VALIDATING MEDICAL DEVICE 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.

In this UL white paper, we’ll discuss 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 white paper concludes with some recommendations for manufacturers on the selection and evaluation of suitable packaging and packaging materials for medical devices.

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 U.S. 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.

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 with the requirements of the ISO 11607 series of standards, Packaging for terminally sterilized medical devices. And 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 actually consists of two separate parts. The first part, 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.

Validation of Packaging Processes Under ISO 11607-2

Under the requirements of ISO 11607-2, all packaging processes related to the SBS must be validated. The goal of validation testing is to demonstrate the efficacy and reproducibility of the packaging process in producing a stable SBS. Various examples of packaging processes subject to validation under the standard include:

- Rigid and flexible blister formation
- Pouch, reel or bag formation and sealing
- Form/fill/seal automated processes
- Kit assembly and wrapping
- Assembly of sterile fluid-path products
- Tray/lid sealing
- Filling and closing of reusable containers
- Folding and wrapping of sterilization sheets

The initial validation evaluation of packaging processes consists of three separate qualification steps, as follows:

- **Equipment installation qualification** - In the instrument qualification (IQ) process, equipment to be used in packaging processes is evaluated to help ensure that it operates as intended. Specific parameters typically include the installation setting and the environmental conditions to which the equipment is expected to be subjected, to help ensure that they conform with the specifications of the equipment manufacturer. Software validation may also be required in cases
where the operation of installed equipment is controlled or managed by software. Finally, the IQ evaluation should include an assessment of operator training, as well as instructions for routine equipment cleaning and maintenance.

- **Operational qualification** - In the second qualification step, operational qualification (OQ), the instrumental parameters for the forming, sealing and/or assembly of packaging systems are evaluated. The goal of OQ evaluation is to help ensure that all predefined packaging process requirements can be fulfilled within predetermined manufacturing limits. OQ evaluation is typically conducted with each type of packaging material used and with each unit of equipment used in the processing of that material. OQ evaluation does not require the inclusion of a medical device within the packaging being evaluated.

- **Performance qualification (PQ)** - The final qualification step, performance qualification (PQ), evaluates whether the packaging processes consistently produce an acceptable SBS under specific operating conditions. Similar to OQ, PQ evaluation is conducted with each type of packaging material used and with each unit of equipment used in the processing of that material. In PQ, samples from three separate packaging production runs that include the intended sterilization process are evaluated and compared with the predefined requirements for the packaging, for example, appearance, seal width, strength and tightness. However, unlike OQ, PQ evaluation is conducted on packaging that includes a medical device.

In addition to the initial validation, packaging processes are subject to revalidation when changes are made to the packaging equipment, packaging materials or any part of the packaging process that could compromise the results of the initial validation or affect the sterility, safety or efficacy of the sterile medical device. Some examples of changes that trigger the need for revalidation include changes in raw materials used in packaging, new equipment, changes in the sterilization process, or any changes in the applicable quality or process control indicators that signal a potential deterioration in the integrity of the SBS.

It is also advisable to consider conducting periodic revalidations of packaging processes. This is because the cumulative effect of multiple minor changes could adversely impact the validation status of packaging processes. Often, a periodic revalidation can be as simple as performing a PQ on a single production run and comparing the results with those from the initial PQ. Results that are consistent with those of the initial PQ are usually sufficient to verify the continued validity of the initial validation results, while deviations may signal the need for further evaluation.

**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 of time 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 of 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. And 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
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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 ASTM D 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.

Some Recommendations for Device Manufacturers

As this paper illustrates, validating packaging for terminally sterilized medical devices is a complex
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process that typically requires years to complete. However, medical device manufacturers can take a number of 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.
Summary and 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.

For additional information about the ISO 11607 series and UL’s testing services related to medical device packaging, email medical.inquiry@ul.com, or visit www.ul.com/medical.