealing, and assembly processes, describes the requirements for developing and validation of those processes to be used for the manufacturing/ preparation of sterile barrier systems.

Key Definitions Provided in ISO 11607-1 include:

- **Sterile barrier system** - A sterile barrier system (SBS) is defined as the "minimum package that prevents ingress of micro-organisms and allows aseptic presentation of the product at the point of use."
- **Protective packaging** - Protective packaging is a "configuration of materials designed to prevent damage to the sterile barrier system and its contents from the time of their assembly until the point of use."
- **Packaging system** - Defined as a "combination of the sterile barrier system and protective packaging," the packaging system must minimize potential safety hazards by: 1) maintaining sterility of the packaged device; 2) providing protection against biological risks; and 3) preventing damage that could lead to device malfunction.

ISO 11607-1 also describes how to validate the integrity of the SBS over the course of the device sterilization process and during subsequent handling, distribution and storage. Validation is typically achieved by demonstrating the integrity of the SBS over the intended shelf-life of the device. Real-time aging is required to fully demonstrate compliance with the standard's requirements. However, accelerated aging may sufficiently validate the integrity of the SBS to allow the sterile medical device to be placed on the market before real-time aging validation has been completed.

Justification of Shelf-life

Manufacturers of packaging materials and systems used in conjunction with sterilized medical devices must also be able to validate claims regarding the expected "shelf-life" of their products, that is, the period during which the seal strength (i.e., aseptic presentation) and integrity of the packaging (i.e., maintenance of sterility assumptions) can be assured. To design a suitable test strategy for the justification of the shelf-life the manufacturer should first describe the typical shelf-life cycle of its device. Under ISO 11607-1, stability testing required to validate shelf-life must be carried out using real-time aging, a process that can take as long as five years or more to complete. However, although real-time aging studies are required, regulatory authorities typically accept test reports that validate packaging stability using accelerated aging studies, pending receipt of data from real-time aging assessments.

Accelerated aging studies are normally conducted in accordance with the standardized test methods described in ASTM F 1980: Standard Guide for Accelerated Aging of Sterile Medical Device Packages. In brief, accelerated aging evaluates the response of medical device packaging following exposure to atypical environmental conditions, such as wide ranges in temperature and humidity. The goal is to simulate in a shortened timeframe the reaction of packaging materials and the integrity of the SBS through to the end of the package's anticipated shelf-life.

Depending of the specific requirements of the medical device packaging, both the accelerated aging as well as the real-time aging study include a battery of different physical and microbiological barrier tests to evaluate various physical properties of the packaging and/or to identify potential degradation of the basic packaging materials. This series of tests is necessary since one single test procedure is not sufficient to detect all the different kinds of unacceptable failures

(e.g., loose or mechanically unstable seals or packaging materials, inadequate peel properties, microbial barrier properties, etc.). Furthermore, the biological safety of the packaged medical device should be evaluated by performing tests as specified in ISO 10993-18 (comparative material characterization) and ISO 10993-5 (cytotoxicity testing). Testing might also cover the migration of any material additives or the corrosion of metal parts. Testing may also include a functional assessment of the packaged sterile device. Sterility testing is not typically conducted unless it is explicitly required by an applicable vertical product standard.

It should be emphasized that accelerated aging studies are not a substitute for real-time aging studies and must be conducted in conjunction with real-time aging assessments. However, accelerated aging studies can help medical device manufacturers gain regulatory approval ahead of the completion of real-time studies, thereby enabling them to bring new and innovative products to market sooner.

Transport Safety

The final aspect of the validation process for medical device packaging systems consists of the evaluation of the packaging system's performance during transportation, distribution and storage. Specific standardized test methods that can be used to demonstrate that the SBS is still in compliance with the requirements of ISO 11607-1 after shipment are mentioned in Annex B of the standard. Evaluation of transportation may encompass three different types of testing.

The first type of testing, non-simulation integrity testing, is detailed in the International Safe Transit Association's (ISTA's) pre-shipment test procedure Series 1 documents and is a helpful method to identify the suitability of an intended packaging system for use with medical devices. The second testing type, partial or general simulation performance testing, is described in ISTA's pre-shipment test procedure Series 2 and Series 3 documents, respectively, as well as in ASTMD 4169, Standard Practice for Performance Testing of Shipping Containers and Systems. General simulation performance testing is intended to simulate the conditions encountered throughout the complete transportation chain.

A third testing type, not mentioned in a standard, is focused simulation, which assesses packaging systems according to exposure data collected during an actual transportation chain. Such testing is dependent on the availability of suitable data and requires the development of a customized test procedure. In addition, collected data is often representative of a unique transportation experience which may not be typical of what is likely to be encountered and may not be repeatable. As a result, focused simulation is not widely used to assess the performance of packaging under transportation or storage conditions.

Depending on the type of packaging materials, test models used in evaluating packaging systems during transportation, distribution and storage may include testing for climatic exposure, compression testing, vibration testing, shock testing, low pressure testing and concentrated impact testing. Following this battery of tests, packaging systems are then physically inspected for any damage that may have resulted. Additional post-test evaluation might also include testing to assess sterility using physical testing and functionality of the packaged medical device.

Ultimately, testing to assess the integrity of packaging during transportation and storage can lead to modification of the packaging system design to better stabilize the device within the package or changes in the actual packaging materials to provide increased protection. Transportation testing may also be a necessary component of an evaluation program for non-terminally sterilized medical devices. After performing the transport simulation, any downstream evaluation testing must be adopted to the product under evaluation.

Recommendations for Device Manufacturers

As this paper illustrates, validating packaging for terminally sterilized medical devices is a complex process that typically requires years to complete. However, medical device manufacturers can take several actions to increase the likelihood of packaging system acceptance and reduce the prospect of delays in bringing new medical devices to market. Specific recommended actions include:

- **Don't delay the specification process** - Packaging specification should be an integral aspect of the development process for new medical devices. Draft packaging specifications and protocols should be formulated at the earliest possible stages and evaluated in conjunction with product requirements to provide time and flexibility to address unanticipated issues.

- **Evaluate third-party packaging options** - Third-party packaging suppliers can be an excellent source of information and ideas on packaging systems that are suitable for specific applications. In many cases, third-party suppliers may also have off-the-shelf packaging solutions that meet or exceed ISO 11607 requirements, thereby eliminating the packaging validation process altogether and speeding the product approval process.

- **Evaluate multiple packaging options** - Achieving the ideal packaging system is likely to involve compromises and tradeoffs as the design team works to address device-specific requirements. Also, even when previously validated packaging systems are not suitable, it may be possible to bypass or eliminate some specific aspects of packaging validation based on how a chosen packaging system is designed or assembled. Exploring a number of possible packaging options can offer greater latitude in meeting stringent or challenging product requirements, and in speeding the packaging validation process.

- **Conduct preliminary testing** - Whether conducted by the packaging system manufacturer or by a third-party testing organization, preliminary testing of specific packaging systems to evaluate the impact of sterilization and transportation can identify and eliminate systems that don't meet specification requirements while also helping to more fully characterize and prioritize packaging systems that do.

Some of the Case Studies:

Market study samples:

Market samples of sterile medical devices were picked up from well-known brands from market/medical outlets and performed a validation on the sample to determine the performance of sterile barrier system of the device.

Design Validation of Shipper Box for Perfume transport:

We found a need for validation of shipper box used to transport perfume. In this case, the client faced an incident where the perfume leaked, damaged the perfume container, and scratched the labels. In order to overcome this, protocol was developed to overcome the incident and validate the perfume packaging to prevent damage during transport to various parts of the world.

Human Factors Engineering services for combination products and medical devices:

Validating poison prevention packaging was done through testing with a real-life scenario. Children were asked to open the packages under normal conditions thus checking the safety aspects of the packaging design and labelling.

Validation of shipper box for transport simulation:

Validating the shipper boxes used for transport of product was accomplished by simulating the transport scenario and checking the suitability of the product packaging during transport.

Design: Questions to Ask?

- What are the guidelines and recognized standards in the countries targeted for product sales?
- What is the list of required tests for my packaging qualification dossier?
- What are my product families?
- What sampling method should I choose for my packaging qualification?
- What type of microbial barrier does the packaging have (airtight or porous)?
- What type of physical barrier does the packaging have?
- Isn't the medical device liable to penetrate the packaging if it falls or due to transport vibrations?
- Is the packaging material compatible with sealing process?
- Is the packaging compatible with shelf life of the medical device?
- Is the packaging compatible with the labelling process?

Reasons for Choosing UL's Medical Device Testing Laboratory in India

- Acknowledged expertise in medical device testing
- ISO 17025 accredited laboratory
- Our experts can assist you with your regulatory processes, and help you determine validation protocols
- Our collaborative interaction with you will save time in having your batches released and reduce your transport costs

Services provided:

Distribution Simulation Testing

1. Room conditioning
2. Conditioning at low and high temperature as per ASTM D4332
3. Compression (Vehicle Stacking testing) as per ASTM D642
4. Vibration testing (Random) as per ASTM D4728.
5. Drop testing as per ASTM D5276

Package Integrity Testing (Test Procedures)

1. Visual inspection according to ASTM F1886/F1886M
2. Bubble test according to ASTM F2096
3. Burst test according to ASTM F1140
4. Heat Peel Seal Strength as per ASTM F88/F88M and EN 868-5.
5. Dye test as per ASTM F1929
6. Measurement of seal width as per ASTM F 2203.
7. Air permeance Non -porous material according to ISO 5636-5- Gurley method

Stability Testing as per ISO 11607-1: (Require both accelerated and real time to be performed simultaneously).

1. Accelerated Aging according to (ASTM F 1980)
2. Real-time Ageing

Summary + conclusion

Working to ensure the safety of sterile medical devices is a key element in efforts to reduce the incidence of HAIs in hospitals and other healthcare settings. The ISO 11607 series of standards defines the validation requirements applicable to packaging systems used in conjunction with terminally sterilized medical devices. The standards detail specific approaches for validating the packaging process or processes, the shelf-life of a given packaging system and the packaging system's ability to withstand the rigors of transportation, handling and storage.

Packaging system validation conducted in accordance with the requirements of the ISO 11607 series of standards can be complex and time consuming. Device manufacturers are therefore encouraged to evaluate packaging specifications early in the product development process, to consider multiple packaging options, and to conduct preliminary testing to avoid setbacks that could delay device approval by regulators. For some device manufacturers, third-party packaging suppliers may be able to provide ISO 11607-compliant solutions that are suitable for their specific requirements. The manufacturer needs to conduct teh three tests of integrity, distribution and stability for their product to cross regulatory hurdle. Some tests are time consuming and need expert opinion for selection of test and monitor the study and interpret the study results as per the expectations of Regulators.

UL provides a complete one-stop-shop, from the beginning of your product design, focused on getting your product into the market

For further information on requirements and validation testing methods applicable to packaging systems for medical devices, contact Medical.Inquiry@ul.com. Or go to UL.com/Healthcare.