

Product and Package Stability Studies

The Application of FDA Guidance

Introduction

In February 2008, the FDA issued 'Guidance to Industry' dealing with physical tests for packaging for sterile medical devices and shelf life testing. The guidance is entitled, "*Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products.*"¹

This guidance seeks to help manufacturers in understanding the challenge of demonstrating that their products maintain the sterility of product throughout their shelf lives.

We set out here to elucidate what that might mean to medical device manufacturers in a practical sense.

The Challenge

The FDA expects 'products labelled as sterile to be free of viable microbial contamination'¹ throughout their shelf life. A major role of the packaging system is to maintain this sterility during shipping and storage. The challenge is to demonstrate this. Not an easy task when microbial contamination in a pack may be impossible to detect visually and the majority of the tests (physical and microbial) available for assessing pack quality are destructive. Furthermore, if a product has a claimed shelf life of five years it is not commercially viable to wait for the full period before testing.

Therefore, validation techniques are used to ensure that the packs are robust and the production processes reliable². Validation depends upon establishing the pack performance as part of the 'design outputs' phase of a project. Followed by regular QA and process monitoring on 'validated' equipment to ensure that this performance is maintained.

The obvious way to check for sterility is to open a pack and carry out a microbiological analysis of the contents. Check that the product is sterile. But, this is an attempt to demonstrate a negative situation. Proving that something is not there is not easy in practice. Testing for sterility can produce both false negatives and false positives. The false negative comes from the possibility that there may be a fault in the pack but no organism, that is viable in your chosen culture medium, has entered the pack. To overcome this we can subject the outside of the pack to an aerosol (or dust) containing known microbes and subsequently analyse the contents of the pack for these known organisms. That gives us a slightly different problem. It is extremely difficult to access the pack contents without contaminating them, even if the outside of the pack is treated chemically following exposure and prior to opening. This increases the likelihood of false positives caused by transfer of microbes to the product within at pack opening.

The guidance document helps to address this challenge by accepting physical testing in place of sterility testing.

Physical Testing

The Tests

The guidance document gives a non exhaustive list of possible integrity tests.

- Bubble tests (an integrity test which measures the minimum pressure required for gas to penetrate the pack membrane / media).
- Pressure/vacuum decay (an integrity test, measuring flow driven by a pressure differential across the pack membrane).
- Trace gas permeation/leak tests, (this integrity test measures flow of a gas from the pack driven by diffusion).
- Dye penetration tests (an integrity test for seal areas).
- Seal force (burst or tensile tests for seal strength),
- or electrical conductivity and capacitance tests (these integrity tests look for anomalies in materials).

The guidance document stresses that these tests do not replace initial sterilisation validation or sterility release tests in manufacturing. They are, however, relevant to a stability evaluation program, or shelf life test program.

It is also stated that the tests require proper validation. Validation methods vary according to the tests used and pack types.

These physical tests should be combined with environmental and ageing factors to simulate the conditions the product may be expected to encounter during transit and storage.

Ageing

Real time aging is often not a realistic option, especially for a new product or packaging system. Ageing can be accelerated for most medical devices and packages by following the Arrhenius equation³, which states that a 10°C temperature rise will double the rate of a reaction. Hence, storage at 55°C delivers one year of equivalent aging in under 6 weeks⁴. The guidance indicates that testing should be carried out at 12 month intervals up to the claimed shelf life.

Environmental Conditions

Prior to transport simulation packages may require conditioning according to the environments they will encounter in practice. Conditions are described in standards from IEC, MIL specs and ASTM⁵. These are typically:

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|-------------|------------------------|-----------------------|
| • Tropical | temperature 38°C | relative humidity 85% |
| • Desert | temperature 50°C | relative humidity low |
| • Frozen | temperature minus 20°C | relative humidity low |
| • Temperate | temperature 23°C | relative humidity 50% |

Shipping

Transport simulation for medical devices is commonly carried out according to ASTM D4169-05 *Standard Practice for Performance Testing of Shipping Containers and Systems*. This testing can incorporate; initial manual handling (ASTM D 5276-98 A), vehicle stacking (ASTM D 642-00 C), loose load vibration (ASTM D 999-01 F), vehicle vibration (ASTM D 4728-01 E), and final manual handling (ASTM D 5276-98 A).

Testing the Package and Product

To identify precisely what testing is required a risk analysis should be carried out.

Questions to ask include:

1. Does the product (or pack) deteriorate with time?
2. Is the product (or pack) labile at raised or lowered temperatures or even normal temperatures?
3. Is the product or pack sensitive to moisture?
4. What environment might the product be stored and transported in?
5. What are the environmental conditions in the hold of a plane or ship and on the dockside?
6. Does the product put pressure on the pack seals or materials?
7. What is the mass of the product and how much can it move around in the pack?

Product Testing

Products are usually tested against their normal QA specifications following aging and conditioning. The Risk Analysis (RA) and Failure Modes and Effects Analysis (FMEA) may indicate additional areas of testing which do not appear in the normal QA routine. An example might be additional tensile testing on joints or volume verification for products containing volatile fluids, both of which may be influenced by temperature fluctuations.

Package testing is dependant upon package design and materials.

Non Porous Packs

The widest choice of testing options is available for hermetically sealed packs. Pressure (vacuum) decay or tracer gas tests can be used to determine the integrity of the entire package. Allowing confirmation of both the web material and weld integrity.

A method described in ASTM F2095 - 07e1 *Standard Test Methods for Pressure Decay Leak Test for Flexible Packages With and Without Restraining Plates* is one option. A better alternative can be, ASTM F2338-05, *Standard Test Method for non destructive Detection of Leaks in Packages by Vacuum Decay Method*. In this test packages are placed in a chamber, which closely fits their profile. The chamber is subjected to a vacuum and leakage from the pack into the vacuum is measured as a pressure increase. This is analogous to pressure decay testing, where a positive

pressure is applied inside the product or pack. It delivers very accurate quantitative results.

There are a variety of gases, which may be used for tracer gas testing; hydrogen (5% in nitrogen), carbon dioxide and helium are all possibilities. For these tests packages can be sealed in an environment rich in the tracer gas. Or, the gas can be introduced after welding by the storage of the packages in an atmosphere of the tracer gas at elevated pressure. A probe is then used to locate and quantify any leaks.

Validation for both methods can be performed using pack perforations of a known size. For practical reasons the minimum hole that can be made is usually 12.5 microns in diameter. The validation is achieved by comparing packs with perforations to packs known to be intact. An integral pack can be tested and shown to pass a test. The same pack can then be perforated and used to challenge the test method.

Medical device manufacturers often question the 'hole' size used for the validation of these test methods. There are certainly some very small bacteria (*Brevundimonas (Pseudomonas) diminuta* (ATCC19146) has a diameter of 0.3 microns and a length of 0.8 microns). Viruses can be even smaller than this (typically in the nanometre range)⁶. However filtration of airborne particles is not just a sieving process. There are variety of other mechanisms which entrap particles⁷ such as diffusion (Brownian motion) inertial Impaction and electrostatic attraction. Hence although a hole may appear large, the filtration efficiency may be greater than initially expected. This is one of the reasons why porous packaging materials are effective at keeping products sterile.

Porous Packs

Different methods are required for the testing of medical device packages which have at least one porous element (for example paper or Tyvek®). Pressure decay and tracer gas tests are not suitable. Integrity testing for these packs is often split into two areas. One test for the materials prior to sealing and a second test for seals in completed packs.

Raw material tests on packaging webs are usually carried out by converters and manufacturers of these items. These tests include bubble point and electrical tests.

One method for examining complete packs is described in ASTM F2228 - 02(2007) *Standard Test Method for Non-Destructive Detection of Leaks in Medical Packaging Which Incorporates Porous Barrier Material by CO₂ Tracer Gas Method*.

Dye penetration testing is a simple alternative for assessing seal integrity. It is described in ASTM F1929-98 (2004), *Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration*. In this test a dye and surfactant are introduced into the pack and channels through the seals searched for visually. The validation method for this test is described within the standard. It involves placing very fine wires across the seal prior to welding. These can then be removed and the channels left behind tested for.

Other Tests

Bubble Test Web Material

Bubble emission testing involves applying a pressure to the lower side of a web material whilst a liquid is placed on the upper surface (it is captured horizontally). As the air/gas pressure is increased underneath the fluid contact surface is monitored. The pressure at which a bubble first appears being recorded. The test is often applied at goods inwards testing to accept web materials. ASTM F2096 - 04 *Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)*, describes a method for finding holes with a diameter greater than 250 microns in both spun bonded polyolefin and non porous packs.

Bubble Test Impermeable Packs

There is also a bubble test, which involves placing packs in a vacuum transparent chamber. The pack is immersed in fluid a vacuum drawn above the fluid, in turn drawing bubbles from the pack. ASTM D3078 - 02(2008) *Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission*. An alternative for large packs is to pressurise the packs internally. ASTM F2096 - 04 *Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurization (Bubble Test)*. Both these tests will only detect gross leaks, over 250 microns wide.

Electrical Conductivity and Capacitance Tests

These tests are often used on web materials. They look for perforations using charged plates either side of the web. An imperfection in the web will allow transmission of current or cause a change in capacitance.

Seal Force Tests

Seal strengths can be analysed using a tensile peel test or a burst test. The burst test is superior, because it is quicker and tests the entire seal line of a package. It is described in ASTM F1140 - 07 *Standard Test Methods for Internal Pressurization Failure Resistance of Unrestrained Packages*. A tensile test is described in ASTM F88 - 07a *Standard Test Method for Seal Strength of Flexible Barrier Materials*.

Conclusion

This particular guidance document seeks to clarify how device manufacturers can demonstrate the stability of their product and packaging substantiating shelf life claims without resorting to unreliable microbiological and sterility test methods. For practical application pressure decay, tracer gas, dye penetration and burst pressure tests are often used at the point of packaging and in stability studies. Whilst electrical and bubble tests are most applicable to material manufacturers and good inwards testing.

Note on materials

Standard test methods do exist for the assessing the materials used in porous packaging for terminally sterilised medical devices.

These include

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

ASTM F2638 - 07 *Standard Test Method for Using Aerosol Filtration for Measuring the Performance of Porous Packaging Materials as a Surrogate Microbial Barrier*

ASTM F1608 - 00(2004) *Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)*

EN868-1- *Packaging Materials and Systems for Medical Devices Which Are to Be Sterilized*

References

- 1 Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products, Center for Biologics Evaluation and Research Food and Drug Administration 22nd February 2008, <http://www.fda.gov/cber/gdlns/contain.htm>
- 2 How to validate a packaging process. Medical Device Technology, March, 2004, Turner, Mark
- 3 How to simulate shelf life for ageing trials: Medical Device Technology, January, 2002, by Turner, Mark
- 4 ASTM F1980 - 07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
- 5 ASTM D4332 - 01(2006) Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing
- 6 <http://en.wikipedia.org/wiki/Virus#Structure>
- 7 <http://www.devicelink.com/mddi/archive/08/06/004.html>

Information is also available in

ASTM F2097 - 08 Standard Guide for Design and Evaluation of Primary Flexible Packaging for Medical Products