



# Validating medical device packaging



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# Executive Summary



According to the U.S. Center for Disease Control and Prevention, approximately 1.7 million patients acquire healthcare-associated infections (HAIs) while being treated for other health issues, resulting in more than 98,000 deaths each year (one in 17 patients).<sup>1</sup> Ensuring the sterility of medical devices is an important tactic in the overall effort to reduce the rate of HAIs and other infections in hospitals and 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.

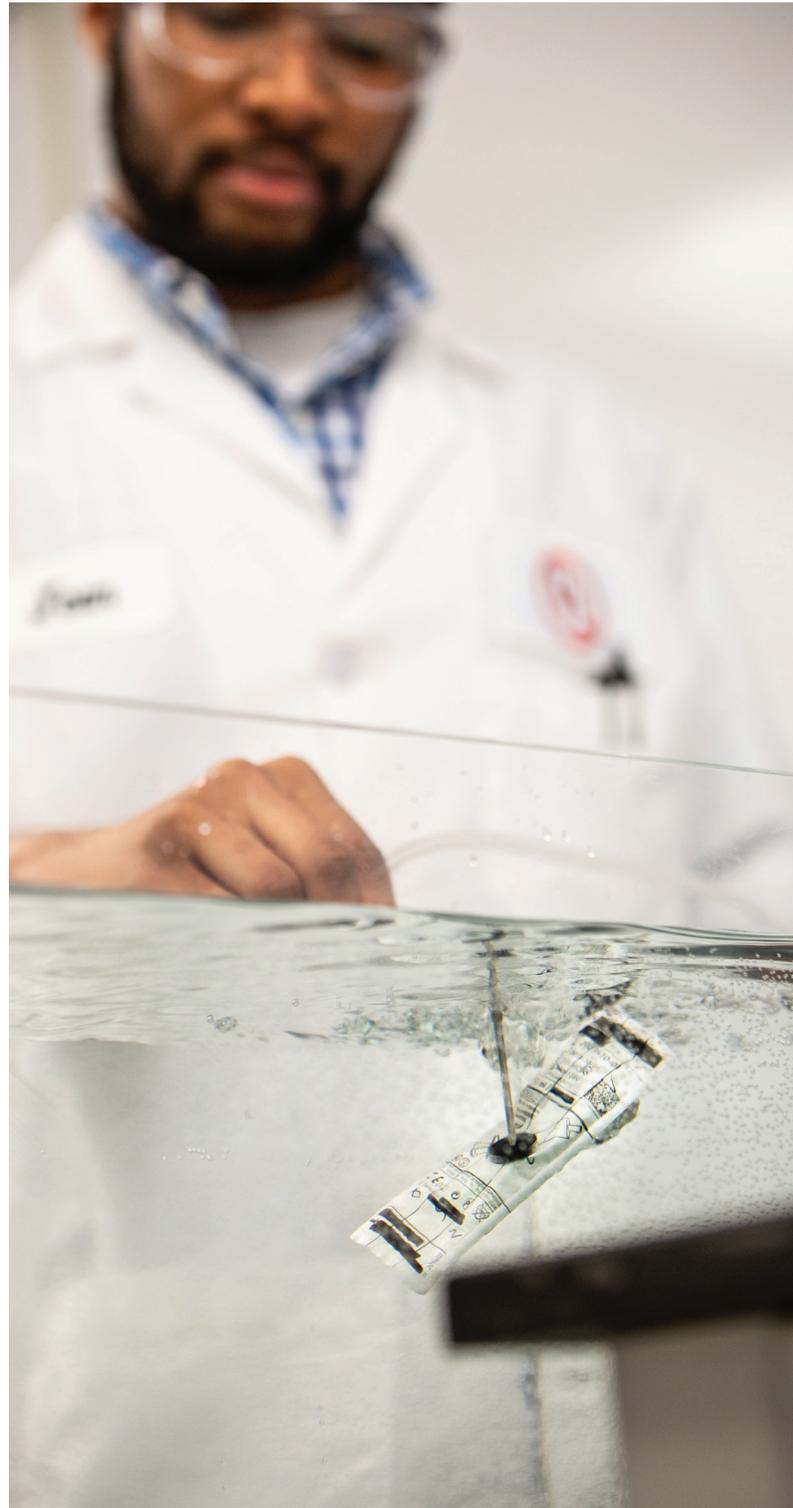
In this UL white paper, we'll discuss the requirements and validation testing methods applicable to packaging systems and/or materials used in conjunction with sterile medical devices. Beginning with a review of the importance of packaging validation for medical devices, the white paper then presents a summary of the requirements in the 2019 editions of ISO 11607-1 and ISO 11607-2, and provides details on validation testing as prescribed in the standards. 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. To illustrate, a search of the medical device recall database maintained by the U.S. Food and Drug Administration (FDA) found that packaging-related issues accounted for 355 Class II medical device product recalls during 2017 and 2018. This represents more than 5 percent of the approximately 6,800 total recalls issued during that period.<sup>2</sup>

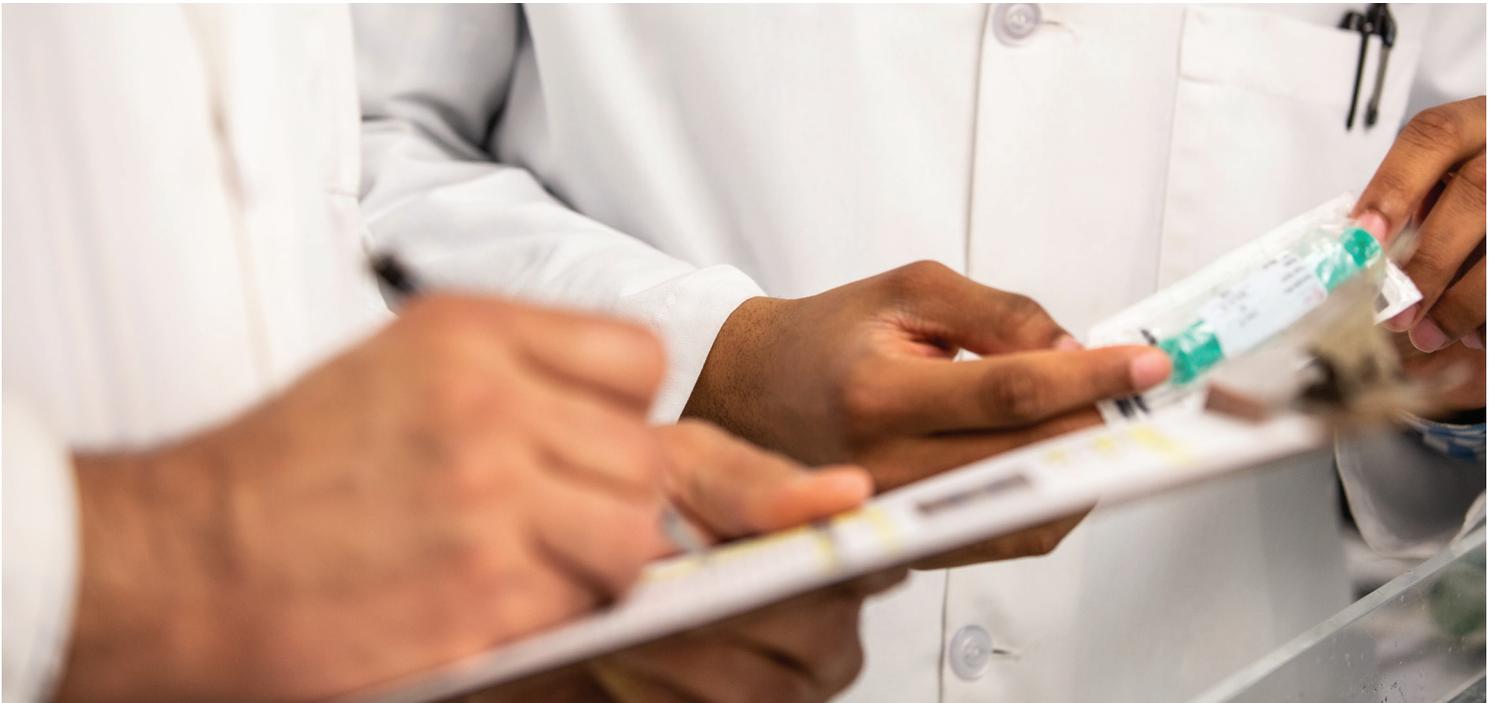
A review of the reasons for these device recalls sheds light on some of the potential health and safety issues associated with defective medical device packaging. Recalls were initiated in response to packaging residue that adhered to the surface of the enclosed sterilized medical device, packaging designs and sealants that failed to maintain the integrity of the sealed package, and packaging that posed a risk of infiltration of moisture and other liquids. Any of these defects could have resulted in the loss or compromise of the sterility of the packaged medical device, potentially exposing patients to harmful pathogens.

According to the FDA, Class II recalls involve a situation in which “a product may cause a temporary or reversible health problem or where there is a slight chance that it will cause serious health problems or even death.”<sup>3</sup> Fortunately, no deaths or injuries have been directly attributed to the medical devices affected by these recalls. However, 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

In an effort to mitigate the potential risks to patients, 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 updated in early 2019, the ISO 11607 series focuses on the packaging for terminally sterilized medical devices and consists of two separate parts. The first part, ISO 11607-1, *Requirements for materials, sterile barrier systems and packaging systems*, establishes design and design validation requirements for sterile barrier systems and packaging systems. The second part, ISO 11607-2, *Validation requirements for forming, sealing, and assembly processes*, describes the requirements and activities for developing and validating the processes used in the manufacturing and assembly of the package system.

Definitions common to both standards align with those found in the 2018 revision of ISO 11139, *Sterilization of health care product - Vocabulary of terms used in sterilization and related equipment and process standards*. Some key definitions include:

- **Sterile barrier system** - A sterile barrier system (SBS) is defined as the “minimum package that minimizes the risk of ingress of microorganisms and allows aseptic presentation of the sterile contents 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) maintain sterility of the packaged device; 2) provide protection against biological risks; and 3) prevent damage that could lead to device malfunction.
- **Preformed sterile barrier system** - This term applies to an SBS that is “supplied partially assembled for filling and final closure or sealing.” Examples of preformed sterile barrier systems include pouches, bags and reusable containers.
- **Aseptic Presentation** - The transfer of sterile contents from its sterile barrier system using conditions and procedures that minimize the risk of microbial contamination.



ISO 11607-1 and 11607-2 adopt similar essential “General requirements,” which include compliance with applicable quality standards (e.g., ISO 9001, ISO 13485, ANSI/AMMI ST 90), the adoption of formal sampling plans and test methods for assessing packaging materials, and the maintenance and retention of documentation validating compliance. But, the 2019 revisions of the standards also incorporate risk management as a general requirement, consistent with the provisions of ISO 14971, *Medical devices - Application of risk management to medical devices*, and other applicable standards.

Both standards also include several informative annexes intended to provide additional guidance on the application of the requirements of each standard.

# Specific Requirements under ISO 11607-1

The specific focus of ISO 11607-1 is on the qualifications of materials, preformed SBSs and SBSs used in the packaging of medical devices (addressed in Clause 5), and on qualifying the design and development of packaging systems (addressed in Clause 6). Some specific properties of materials, preformed SBSs and SBSs evaluated under the standard include: 1) physical and chemical attributes; 2) the strength and integrity of the microbial barrier; 3) biocompatibility and toxicological characteristics; 4) the influence of environmental factors (e.g., temperature, humidity, UV light, etc.); and 5) compatibility with the intended sterilization process.

Requirements specific to the design and development of packaging systems for medical devices are intended to help ensure that the packaging system minimizes any potential health and safety risks to either the user or the patient, while also maintaining the integrity of the SBS. The standard specifies a number of design factors that must be taken into account, including:

1. the physical shape and configuration of the device;
2. the presence of sharp edges or protrusions; and
3. potential exposure to specific risks (e.g., radiation, moisture, mechanical shock, static discharge, etc.).

Importantly, the 2019 revision of the standard also includes a new Clause (Clause 7), requiring the completion of a usability evaluation to verify that the sterile contents of an SBS can be aseptically removed for use. The usability evaluation involves an assessment of specific human factor aspects of the packaging, such as the ability of a user to: 1) easily identify where to initiate the process of opening the package; 2) open the SBS without contaminating or damaging the enclosed device; and 3) remove the device without compromising its sterility.

Clause 8 of ISO 11607-1 describes the performance and stability testing necessary 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, as discussed later in this paper, 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.



A separate new Clause (Clause 10) recommends the visual inspection of all barrier systems that are labelled as sterile immediately prior to use for any breaches or obvious defects in the packaging and, when appropriate, the inclusion of labeling or other information instructing the user to visually inspect the packaging immediately prior to use.

As previously noted, ISO 11607-1 includes several informative annexes, including an annex added in the 2019 revision of the standard (Annex D) that encourages users to adopt “life-cycle thinking” in the design of SBSs to help reduce potentially adverse environmental impacts. The standard also includes a normative annex (Annex C) that specifies a test method to measure the resistance of impermeable materials to the passage of air.

# 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 actual packaging process in the production of a stable SBS. Various examples of packaging processes subject to validation under the standard include:

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

To help organize the packaging processes subject to validation in a given setting, the 2019 revision of ISO 11607-2 requires package manufacturers to establish a “process specification” (Subclause 5.1.2) for the packing forming, assembly and sealing processes. Specifically, the process specification defines: 1) the required process output; 2) the variables and attributes that need to be monitored to maintain the process as required; and 3) the process control parameters necessary to produce the specified process output.



With the process specification in place, the validation of packaging processes then consists of three separate qualification steps, as follows:

- **Equipment Installation Qualification** - In the installation 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** - 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 evaluated under ISO 11607-2 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 (Subclause 5.7). 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

Meeting the requirements of the ISO 11607 series of standards requires manufacturers of packaging materials and systems used in conjunction with sterilized medical devices 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 F1980-16, 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 on 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. 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.

Note 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 (extensively updated in the 2019 revision). 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 D4169, 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 SBS integrity 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 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 current 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 + 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](mailto:Medical.Inquiry@ul.com), or visit [UL.com/Healthcare](http://UL.com/Healthcare).**

## End Notes

1. Health care-associated infections – an overview,” published in Infection and Drug Resistance, 2018 November 15. Web. 25 March 2019. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6245375/>
2. Based on a review of the data available through the Medical Device Recalls database maintained by the Center for Devices and Radiological Health of the U.S. Food and Drug Administration. Web. 25 March 2019. <https://www.fda.gov/MedicalDevices/Safety/ListofRecalls/default.htm>
3. “What is a Medical Device Recall?” from the website of the U.S. Food and Drug Administration, last updated September 26, 2018. Web. 25 March 2019. <https://www.fda.gov/MedicalDevices/Safety/ListofRecalls/ucm329946.htm>

