Integrity Testing Methods for Sterile Barrier Systems

Exclusive research reveals there's confidence in the current state of the art for medical device integrity testing, but a few areas are ripe for growth.

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Testing is one of the most challenging endeavors of packaging development. Over a decade ago in 2006, *Pharmaceutical & Medical Packaging News* published an overview of commonly available methods for testing the integrity of medical device packaging in "How low can you go?", and we've heard that it has helped a few packaging professionals over the years. We've also since heard that sterile barrier systems integrity testing may be a more precise term (per ISO 11607), although other terms such as package, sterile medical package, whole package, and primary barrier continue to be used.

In this report, we'll provide an update on these integrity test methods, detailing any updates and alignment with industry and FDA consensus standards. We'll also include comments from users and other experts along with the results of an exclusive survey to determine today's most popular methods.

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THE SCOPE

From April to June 2018, *Pharmaceutical & Medical Packaging News* surveyed medical device packaging professionals anonymously in "Medical Device Package Integrity Testing Methods Survey 2018." More than 54 professionals took the survey. After filtering out any packaging material/container/equipment suppliers, we surveyed 49 professionals who work for either a medical device manufacturer, pharmaceutical or biologic manufacturer, contract manufacturer/packager, testing services provider, or consultant. We asked these respondents to select any of the methods they use from this list, allowing them to check all that apply:

- Bubble Emission per ASTM D3078-02 (2013)
- Visual Seal Inspection per ASTM F1886-16
- Dye Penetration Porous Packaging per ASTM F1929-15
- Pressure Decay Leak Test per ASTM F2095-07 (2013)
- Internal Pressurization Bubble Test per ASTM F2096-11
- CO_2 Tracer Gas Leak Testing Non-Sealed Packaging per ASTM F2227-13
- CO_2 Tracer Gas Leak Testing Packaging with Porous Barrier Material per ASTM F2228-13
- Vacuum Decay per ASTM F2338-09 (2013)
- Helium Tracer Gas Leak Testing per ASTM F2391-05 (2016)
- Airborne Ultrasound per ASTM F3004-13e1
- Dye Penetration for Nonporous Packaging per ASTM F3039-15
- Vacuum Deflection by Laser Measurement per ASTM F3169-16
- Mass Extraction per ASTM F3287-17
- Whole Package Microbial Challenge Integrity Testing
- USP <1207> container leak testing method not listed above
- Other

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We then asked them to answer these questions:

- What challenges do you face in package integrity testing, and how are you overcoming them?
- Do the tests you are currently using meet your needs? Why or why not?

The answer to that last question provides a great snapshot of industry's confidence in these methods, which appears relatively high. More than three-quarters of the respondents report that these tests meet their needs (see Figure 1 below). One respondent says that "we have a wide range of options to help demonstrate the performance characteristics we want to demonstrate." Another states that "they are accepted by our regulatory bodies that approve our products for sale in different geographies."

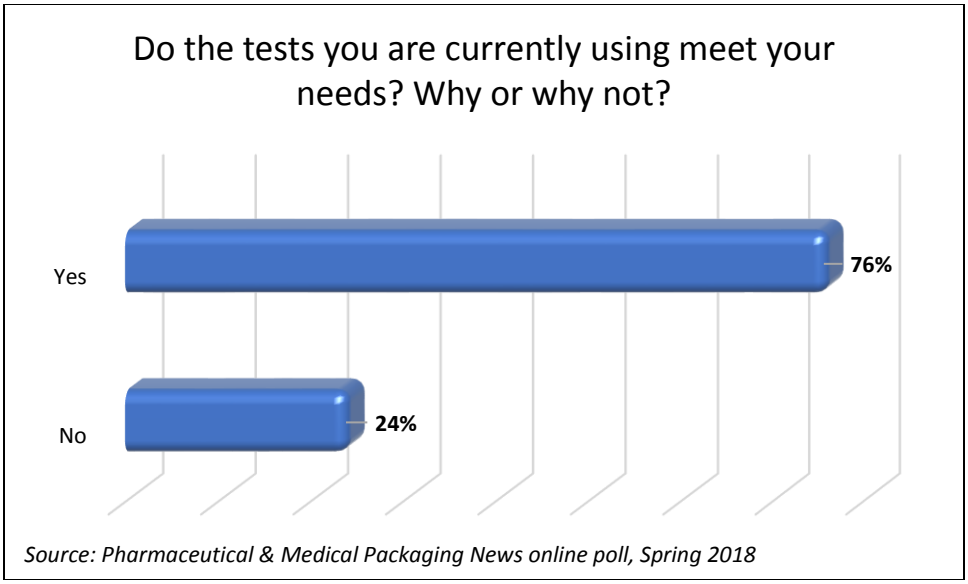


Figure 1: 76% of survey respondents say the tests they are using meet their needs.

A consultant completing the survey remarked that "our customers' needs are basic. They just want to get their product to the end user safely and in a sterile manner. Dye penetration, seal strength, and transportation simulation tests meet their needs."

In addition to collecting survey responses, we also reached out to a number of packaging engineers and experts for their input. After reading our 2006 article, Marie Tkacik, director of product development and optimization at Beacon Converters, says, "The upgrades and additions to ASTM integrity testing since the original article are numerous and show the growth of an industry focused on patient safety. ASTM standards are reviewed every five years, which opens the door for users to submit changes to improve them."

Karen Greene, president of Life Pack Labs, believes "the current methods are working. There's a lot of confidence in the current state of the art."

She adds, "The ASTM methods are effective because they're simple and repeatable. There is enough detail so that users can perform them. As ASTM is a consensus standard setting body, test method users have security in these methods, and their execution is widely known. Additionally, where appropriate, an interlaboratory study [ILS] is executed and test method repeatability and reliability, as well as test method sensitivity, are established."

Scott Levy, packaging engineer at DDL Inc., says that "ASTM has been doing a fantastic job, especially when it comes to revisions to help industry. ASTM gets detailed where it needs to be, and it has given better guidance or clarification. We haven't seen a huge shift because the existing methods give engineers enough confidence. What we have been doing has worked very well, so we haven't seen a shift in approaching packaging validation. Industry has tightened up and that is a good thing—they are all on the same page."

For instance, Levy says the three most popular methods—dye testing, visual inspection, and bubble emission—are good examples of tightening procedures. "The dye penetration method has a new procedure for poly/poly packaging. Engineers are looking at these standards to make them better and faster. The ambiguity is going away so that they are used properly."

"Integrity testing can be cumbersome and time consuming, so a faster whole package test would be desirable."

Nonetheless, Greene says that "there hasn't been a lot of advancements in methods in the years I've been working." Most of these methods are "gross leak detection methods, fairly simple and physical in principle."

While survey respondents find the methods listed above useful, a few do point out a few areas in need of attention. "They provide accurate results," writes one professional. "They are just too slow." Another agrees, stating that "testing is slow. We need a test where multiple packages could be tested at the same time."

In answering the question about meeting needs, one respondent writes: "Yes and no. Yes, because they help us meet minimum regulatory requirements. No, because the question still exists as to what sensitivity we should test to (the methods have varying sensitivities so there is inconsistency in use). Probability of contamination across all variables has yet to be modeled. Furthermore, integrity testing can be cumbersome and time consuming, so a faster whole package test would be desirable. Lastly, it's noteworthy to point out that the entire sterile barrier should be tested, not just the seals. (And if you want a funnier comment, people dislike the dye test because they often stain their clothing!)"

Consequently, our survey and subsequent interviews uncovered a few underserved needs: nondestructive testing, porous package testing, inline testing, highly sensitive methods, and robust microbial challenge testing for whole packages. Note that we write underserved, not unmet, because solutions to these needs do exist; the challenge is finding ones that are also affordable, accessible, and applicable to today's production environments.

THE METHODS

Here are the methods grouped by similarity, with potential sensitivity and user feedback from both the survey and expert interviews. We've also included some commentary from 2006 for historical comparison.

Bubble Methods

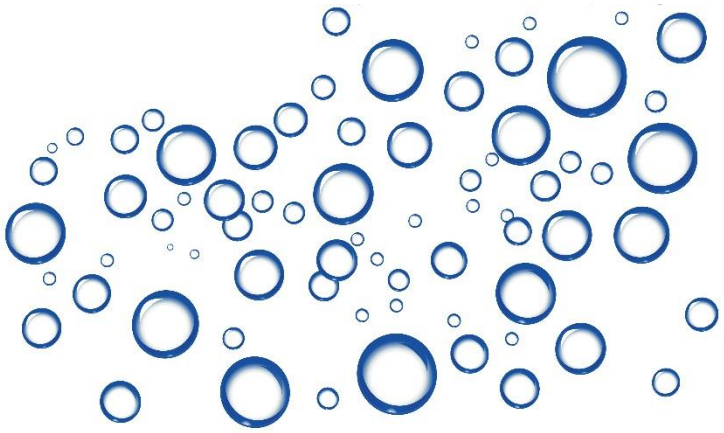
Bubble Emission per ASTM D3078-02 (2013) "Standard Test Method for Determination of Leaks in Flexible Packaging by Bubble Emission" – an FDA Recognized Consensus Standard

Internal Pressurization Bubble Test per ASTM F2096-11 "Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)" – an FDA Recognized Consensus Standard

Potential Sensitivity: 250 µm for the internal pressurization method

ASTM describes D3078 as appropriate for flexible packaging containing a headspace gas by bubble emission. It involves use of a transparent vacuum-tight chamber. Greene says the method "is essentially destructive because the package is immersed in water and the package may be compromised. The package must have a headspace and be nonporous."

ASTM describes F2096 as a destructive method because it involves entry into the package to supply an internal air pressure; it could apply to large or long packages that do not fit into any other package integrity test method apparatus. However, the sensitivity of this test method has not been evaluated for use with porous materials other than spunbonded polyolefin or with nonporous packaging, ASTM states. Greene says that "the test specimen is submerged under water during the actual test, inflated, and observed for leaks."



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Joel Fischer, lab manager at Ametek/MOCON, says that these methods offer two different ways to inflate packages, but both still have a sensitivity of about 250 µm. "That is a gross hole size. For optimization of a new sealing process, the methods are helpful with identifying where a hole is located to help determine what is causing it. However, for quality control purposes, it may not be sensitive enough," he says. He further explains that F2096 is destructive, given the entry into the package, while D3078 is technically nondestructive, given the use of vacuum. Such a nondestructive test would allow further analysis, but typically not release onto the market, given the use of water immersion. (MOCON offers the Lippke 4500 for testing according to F2096.)

“We need to implement bubble leak testing, but space constraints are delaying this.”

Henk Blom, director of technical services for Rollprint Packaging Products, says that “these tests are widely used in the packaging industry as quick tests to detect channels in the package seals or through-pinholes in the package face. A number of members of ASTM Committee F02 (Primary Barrier Packaging) have shared anecdotal evidence that sensitivity might be better than 250 µm, so initial discussions are underway to re-visit and update the current inter-laboratory study (ILS).”

One survey respondent writes that “internal pressurization bubble leak can cause seal width loss if the initial pressure isn't correctly identified.” Another states that “Tyvek leaks are difficult to detect as it is a porous material—bubble emission leak in particular. But I have no experience with any other methods.”

“We need to implement bubble leak testing, but space constraints are delaying this,” explains one respondent.

Another reports that “there is a shift in industry towards paper-based sterile barrier systems due to cost savings; however, no consensus method currently exists for integrity testing of a paper substrate to identify breaches of the material surface (rather than the seal). Some coated papers used for smaller volume sterile barriers can withstand F2096 due to the shorter test time, but the standard is not currently scoped out for that. Visual inspection can be done but is limited to the sensitivity of the viewer (gross defects are more likely to be those detected) and is also not within the scope of F1886.”

In 2006, we shared the following perspective from Donald Barcan, Donbar Industries (Long Valley, NJ), who said that this method “is also very useful when looking for gross integrity defects other than seal defects.”

Visual Method

Visual Seal Inspection per ASTM F1886-16 “Standard Test Method for Determining Integrity of Seals for Flexible Packaging by Visual Inspection” – an FDA Recognized Consensus Standard

Potential Sensitivity: 75 µm

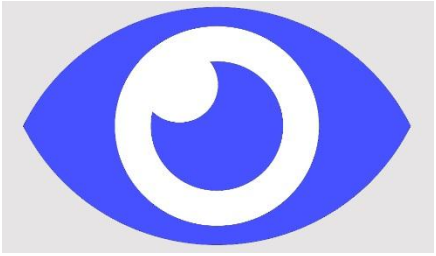
ASTM F1886 is for packages with at least one transparent side. ASTM states that “visual seal defects often will be the first indication of heat sealing process variation…. The ability to visually detect channel defects in package seals is highly dependent on the size of channel, the degree of contrast from sealed and unsealed areas, the amount and type of adhesive between the two package layers, reflecting light angle, types of material used, the use of magnification, and the inspector’s level of training and experience.”

Blom says that “while this test is widely used in the industry, it is likely never used as the only test, or at least, I would not advise using it as the only test. Dye leak tests should also be used (for integrity), as

well as seal strength to ensure that good seals are being made in the process. This test also only works for packages that have at least one transparent web and cannot be used for a foil/foil pouch, for instance."

Jennifer Benolken, medical-device manufacturer (MDM) specialist, packaging engineering, Tyvek, Medical Packaging, DuPont, indicates "visual inspection plays a crucial role in ensuring patient safety—it's not only performed as part of the manufacturing process, but used up to the point of use as a means of verifying the sterile barrier is still intact. It's possible that the process could be automated in production; but the question is whether there would be ROI? The equipment would need to stay in time with production cycles, be more accurate than human inspection, and be cost effective."

A survey respondent states that "visual inspection of certain materials is difficult, but in many cases a UV light box can help."



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Van der Stähl Scientific Inc. offers a system to help. "With our VIU system, we aim to simply enhance and standardize observation," explains Charlie A. Webb of Van der Stähl Scientific. "The biggest issue historically with visual inspection is that each inspector might utilize a host of lighting sources—that is, daylight, incandescent, daylight balanced LED, or florescence lighting at various light intensity. Also, quality teams might use various powers of magnification or naked eye for their inspection and of course this is counter to standardizing a repeatable process. With our system, magnification is fixed so the distance is always the same for every inspector. Also, we magnify at approximately 3X as we do not want to over magnify the test specimen as we believe the goal should be to get a close view of the seal area and yet global enough to see the seal in context. Also, our patented system side lighting array washes over the sealed area to create shadowing that often reveal pleats and fold overs." The VIU system also allows the operator to store the findings after each inspection, recording date, time, inspector's name, lot number, and pass or fail.

2006 Industry Perspective: "Visual inspection is the process most often used to detect package-integrity defects," said Barcan at the time. "The main reason for its widespread use is convenience and low cost. However, the major drawback is that this test is qualitative in nature and is operator dependent."

Dye Penetration Methods

Dye Penetration Porous Packaging per ASTM F1929-15 "Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration" – an FDA Recognized Consensus Standard

Dye Penetration for Nonporous Packaging per ASTM F3039-15 "Standard Test Method for Detecting Leaks in Nonporous Packaging or Flexible Barrier Materials by Dye Penetration" (currently under review as an FDA consensus standard)

Potential Sensitivity: 50 µm in porous and nonporous package seals; 10 µm in nonporous flat sheets

ASTM's method for porous packaging formats can detect leaks equal to or greater than channels formed by a 50 µm wire in edge seals between a transparent material and a porous material. The method offers three approaches for dye application: injection, edge dip, and eyedropper.

ASTM's method for nonporous packaging formats offers two approaches: one for detecting leaks equal to or greater than channels formed by a 50 µm [0.002 in.] wire in edge seals and another for detecting leaks of 10 µm and greater in nonporous flat sheets.

Blom says that "this area has seen significant changes in the last few years, with the introduction of F3039, the dye leak method for pouches that do not contain a porous web (such as a film-to-film pouch, or a foil-to-foil pouch). F1929 (for packages that include a porous web, such as spun-bonded polyolefin or medical grade papers) has also been revised to include an exhaustive ILS study to determine the precision of the test method to detect channel leaks. F3039 has two parts, one for channel leaks in the package seals, and one for through-pinholes in the face of the package. Channel leaks down to 50 µm can readily be detected with F3039, and through-pinholes down to 10 µm can be detected with greater than 90% probability of detection."

Blom and Wendy Mach, packaging consulting manager for Nelson Laboratories Inc., report that the surfactant used as an integral part of testing recipes is on a hazardous substance list and may be difficult to obtain in the future. "The surfactant used in the dye solutions has recently been listed as a substance of concern, and efforts are underway to identify a new surfactant and to reformulate the dye solutions," Blom says. "Some level of re-qualification is also planned, to confirm the sensitivities of these tests."

"Dye leak testing is messy and only challenges the seal."

Adds Mach: "Round robin testing would then hopefully take place in 2019. We may also remove the surface tension requirement and determine a wetting agent value."

Tkacik says that "when it comes to tests such as dye penetration and bubble leak, what can be a limiting factor is the ability to make the defects. Seal channel defects were made with 50 micrometer tungsten wires for the dye test. Smaller size wires were attempted but broke too easily. This automatically limits the sensitivity of the test to find channels. When defects can be made smaller and repeatable, the sensitivity of detection can improve. On ASTM F3039, laser hole drilling took the nonporous dye test for pinholes down to 10 micrometers. The ILS showed over 90% probability of detection down to 20 micrometers."

Survey respondents do have a few concerns. Writes one: "Dye leak testing is messy and only challenges the seal. We use dark colored lab coats and gloves to protect clothing. Our dye leak test method validation covered the seals and the areas adjacent to the seal." Another states that "dye penetration testing on porous packaging materials is challenging. Especially when using paper-based materials, a very good trained eye is required in order to detect small channels due to the suction of the paper."

2006 Industry Perspective: Barcan called this the "the second most popular seal-defect test method." He added: "Many companies, including mine, use dye to verify package defects outside the seal area though it is important to note that the ASTM standard is only for seal defects." However, it is messy, and, "for porous packaging materials, the test has to be conducted quickly, otherwise the dye will permeate the package walls and make channel identification difficult or impossible," said Barcan. "There are coatings available to seal the permeable web and thereby increase the test time. This can greatly improve the seal area test sensitivity for porous packages."

Decay Measurement

Pressure Decay Leak Test per ASTM F2095-07 (2013) "Standard Test Methods for Pressure Decay Leak Test for Flexible Packages With and Without Restraining Plates" — an FDA Recognized Consensus Standard

Potential Sensitivity: 25 µm (Fischer says that "the standards' precision and bias data show results with a known hole of 12.7 µm, but 25 µm diameter hole size is what I've heard most often cited in the industry.")

Vacuum Decay per ASTM F2338-09 (2013) "Standard Test Method for Nondestructive Detection of Leaks in Packages by Vacuum Decay Method" — an FDA Recognized Consensus Standard

Potential Sensitivity: 2 µm nonporous, 75 µm porous

ASTM describes its pressure decay test method as a destructive test for nonporous film, foil, or laminate flexible pouches and foil-sealed trays, as well as porous packages made nonporous with an impermeable film forming coating. Two methods are available: a pressure decay leak test for flexible packages without restraining plates and a test for flexible packages with restraining plates. The methods involve entry into the package to supply an internal pressure of gas through a leak-tight connection.

"The [vacuum decay] method is destructive, but it offers greater sensitivity than other methods and it is not subjective."

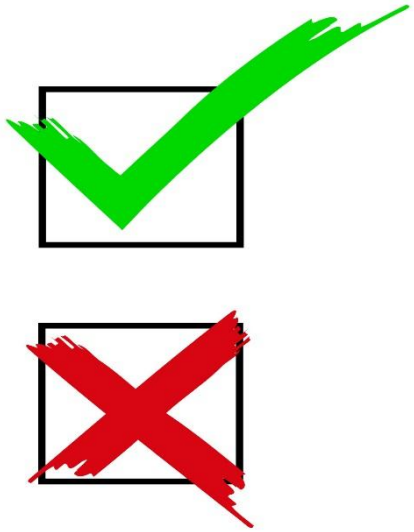
ASTM describes its vacuum decay method as a nondestructive test that detects package leaks by measuring the rise in pressure (vacuum loss) in an enclosed evacuated test chamber containing the test package. It can be used for rigid and semi-rigid non-lidded trays; trays or cups sealed with porous barrier lidding material; rigid, nonporous packages; and flexible, nonporous packages.

For pressure decay testing according to ASTM F2095, MOCON offers the Lippke 4500. "The method is destructive, but it offers greater sensitivity than other methods and it is not subjective," says Fischer. "It can be computer controlled and automated, in comparison to other methods that rely on an operator with a pump and a stopwatch monitoring a package visually for bubbles, or an operator looking for dye coming into or out of a package."

The Lippke itself hasn't changed much over the years, Fischer explains. It involves inserting a needle through a septum attached to the package through which one hose supplies air to pressurize the package, and a second hose monitors that pressure. "The package is inflated to a set point, which depends upon the product and package seal strength; if too great it could create stress on the package or seals or stretch the material, causing creep. Test packages are then monitored for pressure loss as air leaks out of the package over a given time."

Users need to optimize the method, he adds, which can be done by creating sample packages with controlled leaks. MOCON offers a device that uses a fixed orifice to create a precise hole as small as 25

µm for a known defect. “With such traceability and equipment, you can devise a protocol and can validate that it can distinguish between good and bad samples,” he says.



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Greene says that “if you create a defect of a known size, you can develop customized test parameters with the application of package test systems such as MOCON-Ametek’s Lippke 4500 or TMI’s BT-Integra Pak to identify the leak within very brief testing durations. It’s a simple, clean method. Pressure decay is clean and dry, and it is a good method for nonporous packaging. It provides a test method sensitivity for your leak detection method.”

Vacuum decay testing is getting faster and more sensitive, says Oliver Stauffer, CEO of PTI—Packaging Technologies & Inspection. “It is appropriate for indexing systems, such as shuttle-style tray sealers,” he explains. “To perform the method for porous systems, the Tyvek must be masked off.

“We are doing a few things to augment around the method to improve sensitivity and reliability,” he continues. (PTI offers the VeriPac unit for such testing.) “For instance, to find small leaks in packages with little headspace volume, we’ve developed an approach with fixed volume release. This can help with vial-type packaging, which is often a challenge. And to offer a universal approach to testing, we’ve developed a flexible test chamber that can take either small or large pouches and test them with the same method.” PTI is also doing more robotic handling development itself to increase automation around inspection.

Sepha Ltd., Part of the Tasi Group of companies, offers equipment for vacuum and pressure decay, as well as for an approach that Philip Cooper, Sepha’s head of technology and quality, calls “force decay.” (Cooper currently also serves as chair of the ASTM F02.40 subcommittee on integrity.) In this method, a nonporous package is restrained in a jig within a machine. When a vacuum is applied, the force of the expanding package is measured using a load cell. “The package is placed in the jig, a vacuum is applied, and if the package starts to expand under vacuum, this expansion will generate a force. We measure this force and correlate this force to a defect type. Typically, gross defects generate little or no gross force; micron defects initially generate a good gross force, but then the force starts to decay as the air leaks out of the package. This is where the name force decay comes from,” he explains. There is no ASTM method for this approach, he says, but he is considering developing one. Depending upon package type and volume, sensitivities can range from 10 to 100 microns and greater.

Dan Burgess, fellow, packaging engineer, Boston Scientific, says that the “vacuum decay and mass extraction [discussed below] methods allow for whole package assessment and are nondestructive—you can use it during design verification as well as a test when products are returned from the field. But it doesn’t tell you where the leak is. Of course, determination of leak location is a valuable piece of information, but this could be determined using another method such as ASTM F3039 Standard Test Method for Detecting Leaks in Nonporous Packaging or Flexible Barrier Materials by Dye Penetration.”

Tracer Gas

CO_2 Tracer Gas Leak Testing Non-Sealed Packaging per ASTM F2227-13 "Standard Test Method for Non-Destructive Detection of Leaks in Non-sealed and Empty Packaging Trays by CO_2 Tracer Gas Method" — an FDA Recognized Consensus Standard

CO_2 Tracer Gas Leak Testing Packaging with Porous Barrier Material per ASTM F2228-13 "Standard Test Method for Non-Destructive Detection of Leaks in Packaging Which Incorporates Porous Barrier Material by CO_2 Tracer Gas Method" — an FDA Recognized Consensus Standard

Helium Tracer Gas Leak Testing per ASTM F2391-05 (2016) "Standard Test Method for Measuring Package and Seal Integrity Using Helium as the Tracer Gas" — an FDA Recognized Consensus Standard

Potential Sensitivity: 50 µm in trays; 100 µm in seals

"Porous materials have always been a huge challenge for trace gas analysis."

ASTM describes the CO_2 tracer gas methods as nondestructive. F2227 can be used for detecting pinholes or cracks as small as 50 µm in trays, while F2228 can detects leaks as small as 100 µm diameter in seals and pinholes as small as 50 µm in nonporous rigid thermoformed trays, as well as the seal between the porous lid and the tray, but not the porous material itself. ASTM's helium tracer gas method is typically a destructive one for nonporous packages. It offers two approaches: the vacuum mode and the "sniffer" mode.

Jeff Morrow-Lucas, president of Leak Detection Associates Inc., says that "porous materials have always been a huge challenge for trace gas analysis, even more so with helium due to the inherent difficulty in trying to mask permeation effects. Our work with the helium leak method is strictly in foil blister cards and pouches and recently more so in the parenteral packaging arena (vials, syringes, cartridges, etcetera). Unfortunately, we do not do any trace gas (helium) detection in the medical device industry."

Airborne Ultrasound

Airborne Ultrasound per ASTM F3004-13e1 "Standard Test Method for Evaluation of Seal Quality and Integrity Using Airborne Ultrasound"

Potential Sensitivity: 500 µm

ASTM's method involves passing an ultrasound signal through the sealed area of a package or item and evaluating the strength of the ultrasound signal. The nondestructive method can be used to detect seal defects in the size range of 1 millimeter (mm) in nonporous and porous formats.

The method can find small defects in a cost-effective manner, explains Stauffer of PTI, which offers Seal-Sensor noncontact airborne ultrasound testing units. “People are starting to get familiar with the method,” he says, expecting the method to be mentioned in the upcoming revision of ISO 11607.

PTI has worked with Sencorp to add an airborne ultrasound system to inline pouching systems for 100% product inspection after heat sealing. “It has been validated to inspect this final seal,” he says. PTI has also developed a sensor to work with robotic systems that can rotate a sealed pouch for 100% inspection of all four seals, which is in the process of being validated.

Vacuum Deflection

Vacuum Deflection by Laser Measurement per ASTM F3169-16 “Leak Detection in Blister Packaging by Vacuum Deflection Method by Laser Measurement”

Potential Sensitivity: 15 µm

ASTM’s method applies to typically pharmaceutical nonporous blister packs consisting of thermoformed polymer or cold formed aluminum trays sealed with a polymer, paper-backed, or foil-based flexible laminate. The method detects leaks by measuring the deflection of the blister pack surface in response to an applied vacuum.

Cooper says that Sepha offers equipment for vacuum deflection using both vision and laser for measurement, and he says it can achieve sensitivities of 7 microns for pharma packaging and 10 microns for medical packaging. “Vacuum deflection has typically been used for pharma blisters, but we have crossed over into medical packaging for nonporous,” he says.

These methods are not inline, at least not yet. “The challenge is having enough of a buffer time for the measurement technique and to get the throughput required without an enormous machine,” he adds. “An elegant solution is needed that can slide onto a production line with a small footprint.”

Mass Extraction

Mass Extraction per ASTM F3287-17 “Standard Test Method for Nondestructive Detection of Leaks in Packages by Mass Extraction Method”

ASTM’s nondestructive method detects leaks in nonporous rigid and semi-rigid packages by measuring the mass flow extracted from a package while the package is enclosed inside an evacuated test chamber.

Potential Sensitivity: 2 µm for glass vials

Wendy Mach of Nelson says there’s “a lot of excitement” about this method. “It is faster and more-sensitive than other methods like liquid immersion, and it is nondestructive. It is also on FDA’s radar to become an FDA consensus standard.”

The method is appropriate for nonporous materials and formats such as vials, syringes, and IV bags, she says. “We needed something for autoinjector testing—when you submerge them in liquid, it is difficult to get the liquid out of the cracks and crevices, so there is a high risk of false failures.”

SURVEY RESULTS

The two most popular tests methods, each used by 80% of survey respondents, are:

- Visual Seal Inspection per ASTM F1886-16
- Dye Penetration for Porous Packaging per ASTM F1929-15

These methods were followed by:

- 52% of respondents use Bubble Emission per ASTM D3078-02 (2013)
- 46% use Internal Pressurization Bubble Test per ASTM F2096-11
- 35% use Dye Penetration for Nonporous Packaging per ASTM F3039-15
- 22% use Pressure Decay Leak Test per ASTM F2095-07 (2013)
- 20% use Vacuum Decay per ASTM F2338-09 (2013)
- 9% of survey respondents use Whole Package Microbial Challenge Integrity Tests

Methods each used by 4% of respondents:

- CO_2 Tracer Gas Leak Testing Non-Sealed Packaging per ASTM F2227-13
- Airborne Ultrasound per ASTM F3004-13e1
- Mass Extraction per ASTM F3287-17
- USP <1207> methods not listed

Methods each used by 2% of respondents:

- CO_2 Tracer Gas Leak Testing with Porous Barrier Material per ASTM F2228-13
- Helium Tracer Gas Leak Testing per ASTM F2391-05 (2016)
- Vacuum Deflection by Laser Measurement per ASTM F3169-16

And 13% of respondents say they use other tests:

- “Seal strength,” “burst and peel testing” (*editor’s note: these are not integrity methods*)
- “In-house methods validated and expanded on dye penetration concepts”
- Internal Pressurization Bubble Test per ASTM F2096-04
- “Liquid/bacterial immersion”

(See Figure 2 on next page.)

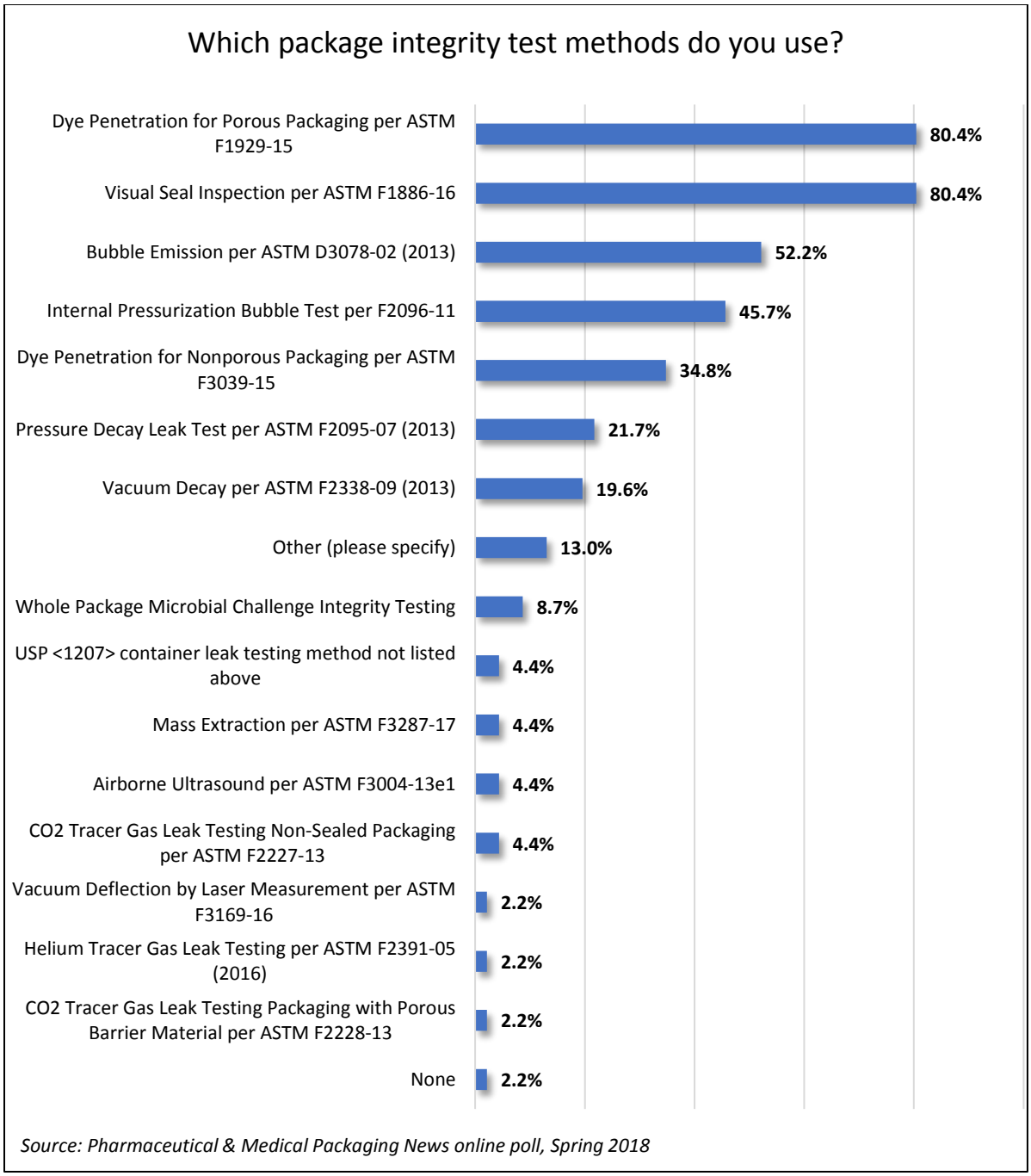


Figure 2: Although selecting the dye penetration test as one of the most-used methods, some respondents also complain that it is messy.

TO-DO LIST

It seems that when developing an integrity testing plan, medical device packaging professionals must balance ease of use, cost, sensitivity, and other factors.

(Image source: iQoncept/Shutterstock)

"There is a lot of opportunity to develop new methods of whole package integrity testing for porous packaging," says Burgess of Boston Scientific. "One current practice for MDMs is to do a combination of visual inspection and dye penetration methods to assess package integrity, but reliance on these methods alone in some cases has led to feedback from regulators that more testing is needed. I think this stems from a belief that there is too much subjectivity associated with visual inspection. This is unfortunate since ASTM and industry has proven through interlaboratory studies and test method validation that visual inspection can be an effective tool for identifying sterile barrier defects."

Burgess says he has tried a few different things, such as sealing around the seal area of a flexible package and then pulling a vacuum under pressure to see whether there is any change. "But it is hard to do so with a flexible package—the amount of pressure required on the seal for a flexible package tends to close off the seal area, reducing the chance that a seal defect would be detected using this method," he says.

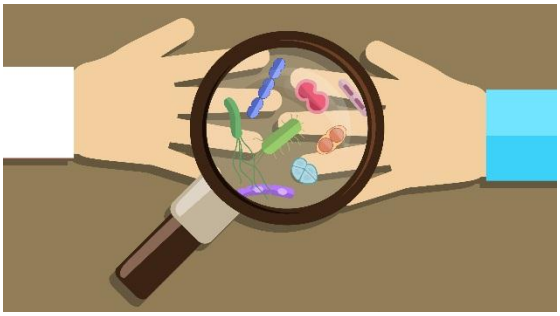
Burgess knows of no active work items in ASTM trying to devise another porous format solution. "Something is obviously needed, but I'm not sure how to solve it from a testing standpoint," he continues. "It is easier to approach from a design standpoint, so I encourage people to use a nonporous design if possible. This approach can work for most any product, even those that require sterilization via gas-based methods such as ethylene oxide. This can be accomplished by turning a porous package (necessary for the EO sterilization process) into a nonporous one post sterilization," he says, pointing to a pouch header that can be sealed off and trimmed away and to vented-style pouches whose vents could be covered after sterilization as examples.

Benolken of DuPont says that "for production purposes, nondestructive whole sterile barrier test methods for porous packaging are still lacking. Methods exist for nonporous packaging, but for porous packaging, the Holy Grail would be an affordable nondestructive method for 100% verification off the line."

Blom says that "people are looking for something easy to do at the side of the machine."

Burgess could even see smart packaging one day playing a role in nonporous package integrity testing. "Sensors inside the package could read the percentage of oxygen present and use that to assess integrity," he says. "The challenge is to use it for porous packaging." Another idea would be to employ "smart fabrics that stretch and move—maybe they could be used to sense a hole."

If monitoring oxygen ingress (for a modified atmosphere package), MOCON offers a sensor that can measure internal oxygen levels, but it cannot yet be terminally sterilized, says Fischer. Until then, another method could be used to measure oxygen levels in stored package samples by directly testing the headspace within the package by inserting a needle-tipped oxygen sensor (OpTech Model P). "This method works well for packages with very small headspaces and those sealed under vacuum," he says. It is destructive, though, he adds.



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As new engineers work to prevent ingress of microbes, Benolken would like to see more collaboration between microbiology and packaging teams. "They need to be working together—neither can do their job without the other one, but the two functions often operate relatively independently from each other."

When considering new approaches to integrity testing, companies should be careful that a method is in place to measure what needs to be done, Stauffer says. For instance, "a system may be marketed as a container closure integrity method, such as a thermal camera to measure the thermal transfer to a seal. A vision system could be looking for a certain texture or knurling pattern imprint, but do those approaches tell you there is an actual seal? It could look sealed and still have a significant defect."

ASTM provides a way to have a method recognized that is reliable and repeatable, he says.

Could Whole Package Microbial Challenge Integrity Testing Make a Comeback?

"Companies typically use barrier test methods ASTM F1608 and F2638 for materials only," says Jane Severin, vice president of technical solutions at Network Partners, speaking of ASTM F1608–16 "Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)" and ASTM F2638-12e1 "Standard Test Method for Using Aerosol Filtration for Measuring the Performance of Porous Packaging Materials as a Surrogate Microbial Barrier," respectively. "There are a few labs globally that use a modified version of F1608 for whole package integrity tests."

Nelson Labs uses a modified ASTM F2638. "We only use a modified version of F2638 because we felt like the way the standard method was written, using a high flow of particles and moving towards a lower flow, may have a blinding effect on the materials," says Mach. "By going from low to high flows we don't have the same concerns."

Mach says Nelson does a lot of whole package aerosol challenge testing for sterile barrier systems. "Our clients are continuing to see requests from FDA and European Notified Bodies to see tests demonstrating microbial barrier properties with actual microorganisms," she explains. However, there isn't a standard, she adds. "ASTM didn't develop a standard around whole package testing due to its high subjectivity associated with the sterility testing."

Mach notes a renewed focus on microbial data in the new EU Medical Device Regulations. "Microbial ranking is sufficient and meets the standard requirements, but it can only be used if the sterile barrier system has 47 millimeter of available porous material with no labels or seals. ASTM F2638 uses a sample

width that is almost twice the diameter. This leaves manufacturers who don't meet these specific requirements with limited options."

Severin reports that she conducted research at Clemson University on whole package integrity testing. "I designed a whole package microbial challenge test where I was able to vary pressure, temperature, and percent RH in ranges typical of the 'real world,'" she says. "I was able to vary the parameters and measure individual effects and interactive effects. The intent was to mimic environmental conditions in a healthcare environment. We developed compelling data; however, the variation was too great, as you can imagine when dealing with live organisms. This work was an extension of research I conducted at Michigan State University School of Packaging on the effect of pressure differential on microbial ingress."

Severin says she plans "to open an ASTM F02 work item and build a consortium to conduct testing to further characterize the healthcare environment in terms of microbial loads, particulate levels, pressure differentials, temperature, and percent RH, etc. To build a sound test method for integrity, it is important to have a deep understanding of the use environment," she says. "We know that before use the physical handling of packages in a healthcare environment can be very rough. We need to characterize this as well. I'd like to study further different common package material substrates and understand the duration of survivability of different common microbes found in healthcare environments. I've read that MRSA can survive in a dormant state on the outside of packaging for more than 10 years.

"The Holy Grail is to replace bubble, dye penetration, and visual inspection with a whole package microbial challenge test. It must be affordable and minimize variation."

"In my opinion, the Holy Grail is to replace bubble, dye penetration, and visual inspection with a whole package microbial challenge test. It must be affordable and minimize variation," continues Severin. "Historically, when whole package testing was performed and was accepted by the FDA, studies showed that the method was fraught with false positives. This ultimately led to its replacement with physical methods in the mid '90s. I would like to change this and develop an affordable, robust method. To move down this path, it will be important to develop compelling data further illustrating the risks of contaminated sterile packaging.

"I believe there is a connection to healthcare associated infections," she adds. "But can I point to data supporting that belief yet? No."

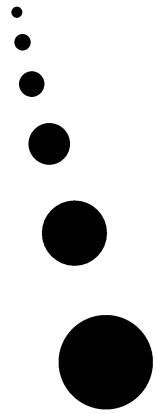
Minimum Hole Size?

When describing ASTM F1929-15 (Dye Penetration for Porous Medical Packaging), ASTM states that "there is no general agreement concerning the level of leakage that is likely to be deleterious to a particular package."

However, the question is still on a few engineers' minds. One challenge expressed in our survey by a testing services provider is "understanding the sensitivity of specific test methods and how they apply to the different package configurations (how sensitive is sensitive enough to detect a breach that impacts the sterile barrier)—we are moving towards more deterministic and sensitive methods."

One consultant completing our survey who stated that the current methods do not meet needs stated that he or she is "looking for a whole SBS integrity test that is sensitive to at least 10 microns or less."

Severin says that in her research, "pressure and hole size had a statistically significant effect on microbial penetration. The critical penetration threshold was less than 100 microns. This research was just the beginning of building a body of knowledge seeking to determine the required level of sensitivity for package integrity testing for sterile packaging." Severin believes that as an industry we need to continue on this path of discovery.



As a graduate student at Michigan State University School of Packaging, Ondrea Kassarjian studied the effects of hole size (100 microns versus 10 microns), the presence or absence of pressure differentials, and the presence or absence of a secondary carton on package sterility. Kassarjian picked up research begun by Severin; both students conducted research under Professor Laura Bix. Kassarjian's research was published in her dissertation in 2011 in "The Effects of Hole Size, Pressure Differential, and Secondary Packaging on Microbial Ingress of Sterile Medical Device Trays."

"To say that there is one hole size would be too narrow, but we did find effects from the variables we tested," says Kassarjian, who is now manager, packaging and labeling, global engineering, Hollister Inc. "The bigger the hole size, the greater the probability of contamination. But even with 10-micron-sized holes, bugs still got in with a pressure differential." Her research found that the probability of contamination also increased with sterile barrier systems under pressure ($p<0.0001$) and increased when a secondary carton was not used. She concluded at the time that the "larger the hole is, the easier it will be for a microbe to travel through it." Also, "it is possible for a microbe to travel through a 10-micron defect," which "supports [the] need to continue integrity tests with high sensitivity."

Kassarjian says that today "we are largely limited to a 50-micron sensitivity with the most widely used methods we have available. The industry consistently uses bubble and dye—they are tangible and low cost, they can be seen, and they can be done faster. People are already testing to the lowest sensitivity that is practical—50 microns with dye. I think industry is doing the best they can with what we have in terms of time and dollars. The healthcare industry itself is under pressure to strip out costs, and that is an obstacle to changing current practices."

And she notes that such methods do continue to be improved. "There's been a lot of great work done recently in dye, and bubble testing under F2096 is due for a revision."

“It would be nice to mathematically model the probability of contamination.”

But Kassarjian would like to see further work. “We are stagnated right now when it comes to integrity test methods.” For instance, “it would be nice to mathematically model the probability of contamination.”

However, “people are stretched too thin these days to do the extra work to help the industry,” she adds. “It takes research and time.” The good news is that “attendance at ASTM F02 meetings is good, and the committee has momentum.”

It seems as though further work on the need for greater sensitivity would need to be definitive. For instance, would greater sensitivity be a necessity?

Tim Galekop, director/owner of Tigamed and a former convener of ISO TC 102 WG 4 Packaging Materials as well as participant in ISO TC 198 WG 7 Medical Packaging, says that “as far as I have always learned and taught, bacteria needs a vector.” In addition, he points out that “in +/-1850 Louis Pasteur proved with his glass swan neck that bacteria cannot go around corners. So bacteria can only go straight forwards, and a tortuous path will be created with fibers that create a lot of bends.”

Citing information from DuPont (here and here), Greene of Life Pack Labs says that “porous barrier materials for sterile medical packaging function as depth filters and follow the physical laws associated with filtration theory. The difference between the particulate concentration before and after passing through the filter medium is known as filtration efficiency. The measured filtration efficiency for any given material will vary over a wide range as a function of aerodynamic particle size and air velocity. Non-porous materials are not operating under the filtration theory. Generally, if a package is determined to be leaking based on the results of the test methods listed within ISO 11607 Part 1, the FDA website for sterility test methods, healthcare packaging professionals, and those allied in bringing medical products to market, that package is considered as lacking in sterile barrier integrity and unfit for the intended application. Work continues on characterizing physical leak properties (hole, void size, and characteristics) to loss of sterile barrier integrity.”

Benolken of DuPont says that “microbes don’t have brains trying to get into sterile barrier packaging. To quote Dr. Mike Scholla, ‘their main goal is to reproduce.’ Regardless, we need to remain vigilant in the prevention of their ingress, as there are many means for them to move around and land in the wrong place at the wrong time.”

Galekop does see justification for testing sensitivities below 10 µm and perhaps go to 4 µm. “In all the working groups, we always spoke about the fact that a particle to carry bacteria should be at least 4 µm. Any other size smaller than 4 µm would not be able to lift the particle and bacteria attached to it. For me this means that a hole of 100 µm is an opening for a complete army of bacteria to get through.”

However, Levy of DDL doesn’t see a shift away from commonly used ASTM methods “until someone shows these methods aren’t sensitive enough and there’s a paradigm shift that these procedures aren’t good enough to promote package sterility. If the industry wants to look at something more sensitive, they’ll have to look back at all their validations and do a gap analysis.” And Levy cautions that more-sensitive testing could lead to overpackaging.

CONCLUSION

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Greene says that pre-formed healthcare package integrity is already very high, by design. “Converters validate their own forming and sealing processes and produce integral components,” Greene says. “And MDMs are required to validate their package forming and sealing processes. In general, we’re making good packages.” In addition, “people are validating test methods and looking at repeatability and reproducibility and test method sensitivity,” she adds. She also points out that “the new EU MDR is raising the bar for sterile packaging performance in the areas of usability and aseptic presentation. Standards setting organizations like ASTM provide tools for industry to help with compliance and validation.”

Testing labs, too, are being held to high standards. Life Pack Labs, for instance, just achieved ISO 17025 accreditation. “From a business perspective, you need to achieve an accreditation if you want to be recognized in the industry,” says Greene. “Accreditation ensures that you have effective quality systems and procedures and policies that cover all areas of operation from management commitment to quality, documentation control, technical, calibration, sampling handling, and reporting the results.”

“At the end of the day,” adds Levy, “Everyone is on board to make safe and effective packaged devices. We’ve come a long way in how packages are perceived and in how we are making them better.”

Kassarjian notes that the last decade had focused on maintaining sterile barrier, but this decade has shifted toward usability of the sterile barrier in terms of aseptic opening and presentation. “The way people are handling packaging could introduce contamination,” she says, so packaging engineers should focus on developing user-friendly packaging.

Stauffer of PTI encourages risk-based analysis when developing a testing plan. However, “not enough clients are focusing on what they need to find, how to find it, and what is critical to the product and patient.” He advises taking a “holistic approach to patient care—it will tease out what risks need to be considered.”

Risks could be increasing, he says. “There will be a lot more pressure in the future on medical device testing. The future is in combination products, often with a pharmaceutical product. And test methods are more robust for pharmaceuticals.”

Cooper is looking forward to the next series of ASTM International meetings in Nice, France, in October 2018. “We are all looking to engage the industry, and we are keen for new members,” he says, “so we can generate new methods that can be useful to industry.”

Burgess says that “in addition to the need for the industry to continue developing ways to assess whole package integrity for porous packages, it’s important to note that a new ASTM standard guide for

packaging test method validation (ASTM F3263-17) has been released that provides guidance specifically for test method validation of packaging test methods. The goal of this method was to provide the industry with guidance and specific examples of how test method validation can be performed. The guide consists of two major sections: variable and attribute test method validation. Since validation of test methods is a requirement of ISO 11607-1, many in the medical device industry were interested and participated in the development of this guide. During the fall ASTM F02 meeting in Nice, several case studies based on application of the guide will be presented."

FURTHER READING

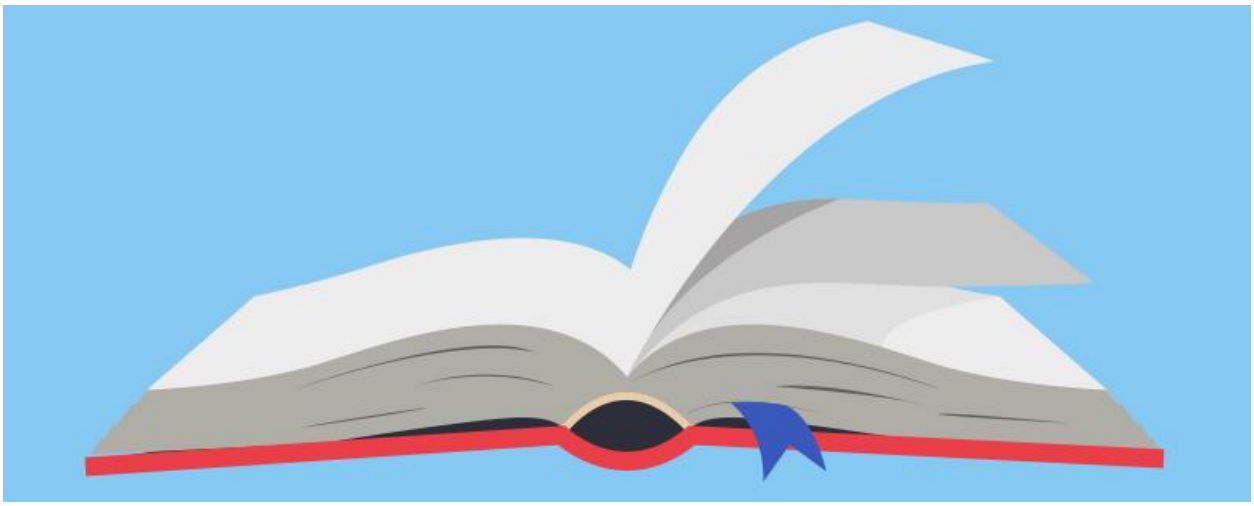

Image source: Designed by Freepik

"How low can you go" published in *Pharmaceutical & Medical Packaging News,* 2006

"Strength and integrity, part one: The basics of medical package testing"
"Strength and integrity, part two: Basics of seal-strength testing"
— by Stephen Franks, T.M. Electronics Inc., published in *Pharmaceutical & Medical Packaging News,* 2002

KEY DEFINITIONS

A **sterile barrier system (SBS)** is the "minimum package that prevents ingress of microorganisms and allows aseptic presentation of product at the point of use."
— ISO **ISO/TS 16775:2014 (en),** Packaging for terminally sterilized medical devices—Guidance on the application of ISO 11607-1 and ISO 11607-2; also ASTM F17-2017 "Standard Terminology Relating to Primary Barrier Packaging"

Package integrity is "the physical capability of a given package to protect its contents with the desired level of protection over a defined period of service; for example, as a barrier to physical, microbiological, or chemical challenges."
— ASTM F17-17 "Standard Terminology Relating to Primary Barrier Packaging"

Seal strength is "a measure of the mechanical strength of the bond between sealed materials of a package."
— ASTM F17-17 "Standard Terminology Relating to Primary Barrier Packaging"

A **leak** is "any opening in a flexible package that is contrary to intention and either lets contents escape or permits substances to enter."
— ASTM F17-17 "Standard Terminology Relating to Primary Barrier Packaging"