

How to Validate a Packaging Process

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Some of the key elements of achieving a validated packaging process are described. A peel-pouch sealing machine is used as an example.

The approach

Packaging a medical device has several critical functions. This article examines how to ensure that the packing process delivers adequate seals to ensure that the required product environment is maintained over the claimed shelf life of the product. Similar principles apply whether the goal is to maintain sterility, a moisture barrier or some other specific atmosphere. A validated production process is required because many of the quality assurance tests for packaging are destructive. Speed of testing can also be a problem, which often leads to an inability to test all packs.

The approach is based on ISO 11607 Packaging for Terminally Sterilised Medical Devices, using a peel-pouch sealing machine as an example. This standard takes a holistic approach to pack manufacture. Some parts of the standard that do not refer to packaging process validation have been addressed in previous articles.¹ As with any validation process it is important to start out with a plan. To make a plan, it is essential to know what is to

be determined. A failure mode and effect analysis (FMEA) is a good place to look for what to test; a pass and fail result must also be defined.

A typical plan

- Brainstorm FMEA and risk analysis
- Define parameters to test
- Identify test methods
- Define desired outcomes
- Perform analysis: factory-acceptance trials (FAT), installation qualification, operational qualification and process-performance qualification
- Verify performance following post-production processes or shelf life.

Brainstorm FMEA

A simplified version of a FMEA chart for a packaging process could follow the reasoning shown in Table I. In the interests of brevity, this Table gives only an outline of an FMEA. Medium severity denotes when there is no danger to the patient because the problem is aesthetic or easily detected. In a full FMEA the implications of the fault need to be quantified together with the rate of incidence and likelihood of detection. This is usually done with a scoring system.

Define parameters to test

The FMEA shows that seal integrity, seal strength and appearance need to be tested. This leads to the question: what process elements do I need to validate? On a pouch-making machine the process variables that affect seal reliability include

- heat transfer to weld area: speed of web through the machine and temperature of heating elements
- pressure applied to the seals.

Pouch-sealing machines are generally insensitive to environmental conditions. If packaging is taking place within a clean room or in another temperature-controlled environment, they can be disregarded. If an intermittent high airflow is present, this may need to be taken into account. Placing the equipment near doors, hatches or air vents can create unpredictable cooling rates and therefore variable performance. This problem may go unnoticed during machine validation and clean-room conditions may not be normal, for example, if it is a new installation not yet populated. It can be indicated by variable results in batch production quality. Correcting environmental problems

may require a repositioning of the equipment, placement of partitions to deflect the airflow or refinement of clean-room control.

Identify test methods

Once it is known which parameters (such as seal strength, continuous seal and resistance to storage) are to be tested, the next step is to determine how to test these. Tests for seal strength are

- tensile strength test (ASTM F-88)
- peel strength (90° tensile shear EN 868)
- burst strength (ASTM F1140).

Tests for seal integrity are

- fibre or transfer adhesive
- dye penetration (EN 868-1 Appendix F/ASTM F1929)
- vacuum decay nondestructive leak test (Vacuum decay method WK1129 is currently being drafted by ASTM)
- underwater internal pressure test
- CO₂ tracer gas method (ASTM F2228-02).

The test for appearance is

- visual inspection.

An electronic vacuum leak or burst test offers several advantages. It provides subjective results, automatic recording of results and economy (inexpensive equipment in comparison to gas analysis or tensile testing); and because it is a test for the entire package, it will always test the weakest point.

F2228-02 is a recently published ASTM standard that describes a non-destructive method for testing medical trays. CO₂ tracer gas is injected into the pack and reanalysed later. This method also has the benefit of providing electronically recorded results.

Table II shows what the test programme may look like. The required result must be defined prior to testing.

Perform analysis

The number of products required for validation may be different from those used in ongoing production. The occurrence column on the FMEA chart (Table III) is a useful place to obtain information to help decide how many items to test.

The FMEA highlights the fact that it is during the initial start-up of a →

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Table I: A simplified FMEA chart for a packaging process.

Pack Failure Mode	Effect	Where detected	Severity
Seal is not welded	Product not retained	At cartoning	Medium
Seal partially welded	Sterility not maintained	May go unnoticed	High
Seal closed but not sufficiently strong	May not survive claimed storage period	May go unnoticed	High
Seal too strong	Difficult to open pack	At point of use	Medium
Burning in weld area	Aesthetic problem	At point of use	Medium
Heat transfer to product	May damage heat-sensitive product	May go undetected	High

Table II: The test programme may look something like this.

Property to Test	Test Method	Positive Result
Seal is not welded	Visual	Weld around pack appears to be complete
Seal partially welded	Pack inflation test	Maximum hole size below calibrated leak level set on calibration machine for nonporous pack
Seal closed but not sufficiently strong	Pack inflation test	Application of vacuum does not cause detectable leakage for nonporous pack. Burst in excess of calibrated level for porous pack
Seal too strong	Tensile shear test	Manual tear to "feel right" or tensile test to calibrated level
Burning in weld area	Visual inspection	No evidence of colour change
Heat transfer to product	Product functional test	No evidence of product degradation

Table III: Example occurrence column on the FMEA chart.

Pack Failure Mode	Occurrence	Detection Rate
Seal is not welded	Low except at machine start up	Low unless completely unwelded

Table IV: Equipment Qualification checklist should include these types of parameters.

Parameter	Measure
Web material and variability compatible with equipment	Tested over range and documented
Temperature, pressure and speed measurement devices available and calibrated if required	Documented
Upper and lower temperature operating range identified for each element	Recorded
Upper and lower pressure range identified for each element	Recorded
Upper and lower speed range identified within temperature and pressure ranges	Operating window recorded
Operation and set-up manuals available	Documented
Maintenance and cleaning procedures and schedules available	Documented
Software validated if bespoke	Documented
Operator training delivered	Documented
Overall machine design and assembly in compliance with cGMP principles	Verified and documented

→ machine that unwelded product is most likely to be experienced. Therefore, the standard operating procedures (SOPs) may require the initial packs to be discarded. Once warmed up, the equipment should be protected by alarms on the elements that affect seal quality. It can be expected that a large number of products will need to be made to find a failure. Existing internal SOPs detailing acceptable quality levels and sterilisation standards should be consulted to determine the number of packs to examine (for example, ISO 3951: Sampling procedures for inspection by variables).

The first phase of a validation study is performed at the machine manufacturer's works. Here, initial ranges can be identified for the variable elements of the process. This is often referred to as a FAT. In ISO 11607 this process starts with Equipment Qualification. A checklist should be used that includes the types of parameters shown in Table IV.

Installation qualification

Once the equipment is in place in its manufacturing environment, the initial validation process is the Installation Qualification procedure. The goal here is to show that the machine is installed correctly and that all documentation is in place. All measurement and alarm devices should be working correctly and all process

elements should perform as expected. Product-specific set-up procedures can also be developed at this stage.

Process Verification or Operational Qualification

This process is used to identify the extremities of the process-operating window of the equipment. Table V shows the variables.

It can be seen that it is necessary to test 2^n variations where n is the number of variable parameters. However, different elements can be grouped together, that is, two different side seals and two different end seals on the same pack can be examined during a machine run at one set of operating conditions.

ISO 11607 also calls for visual inspection to verify that the product is correctly positioned in the pack. This inspection combined with seal integrity testing will identify any damage such as tears or punctures that are caused to the web during packaging or other processing.

Process Performance Qualification

Next is the main area of machine validation, the Process Performance Qualification. Multibatch runs are tested at the extremities of the operating window to ensure that good quality packs are produced when no alarms are sounding on the equipment. This, combined with machine calibration and regular batch checks, provides confidence in the production process. It is normal to run each set of conditions in three separate batches and to look for congruence of results. The full gamut of package validation tests should be applied to the packages produced at this stage.

Verify performance following postproduction

Validated pack samples may need to be further tested to demonstrate that they are not adversely affected by such things as the sterilisation process, transit and storage.

Other considerations

Other important performance considerations for packages, which are not addressed in this article include

- user acceptance
- biocompatibility
- physical product protection
- web-material performance.

Conclusion

There are many variables in the packaging process, including the design of the pack and product handling following packaging. However, there are relatively few tests for examining pack performance. Destructive tests and speed of testing can pose problems for high-volume processes, proving the need for a validated process. As ever, a good plan and logical approach covering the extremes of process variables and handling possibilities can lead to a relatively simple validation process. However, validation does not completely remove the need for batch and in-process checks.

References

1. M. Turner, "How To Leak Test Sealed Packages," *Medical Device Technology*, **12**, 9, pp. 98 (2001).

Further reading

- EN 868 Packaging materials and systems for medical devices that are to be sterilised
- ISO 11607 Packaging for terminally sterilised medical devices
- ISO 5636 Paper and board – determination of air permeability
- ASTM 1140 Standard test methods for internal pressurisation failure resistance of unrestrained packages for medical devices
- ASTM F1980 Standard guide for accelerated ageing of sterile medical device packaging
- ASTM F88 Standard for seal strength of flexible barrier materials
- ASTM F2228-02 Nondestructive detection of leaks in medical packaging which incorporates porous barrier material by CO₂ tracer gas method
- R. Pilchik, *Validating Medical Packages*, CRC Press, Boca Raton, Florida, USA, (2002). [mdt](#)

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Table V: Variables at operating window extremities.

Variation	Temperature	Pressure	Speed
1	Maximum for each element	Minimum for each element	Lowest
2	Maximum for each element	Maximum for each element	Lowest
3	Maximum for each element	Minimum for each element	Highest
4	Maximum for each element	Maximum for each element	Highest
5	Minimum for each element	Minimum for each element	Lowest
6	Minimum for each element	Maximum for each element	Lowest
7	Minimum for each element	Minimum for each element	Highest
8	Minimum for each element	Maximum for each element	Highest