Volume 11 Issue 3

IPI

International Pharmaceutical Industry
Supporting the industry Through Communication

Peer Reviewed

Mergers and Acquisitions
Opportunities and Drivers for CDMOs

Pharmacodynamic Models as Outcome Variables
In Early Respiratory Drug Development

Fighting the Zombies
Imagine if Your Body Kept Functioning No Matter Your Age

How Integrated Packaging and Delivery Solutions
Can Support New Drug Development

www.ipimediaworld.com

Ensuring Container Closure Integrity through a Parenteral Packaging System Approach

Container closure integrity (CCI) is an increasingly relevant issue in the pharmaceutical packaging industry. It addresses the maintenance of integrity to prevent microbial ingress in sterile product packaging until the time of use, as well as to restrict loss of product contents and to prevent the entry of detrimental gases or other materials. In order to ensure that CCI is guaranteed at all times, multiple aspects of parenteral packaging must be considered. This article describes these considerations and highlights the steps being taken in the industry to ensure container closure integrity in a parenteral packaging system.

With the increased focus on container closure integrity, there is a need for the different packaging components of a vial or bottle system (vial, stopper and aluminum seal), to work together as a system. Aluminum seals are gaining importance, due to the EU GMP Annex 1 stating that "the container closure system for an aseptically filled vial is not fully integral until the aluminum cap has been crimped into place on the stoppered vial". With an addition of an aluminum seal, potential gaps between the vial and the stopper are closed by compression, creating a leak-free seal between the vial and its closure.

The vial, elastomeric stopper, and aluminum seal work together to ensure container closure integrity

Revisions to the USP <1207> (2016) further define container closure integrity (CCI) or package integrity as "the absence of package leakage greater than the product package "maximum allowable leakage limit" (MALL). The "MALL" is described as the smallest gap or leak rate that puts the quality of the drug product at risk. A process must be in place to guarantee CCI throughout the full shelf-life of the product. With typical drug product shelf-life lasting approximately two years, the seal must be robust enough to withstand the risk of loosening over time and potentially exposing the drug to unwanted ingress or to loss of medicinal product.

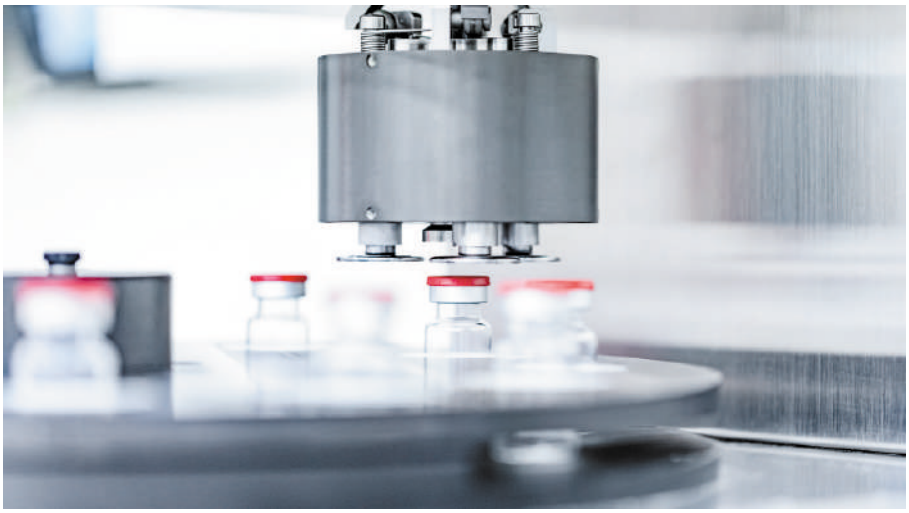
An integral package shall, therefore, prevent microbial ingress, preserving sterility, and maintain the quality of the drug product, and prevent product loss.

Ensuring CCI through Design Expertise and Material Science

The risks associated with insufficient CCI are numerous: loss of sterility being the primary issue, but, in addition, a broad variation of impacts affecting the product quality, such as alterations in potency, pH shifts, oxidation, increase in moisture content, etc.

With the Halobutyl rubbers typically being used for elastomeric closures, there is little concern for permeation through the seal. Halobutyls have a very low gas and moisture transition rate forming an adequate barrier to protect the product. CCI issues are, therefore, mainly related to either defects (cracks, tears, etc.) or an inadequate match of vial, stopper, and seal.

These three components, all with certain tolerances, need to come together as a reliable system to protect the drug contents. For vials, a suitable combination of the three components is typically material- and design-dependent. For the stopper, the design needs to assure a snug fit with the vial. Size, shape, and final seating of the stopper are all considered during the design phase to ensure the stopper meets the proper functional requirements. Stopper formulation is the other critical factor determining an acceptable fit. Rubber formulations must have the capacity to show sufficient visco-elastic behaviour to allow for the material to fill certain "gaps" in the sealing area. The formulation of the stopper ensures that the container closure integrity remains intact when faced with a variety of external factors, such as movement (transport), temperature,



Aluminum seals are specifically designed to allow for sufficient compression force on the rubber stopper once crimped into place.

and pressure (e.g. decrease of external pressure during air transport). Last but not least, the design of the aluminum seal, especially the skirt height, needs to allow sufficient compression force on the rubber stopper flange to keep the components in place over time.

Even the best possible combination of components, however, cannot guarantee seal integrity, if it is not complemented with a suitable crimping process. Whereas a too high compression on the rubber closure may lead to glass breakage, deformation of the rubber closure, and/or poor aesthetics of the crimp, an insufficient force will lead to too little compression resulting in loss of seal integrity.

Testing Methods for Determining CCI

For monitoring seal force, the "residual seal force" (RSF) is an adequate seal quality testing method which is also recognised by the revised USP <1207>. RSF is the force a compressed elastomeric closure flange continues to exert on a vial sealing surface after application of an aluminum seal.

RSF values resulting in aesthetically well-crimped vials can then be further evaluated for proper CCI using deterministic methods like "helium leak". The He-leak rate will indicate whether or not a container closure system is subject to potential microbial ingress.

Moving forward, He-leak tests with a positive outcome, meaning container closure systems with a performant CCI behaviour, can then be brought in correlation with the respective residual seal forces.

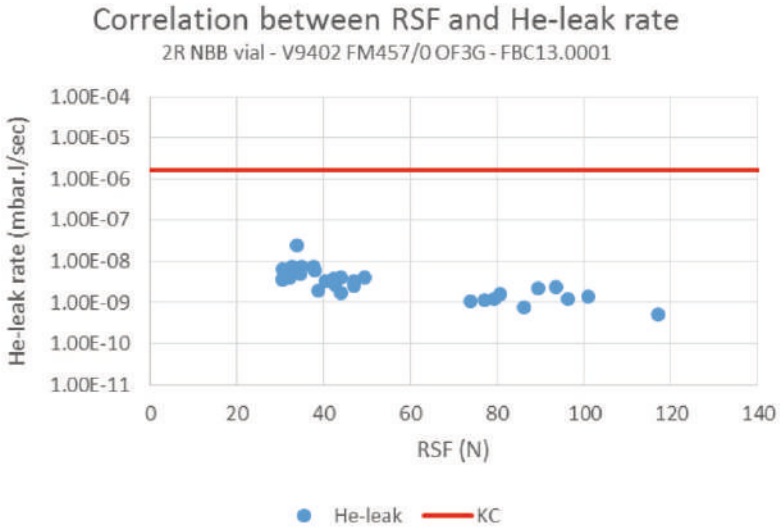
As such, the RSF values become an indicative method to evaluate proper CCI results and can be used to optimise crimping parameters for validation and monitoring of the crimping process in a manufacturing phase.

As the correlation is only valid for a specific combination of vial, stopper, and aluminum seal and crimping process, it is important to test all individual combinations that are under evaluation. A change in one of the components may significantly impact the result of the CCI.

Choosing a Partner with Product Design and Testing Expertise

For drug developers with questions surrounding the safe packaging of their drug product, it is important to choose a partner that fully understands the challenges of the market and offers expertise in both product design and analytical testing. Providing a wide portfolio of products allows drug developers to choose from products already on the market that have been tested over time. Alternatively, for those developers looking for novel solutions for drug packaging, the ability to create custom components gives developers the opportunity to design and formulate the ideal rubber component for their drug, ensuring a proper fit and compatibility. A strong product portfolio and customisation capabilities are complemented by having analytical services in-house to provide assurance that the proposed sealing solutions are robust.

By supporting customers in the selection of components and providing high-quality elastomeric closures and aluminum seals, a strong partner ensures that, as it comes to components, all elements are in place to develop an integral vial closure system that will protect your valuable drug product.



The above chart shows the correlation between RSF values and helium leak rates for vials capped using different capping settings (low – medium – high). Only the capping settings giving cosmetically well-capped vials are considered in this correlation chart

Geert Moens

Geert Moens has a master's degree in public administration and has been working at Datwyler for more than 11 years. After a successful career as Key Account Manager, working together with major pharmaceutical companies across Europe, he is now the Global Platform Leader for Vial Closure Solutions taking strategic initiatives related to Datwyler's rubber and aluminum closures for vial applications.