Product and Package Stability Studies: The Application of FDA Guidance

The United States Food and Drug Administration provides guidance on physical tests to employ to demonstrate that packaging maintains the sterility of products throughout their shelf life. This article discusses what this means in practice for medical device manufacturers.

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First published in the Spring 2009 issue of *Med-Tech Packaging News*.

IMAGE: MET LTD

The challenge

The United States Food and Drug Administration (FDA) expects "products labelled as sterile to be free of viable microbial contamination" throughout their shelf life.[1] A major role of packaging is to maintain this sterility during shipping and storage. The challenge is in demonstrating this and it is not an easy task. Microbial contamination in a pack may be impossible to detect visually and the majority of the tests (physical and microbial) that are 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 reliable.[2] Validation depends on establishing the pack performance during the "design outputs" phase of a project, followed by regular quality analysis (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 perform a microbiological analysis of the contents. But this is an attempt to demonstrate a negative. Proving that something is not there is not easy in practice. Testing for sterility can produce false negatives and false positives. False negatives result from the possibility that although there may be a fault in the pack, the viable organism in the selected culture medium has not entered the pack. To overcome this, the outside of the pack can be sprayed with an aerosol (or dust) that contains known microbes and then the contents of the pack analysed for those known organisms. However, this presents a 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 method increases the likelihood of false positives caused by the transfer of microbes to the product when the pack is opened. The FDA guidance document discussed here, "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products"[1] helps to address this challenge by accepting physical testing in place of sterility testing.

Physical testing

The guidance document provides a nonexhaustive list of possible integrity tests. These include

- bubble tests (an integrity test that measures the minimum pressure required for gas to penetrate the pack membrane/media)
- pressure/vacuum decay (an integrity test that measures flow driven by a pressure differential across the pack membrane)
- trace gas permeation/leak tests (an integrity test that measures flow of a gas from the pack driven by diffusion)
- dye penetration tests (an integrity test for seal areas)
- seal force tests (burst or tensile tests for seal strength)

■ electrical conductivity and capacitance tests (integrity tests that look for anomalies in materials).

The guidance document stresses that these tests do not replace initial sterilisation validation or sterility release tests during manufacturing. They are, however, relevant to a stability evaluation programme or a shelf life test programme. It is also stated that the tests require proper validation. Validation methods vary according to the tests used and pack types.

The physical tests outlined here 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 ageing 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 equation,[3] which states that a temperature rise of 10 °C will double the rate of a reaction. Hence, storage at 55 °C delivers one year of equivalent ageing in less than six weeks, as stated in ASTM F1980-07 Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices.[4] The guidance indicates that testing should be conducted 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 International Electrotechnical Commission standards; US Defense standards, often termed MIL specs; and in ASTM D4332-01 (2006) Standard Practice for Conditioning Containers, Packages, or Packaging Components for Testing.[5] Typically, these are

■ Tropical: temperature 38 °C, relative humidity 85%
■ Desert: temperature 50 °C, relative humidity low
■ Frozen: temperature –20 °C, relative humidity low
■ Temperate: temperature 23 °C, relative humidity 50%.

Shipping

Transport simulation for medical devices is commonly performed 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 package and product

To identify precisely what testing is required, a risk analysis should be performed. Questions to consider include:

■ Does the product (or pack) deteriorate with time?
■ Is the product (or pack) labile at raised or lowered temperatures or even normal temperatures?
■ Is the product or pack sensitive to moisture?
■ What environment may the product be stored and transported in?
■ What are the environmental conditions in the hold of a plane or ship and on the dockside?
■ Does the product put pressure on the pack seals or materials?
■ 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 ageing and conditioning. The risk analysis and failure modes and effects analysis may indicate additional areas of testing that do not appear in the normal QA routine. An example may 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 dependent on package design and materials.

Nonporous packs

A wide 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; they allow confirmation of the web material and weld integrity. One option is a method described in ASTM F2095-07e1, Standard Test Methods for Pressure Decay Leak Test for Flexible Packages With and Without Restraining Plates. A better alternative can be, ASTM F2338-05, Standard Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method. In this test, packages are placed in a chamber that 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 similar to pressure decay testing, where a positive pressure is applied inside the product or pack. It delivers accurate quantitative results.

A variety of gases 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 with 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 extremely small bacteria. For example, 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 a variety of other mechanisms that entrap particles[7] 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 testing medical device packages that 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 divided 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 performed by the 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 CO_2 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 are searched for visually. The validation method for this test is also described in the standard. It involves placing fine wires across the seal prior to welding. These wires are then removed and tests are performed on the channels that remain.

Standard test methods exist for assessing the materials used in porous packaging for terminally sterilised medical devices, see Table I.

Table I: Standard test methods for assessing the materials used in porous packaging for terminally sterilised medical devices include:

- ISO 11607-1:2006 Packaging for Terminally Sterilised 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 Sterilised

Other tests

Bubble test web material. Bubble emission testing involves applying 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 is recorded. The test is often applied at goods inwards before web materials are accepted. ASTM F2096-04 Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurisation (Bubble Test) describes a method for finding holes with a diameter greater than 250 microns in spun bonded polyolefin and nonporous packs.[8]

Bubble test impermeable packs. There is also a bubble test, ASTM D3078-02 (2008) Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission, that involves placing packs in a vacuum transparent chamber. The pack is immersed in fluid and a vacuum is drawn above the fluid, which in turn draws bubbles from the pack.[9] An alternative for large packs is to pressurise the packs internally as described in ASTM F2096-04.[8] Both of these tests will only detect gross leaks of more than 250 microns wide.

Electrical conductivity and capacitance tests. These tests are often mployed 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 Pressurisation Failure Resistance of Unrestrained Packages. A tensile test is described in ASTM F88-07a Standard Test Method for Seal Strength of Flexible Barrier Materials.

Reliable testing

The FDA guidance document referred to in this article seeks to clarify how device manufacturers can demonstrate the stability of their product and packaging and substantiate 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, whereas electrical and bubble tests are most applicable to material manufacturers and goods inwards testing.

References

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2. M. Turner, "How to Validate a Packaging Process," *Medical Device Technology*, **15**, 3, 20–23 (2004).
3. M. Turner, "How to Simulate Shelf Life for Ageing Trials," *Medical Device Technology*, **13**, 1, 90 (2002).
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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. www.devicelink.com/mddi/archive/08/06/004.html
8. ASTM F2096-04 Standard Test Method for Detecting Gross Leaks in Medical Packaging by Internal Pressurisation (Bubble Test).
9. ASTM D3078-02 (2008) Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission.

Further reading

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

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First published in the Spring 2009 issue of *Med-Tech Packaging News*.