Title: Container Closure Integrity for Sterile Drug Products					
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Container Closure Integrity for Sterile Drug Products

Introduction

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

9. Challenged Containers that Show Microbial Growth Upon Microbial Ingress Testing should be inspected to determine whether defects in the container closure seal permitted microbial ingress. All defects observed should be described and documented. An investigation should be conducted to determine the cause of the contamination, including a comparison of the contaminant organism(s) to the challenge organism.

10. Non-Microbial Methods for Container Closure Integrity Testing should be based on validated studies that correlate the test method to microbial ingress testing. Non-microbial integrity tests should be used during routine processing, at a minimum:
    - During equipment set-up;
    - As an In-Process Control (IPC) test;
    - On representative samples of the finished batch/lot; and
    - On stability samples during the shelf life and at lot expiration date.

11. If Residual Seal Force (RSF) is Used, the minimum acceptable RSF specification throughout the shelf life of the product should be the lowest RSF value that is demonstrated to prevent ingress of microorganisms in the microbial ingress test. The RSF action level used during processing should take into account relaxation of the closure over time and should be greater than the minimum RSF identified in the microbial ingress test.

    If another non-microbial method is used, the specification throughout the shelf life of the product should be established at a value that is demonstrated to prevent ingress of microorganisms in the microbial ingress test. The action level used during processing should take into account relaxation of the closure over time and should be tighter than the limit identified in the microbial ingress test.

12. In-Process Controls (IPC) Used to Verify Container Closure Integrity include, and are not limited to, the following:

    - Torque monitors for screw capping equipment;
    - RSF or other validated non-microbial ingress test results determined on-line or off-line for glass vials with elastomeric closures;
    - Headspace analysis for products requiring inert gas headspace; and
    - Visual inspection of seals.

13. In-Process Control (IPC) Sampling and Test Procedures for container closure integrity testing should be written and approved and include, and not be limited to:
    - Number of samples to be tested per batch/lot,
    - Test methods,
    - Test equipment,
    - Acceptance criteria, and
    - Retest criteria and methods.

