Staying Ahead of the Pack

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In a world of hungry microorganisms, it is critical that medical devices designed to heal do not inadvertently do the opposite by infecting the patient. To prevent infection, a device's packaging, or "sterile barrier system," must maintain sterility over the product's entire shelf life. In fact, packaging can potentially be the weak link in the chain of steps designed to keep a product sterile from the time of production to its final use.

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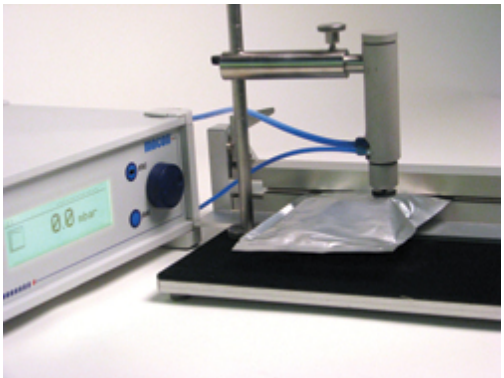


Responsibility for maintaining safety and sterility is shared by development engineers, packaging developers, packaging managers, product managers, and quality auditors. A traditional method for testing a package's sterile barrier system, at any point in its life, has been to bathe it in a contaminated solution and then test by culturing the contents to be sure that microbes have not penetrated the package. While workable, this microbial challenge testing has several drawbacks. First, because culturing is a growth process, it is invariably time consuming. Second, errors in handling the package or its contents in the testing process can lead to accidental contamination and false positives. Finally, there is also a risk of false negatives if the microbes used in testing behave differently than expected.

Opening the Door to Integrity Testing

For all these reasons, there has been discussion of using package integrity testing instruments to support or replace traditional sterility tests. In 2008, the FDA finalized guidance regarding "container and closure system integrity testing . . . as a component of the stability protocol for sterile products." The guidance states that physical testing can be used to verify that the seals are leak free and continuous.

In its guidance, the FDA lists four advantages of container and closure system

integrity tests. These include:

• The ability to "detect a breach... prior to product contamination"
• The ability to "conserve samples that may be used for other stability tests"
• The fact that they "require less time than sterility test methods"
• The fact that "the potential for false positive results may be reduced"

However, integrity testing offers other benefits as well. Like traditional microbial challenge testing, it can be used during package development for periodic checks on production or when critical events occur. Unlike the microbial challenge though, integrity testing doesn't incur the delay required for culturing, making it far more convenient and usable. Nor does it require highly trained specialists or incur the same risk of operator error.

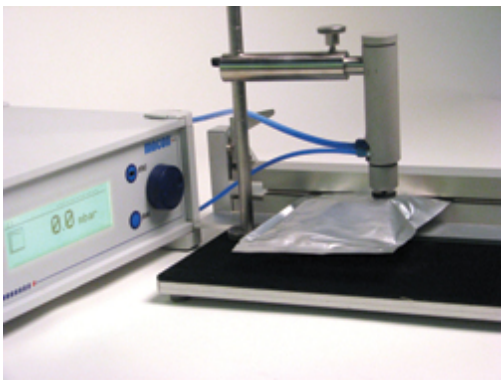
Ease of testing means packages can be tested more often over their anticipated lifecycle. This can be critical for packaging that is shipped, handled, and otherwise challenged in ways that may affect its ability to keep contents sterile. Package integrity testing using instrument methods can be more sensitive, repeatable, and reproducible and, therefore, more reliable.

The FDA's guidance notes specific limitations of traditional sterility testing, including:

• The fact that they "will only detect viable microorganisms present at the time of the test"
• The fact that these organisms "can only be detected if they are capable of growth in the specified culture medium"
• The risk of "potential interference due to adventitious microbial contamination . . . at the time of testing"
• The fact that "sterility tests are always destructive of the samples"

In this document, the FDA, for the first time, officially allows physical testing to support sterility testing. The agency lists as acceptable physical testing methods "any properly validated . . . container and closure integrity test (e.g., bubble tests, pressure/vacuum decay, trace gas permeation/leak tests, dye penetration tests, seal force or electrical conductivity, and capacitance tests, etc.)"

Complex Requirements



While many take packaging for granted as something to be opened and thrown away, a package system is a complex entity often consisting of a variety of materials assembled in a multi-step process. Each package must be carefully designed not just to hold its contents, but also to protect them in transport and handling and be easily opened at the point of use. And, of course, the package must keep its contents sterile until they are used. A breach at any point in the sterile barrier system can render the contents unusable or potentially dangerous.

There is no universal means of package integrity testing, and methods are not all equal. As packages must be adapted to their contents, testing must be adapted to package design, materials, and sealing mechanisms. Testing systems may have to evaluate packages incorporating flexible, semi-rigid, and rigid designs; porous and non-porous materials; laminated polymer, paper, and foil materials; and a variety of sealing technologies. The packages being tested may be unfilled, or filled with solid, liquid, or powdered materials. Further, a validated testing system should comply with recognized consensus standards, such as those published by ANSI/AAMI/ISO and ASTM International. If it stores data, it should comply with applicable electronic data regulations as well. Finally, it should also be simple to operate, requiring a minimum of specialized training.

Test Methods

Depending on package design, a variety of package integrity testing methods may be employed.

• Burst and creep testing entails pressurizing the inside of the package and measuring the pressure required to either cause seals to separate or packaging materials to rupture. Some packages use porous materials, allowing the contents to be gas sterilized through the porous package walls after the package has been sealed; burst testing of these packages can require higher inflow capability in order to achieve sufficient pressure to challenge the package.
• Pressure decay testing identifies failure of a package's seal or materials by measuring the package's ability to maintain a constant internal pressure typically 50% of burst pressure over a period of time.
• Precise leak testing identifies the size of a leak by measuring the flow rate required to maintain constant pressure within the package.
Multi-testing allows the operator to perform sets of tests flexible combinations of

leak testing, creep, and burst testing on the same package sequentially. By combining tests, researchers can gain a clear understanding of a package system's resistance to peel and of seal strength under varying conditions.

Conclusion

In packaging medical products that impact lives and health, the costs of poor quality control can be enormous. In today's fast-moving global markets, the stakes are higher than ever. As competition and time pressures have grown, the industry and its regulators have come to recognize that traditional testing methods can be slow and potentially risky. Package integrity testing has been acknowledged to be an important tool for ensuring the safety of package systems and the products they protect. Package integrity testing, either by itself or as an adjunct to other traditional testing methods, is now helping designers and manufacturers deliver safe medical products both quickly and cost effectively.

Online

For additional information on the technologies and products discussed in this article, see *MDT* online at www.mdtmag.com [2] or Mocon Medical Packaging at www.moconmedical.com [3].

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