Liquid Immersion Microbial Challenge Tests: Microbial Testing for Container Closure Integrity

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Introduction

The container closure system for pharmaceutical products intended to be sterile is critical and this criticality relates to the physical properties of the container closure system in that a poorly designed or manufactured system will result in microbiological penetration. Factors to take into account with, for example, rubber-stoppered glass vials include having the correct dimensional specifications for the internal diameter of the neck opening and its depth, the internal and external diameters of the flange. Other factors are the concentricity of the flange, the neck and the body of the vial. Any angularity of the flange versus the vertical center line of the vial must be specified; so must the physical finish of the surface of the flange and internal neck bore to ensure satisfactory mating with the closure. Closures must be specified in terms of diameters, depth, thickness and elasticity.

In some situations it may be evident that a container closure system has failed to maintain sterility. The contents of a broken ampoule have no assurance of sterility. Other deficiencies in container closure systems may pose greater threats because they go unnoticed. It is these more subtle problems that demand that containment systems for sterile products must be demonstrated by microbiological means to meet their intended purpose of maintaining sterility. From a regulatory standpoint, regulators require that methods and results demonstrating the microbiological integrity of container closure systems for sterile products should be included in drug applications for both human and veterinary applications. In its Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing, Current Good Manufacturing Practice, FDA states that (1): “A container-closure system which permits penetration of microorganisms is unsuitable for a sterile product”. Whether testing is conducted as part of validation, for stability studies or as part of inspection needs to be determined (2) (obviously the microbial focus here does not lend itself to a routine test).

Tests to verify the container-closure can be grouped as microbial tests or non-microbial (physical) tests. Physical tests include the dye test; vacuum testing (typically leak testing with sensitivity to detect leaks down to approximately 5-10 microns); gas leakage determined using a bubble test; liquid leakage detected by atomic absorption of a copper ion tracer solution; laser-based gas headspace analysis using a frequency modulation spectroscopy; high voltage leak detection (which detects package defects using an electrical current); or a helium leak rate test (which quantitates the flow rate of helium from leaks in packaging after having been flooded with helium as a tracer gas). USP <1207> series describes several common container closure integrity testing methods, with tests divided into those considered deterministic and those considered probabilistic. Many of these tests are outlined in articles by Fornico (3), Glad (4) and Booth (5).