11 Frequently Asked Questions about ISO 11607-1

ISO 11607-1 is the principal guidance document for validating terminally sterilized medical device packaging systems. Packaging must comply with ISO 11607-1 in order to satisfy European regulations and obtain a CE Mark. ISO 11607-1 is also a FDA Recognized Consensus Standard which is used in satisfying portions of device premarket review submissions. Fulfilling the requirements within ISO 11607-1 ensures that a medical device packaging system allows sterilization, provides physical protection and maintains sterility up to the point of use.

ISO 11607-1 consists of four key areas:

1) Stability Testing (accelerated aging and real time aging)
2) Performance/Dynamics Testing
3) Package Strength Testing
4) Package Integrity Testing

This ISO standard also addresses packaging materials by presenting requirements for their physical properties and material performance as well as requirements for sample size, labeling, documentation.

DDL receives many questions from medical device manufacturers and packaging engineers regarding ISO 11607-1. Here are eleven of the most frequently asked questions with answers based on our experience.

1) Why is testing performed at every step of the packaging validation process?
Performing package strength and package integrity tests throughout the validation process helps to more easily determine the root cause of any failures. If testing were left until the end of the process and a failure were to be found, it would be very difficult to determine the point at which failure actually occurred in order to take corrective action and as a result would cost the developer valuable time and money.

2) Why does the standard separate accelerated aging and real time aging from performance/dynamics testing?
ISO 11607-1 defines stability testing (i.e. accelerated aging and real time aging) and performance testing (i.e. environmental and distribution simulation) as separate entities, evaluating different aspects of the sterile barrier package. This allows the tests to be carried out separately and not as a sequential series of tests on the same packages.

This separation allows the evaluation of the effects of aging via whole package integrity and seal integrity testing at time intervals specified by accelerated and real time aging protocols. Test samples are pulled from the aging populations in order to evaluate physical package integrity over time. An example of a whole package integrity test is ASTM F2096, “Standard test method for detecting gross leaks in porous medical packaging by internal pressurization (bubble test).” An example of a seal integrity test is ASTM F1929, “Standard test method for detecting seal leaks in porous medical packaging by dye penetration.” Seal strength can be characterized by executing a test such as ASTM F 88, “Standard Test Method for Seal Strength of Flexible Barrier Materials”. In addition, having some advance knowledge of the behavior and performance of the selected packaging materials through an accelerated aging protocol helps the packaging engineer anticipate potential negative effects of extended high temperature exposure on materials and seals.
This separation also allows the interaction between the packaging system and the protected product(s) to be evaluated as they respond to the stresses imposed by the manufacturing processes, sterilization processes and the handling, storage and shipping environments. This interaction can be evaluated via packaging system performance testing such as ASTM D4169 followed by whole package and seal integrity testing on the same packages.

The data obtained as a result of separating stability and performance testing provides the packaging engineer with valuable information on the packaging materials' integrity performance over time and the packaging system’s integrity performance throughout the manufacturing process, sterilization process and the subsequent handling, storage and shipping environments.

Creating a sequential aging and package performance protocol will create a very rigorous validation of the packaging process. However, choosing not to perform sequential testing and carry out stability and performance testing as separate entities still allows for compliance with the ISO 11607-1.

3) **Is environmental extremes testing considered a requirement of ISO 11607-1?**

It is not accurate to say that environmental extremes testing is a requirement. However, the standard indicates in several sections (6.2.3 (h), 6.2.3. (j), 6.3.5 and 6.4.4 (NOTE)) that the package design shall consider the effects of distribution, storage and handling; this is where environmental extremes should be taken into account.

4) **What is a reasonable rationale for sample size selection?**

The selection of sample size is a difficult question, as it depends upon the level of risk severity and risk probability associated with the process. If the process of making a package causes many defects in itself, and the process cannot be refined to reduce the defects, then the sample size may need to be higher. Likewise, if the result of a defect may cause significant harm to a patient, then more testing will be required to ensure that the defect is found before it can cause harm. For packaging, the process can usually be refined by compliance to standards like ISO 11607 to produce packages that have a high probability of withstanding hazards and reaching their intended destinations without failure. Also, a well-established quality control process ensures that the packaging process is in control within its specified limits of operation as defined in the process validation.

5) **Is it true that dye penetration is unreliable for packages using Tyvek?**

No, this is not true. However, it takes special care and training to identify the difference between a true channel versus a permeation of dye fluid through the Tyvek. If a channel leak is present, the dye will migrate through in a matter of seconds. If the dye is allowed to be in contact with an area of Tyvek for too much time, it will permeate through. The usual length of time to allow the dye to be in contact with a seal is about ten seconds.
6) Why do you need to include the IFU when testing?
The IFU is a component within the package system that is typically inserted into the protective package. Many times it is loose and thereby allowed to move around within the package. We've seen instances where the IFU causes damage to the sterile barrier system. In one instance, a staple caused a tear in the poly component of the pouch. Evaluation under dynamic shipping and handling conditions while using ‘complete’ package system would have revealed this problem.

7) Can microbial challenges be eliminated from package validation? If so, how can the results of physical testing be justified without correlation to microbial data?
For package validation, microbial challenge testing is performed infrequently or not at all by most medical device manufacturers. The use of physical testing to prove the maintenance of package integrity where a validated sterilization process has been demonstrated is sufficient evidence to indicate that the product is sterile.

Porous package substrates must be challenged and demonstrate that the substrates themselves are microbial barriers. This is addressed in the note associated with ISO 11607-1, Section 5.2.3; within Annex B of the standard there are four suggested test standards referenced for microbial barrier testing including ASTM F1608 “Standard Test Method of Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)”. For non-porous materials, the manufacturer can demonstrate that a substrate is impermeable through the use of ISO 5636-5 and in that manner satisfy the microbial barrier requirement; this is addressed in Annex C of ISO 11607-1.

8) In some medical devices, double pouch packing is used although these devices are light in weight. What is the specific reason of using a double pouch?
Usually when a dual or double pouch is used it is for providing a dual sterile barrier because the delivery of the device to the sterile field requires that the inner package be dropped into or is handed in the sterile field. There is no requirement from FDA that all devices have a dual barrier. Rather it depends on the clinical application of the device.

There are many aspects to consider when designing a package for a terminally sterilized medical device. ISO 11607 provides a basis to evaluate the capability of the package design to deliver the medical device to the end user in the condition to which it is intended to be used, without compromise to patient health and safety and product efficacy. Many questions regarding the interpretation of the standard’s requirements have been raised. The answers to these frequently asked questions provide one interpretation based on years of experience and technically sound reasoning. There are many pathways to compliance and documenting the rationale for the pathway that is chosen.

9) Is it a recommendation or a requirement that testing be conducted on a product produced under “worst case” parameters as opposed to a product produced under nominal conditions?
Testing under “worst case” production parameters is a requirement for the manufacturer. The reasoning is that if the sealing machines, for example, are operating at the high or low extremes of established parameters, then there is a possibility that while the packages might meet production quality requirements they may not possess the strength or integrity needed to survive the rigors of shipping, handling and storage.
10) How can you ensure that the pouch manufacturer is using their ‘worst case’ pouches for package validations? Do you need to request this from the pouch manufacturer?

You can trust your manufacturer or obtain a certification that they have produced the packages under worst case conditions. You should request that packages for performance qualification testing are produced under the manufacturer’s worst case conditions but within their determined tolerances. In order to comply with this provision, as stated in section 6.3.4, packages must be produced specifically for the performance evaluation (final package validation) as opposed to taking packages from a normal production lot. So, a special manufacturing run should be conducted with the machine set up to produce “worst case but acceptable” packages.

11) How does “worst case” manifest itself in a package design?

In a sterile barrier system, seal strength is probably the first property to be affected under “worst case” processing. Another way in which this processing scenario is manifested is through the embrittlement of materials due to overheating. As mentioned above, ISO 11607, Annex B addresses the physical properties and material performance of packaging materials and includes suggested physical tests for brittleness.

There is no definition of “worst-case” provided by the standard. This is left to the manufacturer who must consider the package, the product to be protected and processes involved, providing a rationale or justification for their “worst case”.

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