

Container Closure Integrity for Sterile Drug Products

General Discussion

This document provides guidance for ensuring that the integrity of the container closure system will protect the product over its shelf life.

1. The Suitability of the Container Closure System should be confirmed by testing the quality attributes of the drug product over its shelf life.
2. Studies should be executed to simulate the effects of environmental stresses, handling, and use conditions on the container closure system including, and not limited to:
 - Temperature, pressure, and relative humidity extremes; and
 - Shock and vibrational stress (e.g., shipping trials).
3. Packaging Evaluation of Multi-Dose Vials should include testing for coring of the stopper and leakage by repeated puncturing of the stopper using the recommended gauge needle for the number of times needle puncture is likely to occur.
4. Critical Factors That Affect Container Closure Integrity should be defined in written Standard Operating Procedures (SOP), controlled, and monitored and including, and not be limited to:
 - Package component composition, dimensions, coatings, and critical defects;
 - Sealing/packaging operation variables of time, temperature, pressure (seal force), gas flow rates, and torque;
 - Processing variables of packaging components including washing, drying, siliconization, depyrogenation, and sterilization; and
 - Final product processing, such as terminal sterilization or lyophilization.
5. Critical Process Parameters and Critical Process Parameter Ranges for assuring container closure integrity should be provided in SOPs and include, and not be limited to, the following:

Bottles/Vials with Elastomeric Stoppers:

- Sealing/capping machine speed;
- Crimp or spring force settings; and
- Time between closure insertion and package sealing to prevent loss of headspace gas or vacuum, if applicable.

Ampoules:

- Time for thermal sealing;
- Gas flow rate on ampoule sealing lines; and
- Time between product filling and sealing to prevent loss of headspace gas, if applicable.

Plastic Containers:

- Time, temperature, and pressure controls for thermal sealing equipment;
- Time between product filling and sealing to prevent loss of headspace gas, if applicable; and
- Torque for screw caps.

Metal Tubes: