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Porous Sterile Barrier Integrity Testing: Failure Anomalies

False positives can occur when performing sterile integrity testing. Understanding how to identify them can help minimize their occurrence in future package designs.

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Some medical device manufacturers struggle with the possibility of false-positive results when performing sterile integrity testing (bubble-leak or dye-penetration tests) on a flexible sterile barrier system (SBS) containing porous materials. A false positive can occur when a flexible pouch containing a porous material is bent, folded, or creased. The folding causes internal sheet separation of the porous web.

Separation can happen when a pouch is folded to fit into a shelf container or is folded or bent during distribution stress testing. The folding of porous barrier materials is not recommended, but it is often done anyway or difficult to avoid. Sheet separation has been observed in all types of porous sheet materials currently available to the industry. Although not a part of this study, folding is also a common cause of film failure or stress cracking in a porous SBS.

A study conducted by DuPont Medical Packaging has shown that sheet separation does not compromise the sterile barrier of Tyvek material. Any leakage of air or dye happens along the transverse direction of the material, not between the porous web and opposing nonporous web material as occurs in a seal failure. When performing integrity tests, operators must analyze anomalies carefully and determine whether the seal has failed or whether the result is a false positive. It may be necessary to perform further investigation on samples that exhibit potential false positives. See the sidebar "Sterile Barrier Study" on page 96 for complete details of the study procedure. This study evaluated only Tyvek.

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Practices and Pressures

It is never recommended to fold flexible barrier materials. However, inadvertent SBS folding can happen during distribution and handling. Packaging system designs affected by cost constraints also often contribute to materials becoming folded. It is a common practice when designing packaging systems for new products to use as many existing package components as possible. This practice results from an imperative to avoid small-volume purchases of a new, optimally sized component. And it increases the volume of purchases of existing components that may not fit the new application well. The higher volume requirements usually result in lower per-unit component costs. This may be a good sourcing decision, but using an improperly sized shelf box—one that requires the flexible SBS to be folded before loading—can result in sheet separation of the porous material. Folding can also cause flex cracking of films.

Another factor is that packaging engineers face a constant pressure to reduce the size of the packaging system. Storage space in healthcare facilities is always at a premium. Engineers are also pressured to reduce solid-waste materials. Factoring in this consideration also contributes to the need to reduce the shelf container size.

The Effect of ISO 11607

Both testing contractors and device manufacturers are reporting the sheet-separation phenomenon more frequently than in the past. Several factors seem to be contributing to the increase in reported instances. Probably most important has been the advent of the international standard ISO 11607, "Packaging for Terminally Sterilized Medical Devices."[1] The generation of

STERILE BARRIER STUDY

Study Scope

A microbial ranking test was conducted at the request of DuPont Medical Packaging at contract test facility Ethox Corp. (Buffalo, NY) in March 2004. The purpose was to evaluate a material anomaly of sheet separation of DuPont Tyvek 1073B. Sheet separation is caused when Tyvek is folded to fit in the shelf carton. This phenomenon is detailed in Section 7 of the DuPont Tyvek Technical Reference Guide for Medical Packaging. The testing was to determine whether a loss in filtration efficiency occurred and, therefore, whether the sterile barrier characteristics of the sheet were reduced.

Discussion

Samples of DuPont Tyvek 1073B were split in half to simulate a worst-case condition that a Tyvek- and film-peel pouch could encounter if the pouch were folded and if delamination within the Tyvek sheet occurred. The split sheets were subjected to testing per ASTM International F1608, "Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)." All medical styles of Tyvek are regularly tested for this attribute, and the split samples were included in a group of production samples.

Cited Documents

Documents used during the testing included the following:

- ASTM International F1608-00, "Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)."[1]
- ASTM International F2096-01, "Standard Test Method for Detecting Gross Leaks in Porous Medical Packaging by Internal Pressurization (Bubble Test)."[2]
- *Technical Reference Guide for Medical Packaging*, H97756, rev. 10/03.[3]

Test Samples

The samples were placed in the F1608 test apparatus sample holders with the inner surface (or fuzzy side) facing the challenge source. This simulated the Tyvek orientation in a pouch exhibiting this anomaly.

Results and Summary

The test results had log reduction values (LRVs) ranging from 3.72 to 5.07. There were no deviations reported from the Ethox Work Instructions, which provide step-by-step instructions on how to perform testing to ASTM F1608.

Summary Discussion

The roll-average LRV values for intact sheets were as follows: 1073B = 5.20, 1059B = 4.70, and 2FS = 3.20. The microbial barrier test results are comparable to or better than porous barrier materials. While it is up to device manufacturers to set an acceptable minimum LRV based on a given application, the split-1073B sample results indicate adequacy for providing a barrier to the ingress of contaminants that could compromise the sterility of the contents.

Conclusion

If the failure mechanism (sheet separation) is the same as observed in the test samples, then sheet separation, pouch size, pouch configuration, and films used in the SBS (pouch) will have no effect on sterile barrier integrity. With seals intact, the side of the pouch made with Tyvek still exhibits microbial barrier properties adequate to maintain sterility of the contents.

References

1. F1608, "Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)" (West Conshohocken, PA: ASTM International: 2004).
2. F2906, "Standard Test Method for Detecting Gross Leaks in Porous Medical Packaging by Internal Pressurization (Bubble Test)"(West Conshohocken, PA: ASTM International, 2004).
3. *Technical Reference Guide for Medical Packaging* [online] (Wilmington, DE: DuPont Medical Packaging, 2002); available from Internet: http://medicalpackaging.dupont.com/Tyvek_HDPE/en_US/pdf/tyvekrefguide.pdf.

integrity tests by ASTM International, Subcommittee F02.60, Medical Device Packaging, and the industry's heightened awareness of required testing referenced in ISO 11607 have led to the increase in reported cases.

The industry now has tools for integrity testing that were not previously available. These tests are more sensitive than older tests such as visual inspection and dust-drum tests.

Operators are becoming more familiar with the new tests and are implementing them more diligently. Before the advent of medical device regulations, including GMPs and the quality system regulation, the device industry paid little attention to packaging. Stress testing or performance tests to evaluate the package design performance were uncommon and, as a result, posttest sample analysis was neither needed nor performed. The sheet-separation phenomenon, therefore, was never an issue.

Test operators at two large medical device manufacturers and a contract test facility have indicated that the number of false positives and their own recognition of sheet-separation phenomena have increased dramatically as they have become familiar with the test methods.

What Is a False Positive?

Flexible porous sheets may separate internally when folded because the manufacturing process makes the exterior surfaces less flexible than the interior. The process of bending the sheet causes deformation within the flexible inner part of the sheet. This deformation

causes tension forces within the sheet that, when sufficiently high, can cause fibers to separate. At this stage, these fibers are the only mechanism holding the sheet together. The tighter the bend, the greater the forces become, until the loads become excessive. The fiber structure holding the sheet together then gives and compresses on either side of the bend while expanding and creating a gap between internal fibers at the bend. When the sheet is unbent or flattened out, a less-dense area, or gap, is formed in the sheet's interior. To better understand how this anomaly is formed, see Figures 1 and 2. These areas in the porous sheet are separations within the softer inner layer between the outer surfaces. The original fiber mass is still there; only the bulk density has decreased.

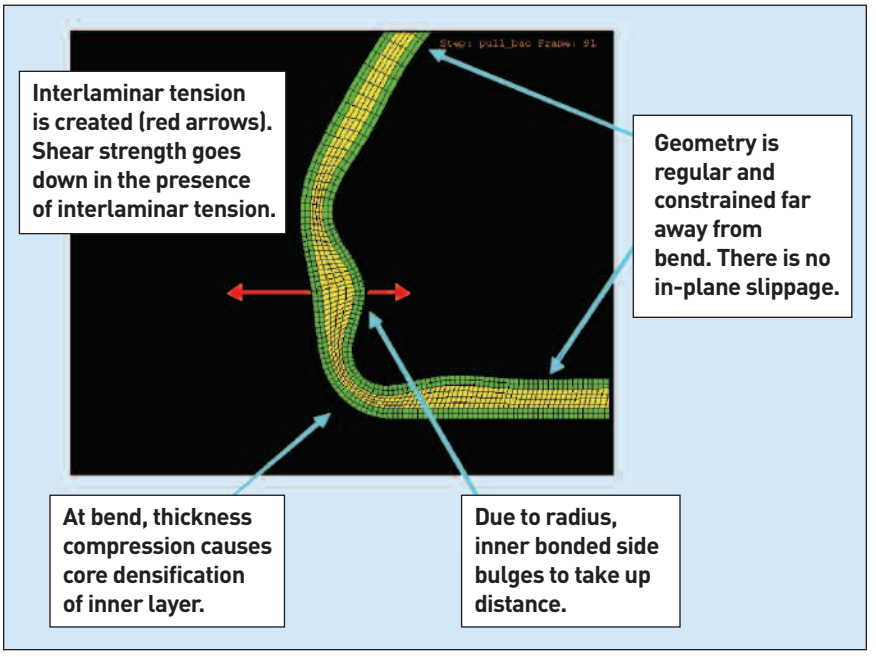

Figure 1. A combination of problems cause porous sheets to separate when folded.

When Is a False Positive Found?

A false positive occurs when evaluating the integrity of a porous SBS by means of ASTM International integrity tests. These tests include the following:

- F1929, "Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration."[2]
- F2096, "Standard Test Method for Detecting Gross Leaks in Porous Medical Packaging by Internal Pressurization (Bubble Test)."[3]
- D3078, "Standard Test Method for the Determination of Leaks in Flexible Packaging by Bubble Emission."[4]

Test Anomalies

When a material anomaly is present in a sample during dye-leak or bubble-leak integrity testing, a false-positive can occur. These tests reveal a less resistant path (reduced bulk density) or a more permeable area through which the dye or the air can pass when seeking a route out of the package. The porous member of the package always reaches its bubble point first in the wrinkled or creased fiber-separated area. For such samples, there is little or no loss in the transverse direction or in through-the-web filtration efficiency; the sterile barrier characteristics of the porous sheet are not compromised.

Figure 2. In this 50× magnification, the anomaly where a porous sheet was folded is evident.

Package Integrity

An outside laboratory evaluated the integrity of an uncoated Tyvek 1073B, polyester (polyethylene)/low-density polyethylene pouch that exhibited this anomaly. The lab performed a microbial ranking test [ASTM International F1608, "Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)"].[5] Per ASTM F1608, microbial barrier is the measure of the ability of a porous substrate to prevent bacterial penetration. A completely impermeable control sample (microbial penetration is zero) is challenged with 1 million (10^6) colony-forming units (CFU). That number of CFU has a $\log_{10}$ value of 6. If a sample challenged in the same way as the control allows 10 CFU ($\log_{10} = 1$) to penetrate, then its log reduction value (LRV) is 5 (6 – 1 = 5). Therefore, the higher the LRV, the more resistant the packaging is to bacteria and microorganisms. To test for the worst-case scenario, the Tyvek samples were split approximately in half, resulting in test samples only half as thick as a full sheet of Tyvek 1073B. The average for the tests was a LRV of 4.15.

To cause sterility loss with a typical delamination channel anomaly in an SBS, a contaminant would have to enter the channel, migrate up that channel to the point where that channel overlaid the inside of the pouch, migrate through the remaining layer of the porous material into the bag, and finally land on the device component inside the SBS and survive. Needless to say, the chances of this happening are remote. Tyvek continued to provide an adequate microbial barrier without compromising package integrity. Although the test results indicated a small reduction in the LRV of the samples, all results were significantly better than those obtained with other commonly used porous materials (see Figure 3).

The LRV of a half sheet of Tyvek 1073B was very close to that of a full sheet. It is important to note that under normal transportation, distribution, and storage conditions, the top 5–10% of the Tyvek does all the filtration. It is safe to assume that it would still be an excellent SBS as long as the seals and flexible materials were not compromised in some way. DuPont has never

recommended the folding of Tyvek.

The test used to rank porous barrier material—as well as the integrity tests discussed—does have drawbacks and limits. One of the most difficult jobs for packaging engineers using a breathable substrate in an SBS is finding leaks when the package system is actually designed to leak or breathe. Running an LRV test never indicates whether a porous material is an adequate sterile barrier; it simply provides a way to compare one material with another.

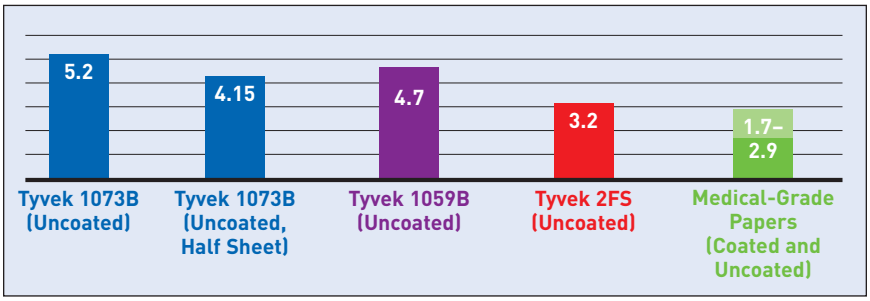

Figure 3. Tyvek 1073B and three other materials were tested according to ASTM F1608. The log reduction value (LRV) of a half sheet of Tyvek 1073B was 4.15, which was very close to the LRV of a full sheet.

How to Evaluate for False Positives

It is important to know how to evaluate porous barrier materials to determine whether a false positive has occurred during testing. The several methods for identifying a false positive include the following:

- Microscopic examination of the sheet edge in the area of a suspected seal failure can help determine whether there is an actual failure or a false positive.
- Once the dye has dried and the film has been removed from the substrate, dye penetrating through a true seal failure will stain the surface of the film.
- Dye color will be more intense when showing through a seal failure than when showing through a sheet separation.
- Channel edges will be more defined in seal failures; wicking dye will be visible through some amount of the porous substrate, and dye color will be less intense.
- Dye will diffuse into the sheet, and edges will not be well-defined in areas exhibiting sheet separation.
- Dye wicking into the sheet and crossing the seal area (within the sheet) will occur at a slower pace than dye channeling through the adhesive layer in the sheet surface.
- When viewed from the porous side of the sample, the dye color will be more intense from wicking than it would be from channeling.

It is critical to know when a seal failure is present. A dye test will produce a definitive result within one second. For an area of sheet separation to be found, the dye must first wick through the porous material. Unlike a true seal failure, wicking will cause a delay in the dye path across the seal separation area. In addition, visual inspection of a sheet separation on the porous side of the pouch reveals a greater spread of the dye through web than occurs in a sample with a seal failure. The dye is resident in the sheet longer with sheet separation, and it soaks or wicks out around the sheet more.

Conclusion

The information presented here should help packaging engineers understand what test operators see with false positives. A round-robin, interlaboratory research study done by ASTM Subcommittee F02.60 for F1929 did not examine samples with creases or folds. As a result, the false-positive phenomenon was not observed and, therefore, was not evident in the final results. This phenomenon needs to be addressed in more detail in the next revisions of ASTM D3078, F1929, and F2096. The revisions should also include annexes with detailed discussions addressing this anomaly.

Demonstrated methods for distinguishing between seal failure and sheet separation include:

- Dye-penetration testing.
- High-powered microscopic photos of a seal's edge that reveal sheet separation within a porous sheet.
- Waiting for the dye solution to dry and then peeling open the pouch to examine it for a blue dye witness mark on the film seal surface.

Whenever a leak in the seal area is observed during dye or underwater pressure-differential integrity testing, it is essential to get a second opinion about what is being observed to fully understand the nature of the leak. Further verification of the leakage can help avoid failing a test protocol due to a false positive. In addition, to help minimize the occurrence of false positives in future designs, implement designs that incorporate properly sized shelf containers in order to reduce the severity of folding or bending of the package.

References

1. ISO 11607, "Packaging for Terminally Sterilized Medical Devices" (Geneva: International Organization for Standardization, 2003).
2. F1929, "Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration" (West Conshohocken, PA: ASTM International, 2004).
3. F2906, "Standard Test Method for Detecting Gross Leaks in Porous Medical Packaging by Internal Pressurization (Bubble Test)"(West Conshohocken, PA: ASTM International, 2004).
4. D3078, "Standard Test Method for the Determination of Leaks in Flexible Packaging by Bubble Emission" (West Conshohocken, PA: ASTM International, 2002).
5. F1608, "Standard Test Method for Microbial Ranking of Porous Packaging Materials (Exposure Chamber Method)" (West Conshohocken, PA: ASTM International: 2004). ■