ARTICLE

MEETING REGULATORY GUIDANCE: A Holistic Strategy to Ensure Container Closure Integrity of Sterile Injectable Vial Product

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Recent regulatory guidance has triggered changes in industry best practices in the area of container closure integrity testing (CCIT). The increasing implementation of deterministic analytical methods for CCIT has enabled deeper insight into the performance of primary packaging with respect to container closure integrity (CCI). However, assuring good CCI of sterile injectable product goes beyond CCI testing. A more science-based holistic approach that includes robust design & qualification of the process and the implementation of appropriate process controls is required. This article describes a framework enabling such a holistic approach to CCI that assures both the primary packaging and the process contribute to good CCI of sterile injectable vial product.

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EVOLVING REGULATIONS ON CONTAINER CLOSURE INTEGRITY

A previous article [Ref. 1] described the recent evolutions in regulatory guidance that are driving changes in industry best practices for CCIT. The USP <1207> chapter titled 'Package Integrity Evaluation – Sterile Products' was implemented in late 2016 and represents the most thorough guidance document to date on container closure integrity concepts for sterile injectable product [Ref. 2]. The chapter gives an overview of CCI testing technologies and describes concepts for CCI control using a product life cycle approach. The chapter also recommends that deterministic CCIT methods based on quantitative analytical measurements be used to generate science-based CCI data that, coupled with a risk-based approach, enables informed decisions about a CCIT strategy in commercial manufacturing. Another regulatory document, the second draft revision of the EU Annex 1 requirements for sterile product manufacturing, was released in February, 2020 [Ref. 3]. The document contains new requirements for CCI testing in manufacturing including the use of scientifically valid sampling plans, validation of transportation or shipping requirements that may negatively impact the integrity of the container (e.g. by decompression or temperature extremes), and the appropriate qualification of process controls such as raised stopper height sensors. Other world regulatory bodies, such as in China and Japan, are updating guidance requirements for CCIT based on the concepts described in USP <1207> while others, in Russia and Korea for example, have put an increasing emphasis on CCI testing & control for finished sterile product. These recent development in requirements from pharmaceutical regulators have made clear that improved CCI testing practices are desired. The industry has responded with many companies conducting a review of their internal CCIT practices followed by the implementation of new CCIT methodologies where appropriate [Ref. 4].

A HOLISTIC APPROACH TO VIAL CONTAINER CLOSURE INTEGRITY

The USP <1207> chapter gives an overview of CCI testing technologies. In particular, the chapter recommends the use of analytical deterministic methods to generate robust CCI data: 'deterministic leak test methods are preferred over probabilistic methods when other key method selection criteria permit'. The reason for this recommendation is multifold:

- Deterministic CCIT methods are based on analytical measurements and can therefore be validated for detecting a critical leak using an analytical method framework.

- Many of the deterministic CCIT methods are rapid and/or non-destructive. This enables analysis of statistically valid samples sets which is crucial for achieving and demonstrating statistical confidence in the primary packaging performance and the process.

The above two points are important for enabling the product life cycle approach described in USP <1207>. Robust package integrity data should be generated throughout the product life cycle and serves as input for an ongoing database of CCI data (the package integrity profile). This collection of robust package integrity data then serves as a risk management tool to ensure that CCI of finished product meets the product quality requirements. As described in the previous article, the framework described in USP <1207> is currently driving changes in industry best practices for CCI testing, including:

- Implementation of a 'toolbox' of CCI test methods optimized and chosen on a per product configuration basis rather than the application of a single legacy test method in a one-size-fits-all approach.

- Generation of science-based data in robust CCI product and process studies and in method development & validation studies which demonstrate the ability to detect a critical leak.

However, a holistic approach to CCI involves more than generating robust CCI data during the product life cycle. The chapter subsection USP <1207.3> Package Seal Quality Test Methods describes measurements that can be made to test the package seal quality. These test methods are not a CCI test but are measurements that indicate the quality of a package seal and give insight into the quality of the sealing process. A seal quality test for a capped and crimped stoppered vial described in USP <1207.3> is the measurement of the Residual Seal Force (RSF) of the compressed rubber stopper. When a stoppered vial is sealed, an applied stress

(sealing force) deforms or compresses the elastomeric stopper against the vial sealing surface during the capping process. Sufficient compression of the stopper is critical for achieving and maintaining good CCI. The compression of the stopper during capping induces a corresponding strain in the stopper, creating a contact stress at the vial/stopper interface. The strain is "locked-in" by applying and crimping an aluminum ferrule over the stopper. This locked-in compression is the Residual Seal Force and is the stress a compressed rubber stopper flange continues to exert on the vial's sealing surface after crimping of the aluminum seal to maintain good CCI. The traditional method used by operators to determine good vial seal tightness is an informal 'twist cap' test in which the operator attempts to manually twist the cap and crimp to ensure that it is tight. This is a subjective test and is certainly not a science-based measurement that can be used for qualifying capping and crimping line settings. The use of RSF testing enables a quantitative approach to characterize, optimize, qualify, and monitor the vial sealing process. Figure 1 shows examples of RSF data generated on samples that were stoppered, capped and crimped on a vial production line. The initial data plotted in blue show that the line was not optimized – RSF values were highly variable sample to sample, and on average were below the desired target value required to maintain good CCI. The capping and crimping line settings were therefore adjusted and RSF testing on a later series of samples is plotted in gray. It is clear that the optimized capping and crimping settings produced vials having less variability in the stopper compression force as well as a higher average value meaning that the vials were sealed more tightly.

Summarizing the information described in this section, we come to the conclusion that a holistic approach to sterile vial container closure integrity involves generating robust analytical data to achieve two main objectives:

a) verify good performance of the primary packaging system with respect to CCI, and
b) optimize and validate the vial sealing process.

In this framework, deterministic CCIT methods and RSF testing are analytical tools that enable the generation of science-based data that give assurance of good CCI. Well-designed packaging development CCI studies utilizing statistically valid sample sets and analytical deterministic CCIT methods can generate robust data giving deep insight into performance of the primary

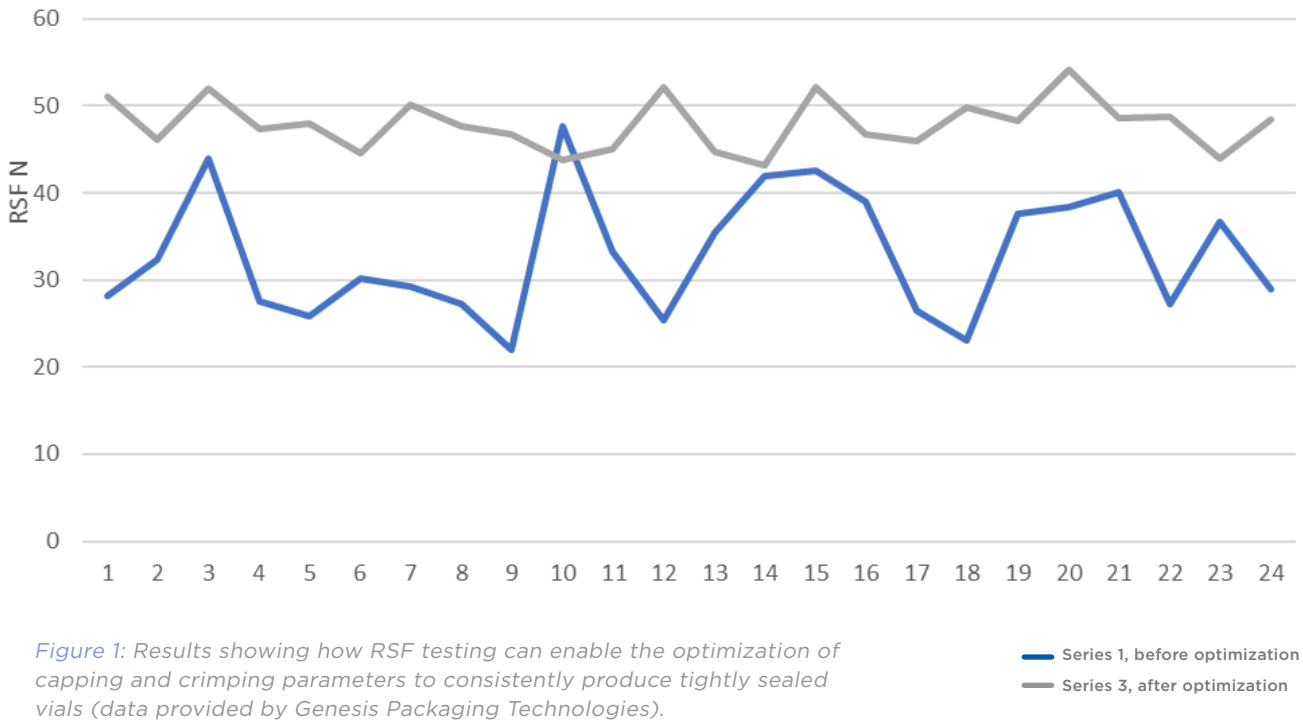

Figure 1: Results showing how RSF testing can enable the optimization of capping and crimping parameters to consistently produce tightly sealed vials (data provided by Genesis Packaging Technologies).

packaging components with respect to the system's inherent package integrity and CCI performance during (extreme) storage conditions, transport, and over shelf life. In manufacturing, RSF studies enable quantitative optimization and validation of the vial capping & crimping process. The link to good CCI can be demonstrated by performing CCI studies that correlate RSF to the results of a CCIT method. An example of this approach can be seen in Figures 2a and 2b which plot RSF–headspace CCI correlation data of a pharmaceutical vial product requiring deep cold storage [Ref. 5].

Carefully designed CCI studies were performed on statistically valid sample sets consisting of stoppered vials prepared with different capping & crimping settings. Various vial-stopper combinations were used to investigate if there were specific primary packaging components that delivered optimum CCI performance at the deep cold storage temperature. The different capping & crimping settings produced samples over a wide range of RSF values corresponding to vials that were loosely to tightly sealed. After storage at -80°C, the samples were tested for maintenance of CCI using a non-destructive

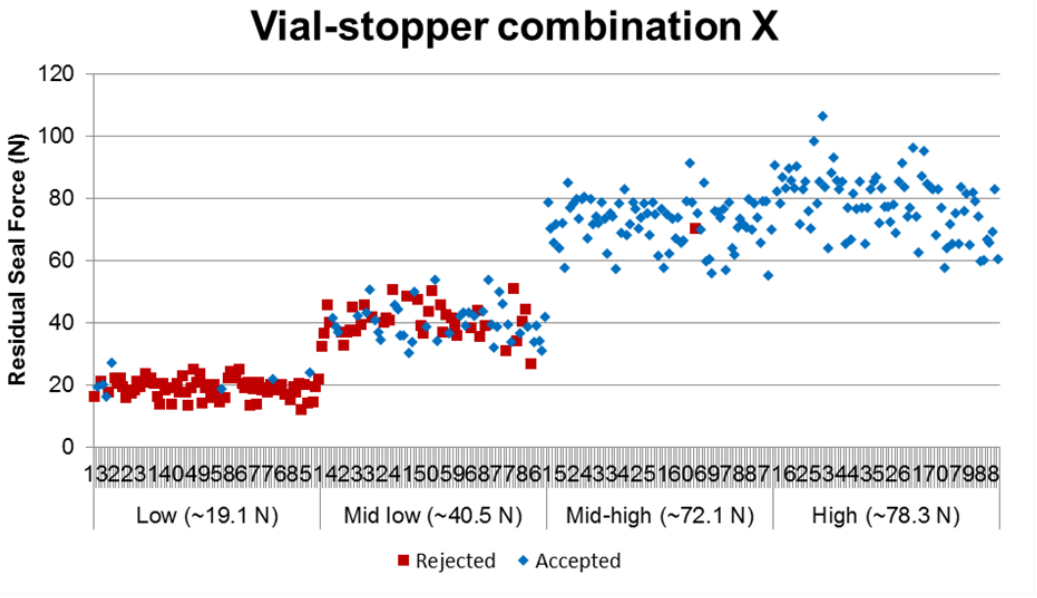

Figure 2a: Plot of RSF values of vial-stopper combination X samples prepared with four different capping & crimping settings. Samples failing a headspace CCI test after deep cold storage are plotted in red. This statistical RSF-headspace CCI correlation data shows high CCI failure rates of these primary packaging components if these components are not tightly capped and crimped [Ref. 5].

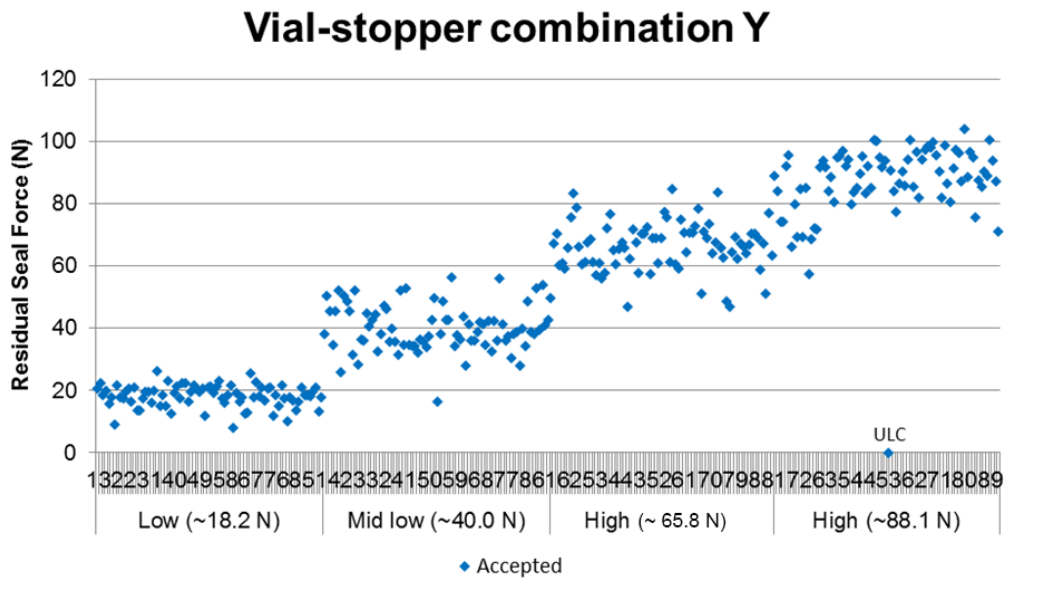

Figure 2b: Plot of RSF values of vial-stopper combination Y samples prepared with four different capping & crimping settings. None of the samples failed a headspace CCI test after deep cold storage. This statistical RSF-headspace CCI correlation data shows good CCI performance of these primary packaging components during deep cold storage over the full range of RSF values (loosely to tightly crimped) [Ref. 5].

headspace method. Figure 2a plots the RSF values of the samples prepared using vial-stopper combination X and four different capping & crimping settings. Vials that failed to maintain good CCI during storage at -80°C are plotted in red. It is clear that this vial-stopper combination does not deliver good CCI performance when loosely capped & crimped (low to mid RSF values). It is necessary for the process to produce high RSF values (tightly capped & crimped) to maintain good CCI at the deep cold storage temperature. On the other hand, the results for vial-stopper combination Y plotted in Figure 2b demonstrate that these primary packaging components maintained good CCI over the full range of RSF values (loosely to tightly capped & crimped). In the case of vial-stopper combination Y, the process can be validated with a much larger design space that delivers good CCI. In this project, additional studies throughout the product life cycle produced robust analytical CCI data giving deep insight into product and process, enabling science-based decisions for the choice of packaging components, optimization and validation of production lines, demonstration of equivalence of production lines over multiple sites, transport validation, and demonstration of good CCI over shelf life. Such a framework can be used as a general robust holistic approach to ensure good CCI of sterile vial product.

SUMMARY

Container closure integrity plays an important role in maintaining the sterility and stability of sterile injectable products. Global regulators have recently evolved guidance and expectations for CCI recommending analytical deterministic CCIT methods and science-based process validation and control. Executing studies that generate robust CCI data on statistically valid sample sets throughout the product life cycle can satisfy these raised expectations and fits with a Quality by Design approach for making science-based decisions about the design of the manufacturing process. A body of robust CCI data also serves as input for Quality Risk Management enabling a proactive means of identifying, scientifically evaluating, and mitigating potential risks to quality. For sterile vial product, using RSF testing as a quantitative seal quality method and correlating RSF results with analytical non-destructive CCI measurements enables the generation of large data sets that can be used in various product life cycle activities including the choice of appropriate packaging components, validation of the capping & crimping process, and implemenation of an effective CCI control strategy. This article has described a robust general holistic approach, summarized in the table below, that can be used to ensure container closure integrity of sterile vial product.

A SCIENCE-BASED HOLISTIC APPROACH TO STERILE VIAL CONTAINER CLOSURE INTEGRITY ACROSS PRODUCT LIFE CYCLE ACTIVITIES
1. Develop an appropriate deterministic CCIT method specific for each product package system to use in packaging development CCI studies
2. Design and execute CCI studies using statistically valid sample sets to choose and qualify the appropriate primary packaging components (vial / stopper combination) and determine CCI-RSF correlation
3. Design and execute process studies using statistically valid sample sets and RSF testing to characterize and optimize the sealing performance of each production line
4. Determine acceptable limits for capping & crimping settings per individual production line and qualify the line for good CCI with statistically valid sample sets
5. Generate statistical data on samples from the process to verify CCI-RSF correlation
6. Use the validated CCIT method for shipping validation, batch testing, and shelf life testing as appropriate

Because industry best practices are evolving due to new regulatory guidance and expectations, a certain amount of uncertainty in industry CCIT best practices is to be expected in the near term. However, a general approach that includes increased generation of science-based CCI data to enable informed risk assessments and robust validation & control will help prepare the industry for the future.

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