30 Sterile product-package integrity testing

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Package integrity, also called container–closure integrity, is the measure of a primary package's ability to keep the product in (including vacuum or inert gas headspace, if present) and to keep potential microbial, particulate, and chemical contaminants out. Package integrity is a requirement that must be met throughout the product's life cycle, beginning from early development phases. A variety of tests are available for use by the pharmaceutical industry to measure parenteral product-package integrity, although no one test can be recommended for all parenteral package integrity testing. Historically, microbial ingress tests were considered the definitive standard, although regulatory agencies increasingly prefer validated physical test methods less subject to variability. Container–closure integrity verification of all units in marketed product lots has become a reality for many dosage form packaging types.

U.S. AND EU REGULATIONS AND GUIDANCES

Prior to the mid-1990s only sterility of the packaged product was required by the U.S. Food and Drug Administration (FDA) as verification of package integrity. Since 1994, the U.S. FDA issued several Guidances for Industry addressing this topic. First, the 1994 U.S. FDA Guidance for Industry describing sterilization process validation submission documentation requires a demonstration of a container–closure system's ability to maintain the integrity of its microbial barrier, thus indirectly verifying a drug product-package's sterility through its shelf life. Sterility testing alone is insufficient for this purpose (1).

Then in 1999, the FDA issued a comprehensive guidance discussing container and closure systems for packaging human drugs and biologics (2). Pharmaceutical packaging should be shown suitable for its intended use, including protection—the ability of the container–closure system "to provide the dosage form with adequate protection from factors (e.g., temperature, light) that can cause degradation in the quality of that dosage form over its shelf life." Package integrity-related causes of degradation cited include loss of solvent, exposure to reactive gases (e.g., oxygen), absorption of water vapor, microbial contamination, and contamination by filth. Package suitability verification in any new product submission must therefore include package integrity study results, and specifically, data extended throughout the product's full shelf life.

A 2008 FDA Guidance for Industry addresses the issue of integrity testing as part of pre and postapproval stability protocols for sterile biological products, human and animal drugs, including investigational and bulk drugs (3). As noted, stability testing must include a method(s) that supports the continued capability of containers to maintain sterility. While sterility testing satisfies this requirement, the Guidance acknowledges practical and scientific limitations to this approach, allowing the substitution of other integrity tests in stability protocols. Good scientific principles are recommended in selecting integrity tests, taking into consideration the container–closure system, product formulations, and, where applicable, routes of administration. How the method relates to microbial integrity should be noted.

The 2008 revision to Annex 1 of the European Union Good Manufacturing Practices (GMPs) for sterile products states that "Containers closed by fusion, e.g., glass or plastic ampoules should be subject to 100% integrity testing. Samples of other containers should be checked for integrity according to appropriate procedures" (4). Additionally, "Containers sealed under vacuum should be tested for maintenance of that vacuum after an appropriate, pre-determined period." Concerning stoppered vials, "Vials with missing or displaced stoppers should be rejected prior to capping." Another reference to integrity testing in the EU GMPs states: "Filled containers of parenteral products should be inspected individually for extraneous contamination or other defects." Direction is given for human inspection, and "where other

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