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Lonza
Integrated Biologics

White paper

Industry-backed, data-driven approaches to enhancing container closure integrity

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Today's pharmaceutical landscape comes with many challenges: increasingly complex new molecules, supply disruptions, rising costs, and evolving regulations. This is fostering a booming CDMO market, where manufacturers can leverage the expertise, experience, and capacity they need to expedite drug development and patient access.

For any CDMO, a cornerstone of success is a reputation for unwavering quality, which is why it is critical to implement stringent quality control measures that safeguard the integrity of a customer's product during its development and manufacture and throughout its shelf life. Despite this, a lack of sterility assurance is regularly cited in drug recall notices across the industry, and nearly every weekly enforcement report from the FDA includes at least one infraction related to sterility or container closure integrity (CCI).[1] This regulatory emphasis on CCI is a global focus, with the new EU GMP Annex 1 released last year expanding its expectations for CCI of sterile pharmaceutical products, including the implementation of a contamination control strategy and integrity testing of product samples using validated methods.[2] Therefore, while CCI compliance has been traditionally limited to stability and release, it now requires a more holistic approach that aims to incorporate quality control into all phases of product design and development.

In our continued dedication to being a leading outsourcing partner, We have collaborated with experts across the industry to detail a comprehensive science- and risk-based approach into our practices throughout our development and manufacturing network for parenteral combination products. The industry-accepted methodology is now built into Lonza's practices throughout its development and manufacturing network, benefiting customers worldwide.

A holistic approach to CCI

Anticipating and preventing problems before they happen is at the core of any quality control program, which is why the industry's holistic approach to CCI considers all aspects of a product's life cycle. As illustrated in Figure 1, Lonza's adoption of this methodology has led its Drug Product Services (DPS) team to incorporate preventative measures and risk-based testing into four key areas: Container Closure System Development, Material Qualification, Drug Product Manufacturing, and Distribution and Storage.

The goal is to look beyond just release and stability testing on the final product to preserve CCI, beginning with the foundation of this strategy: container closure system development.

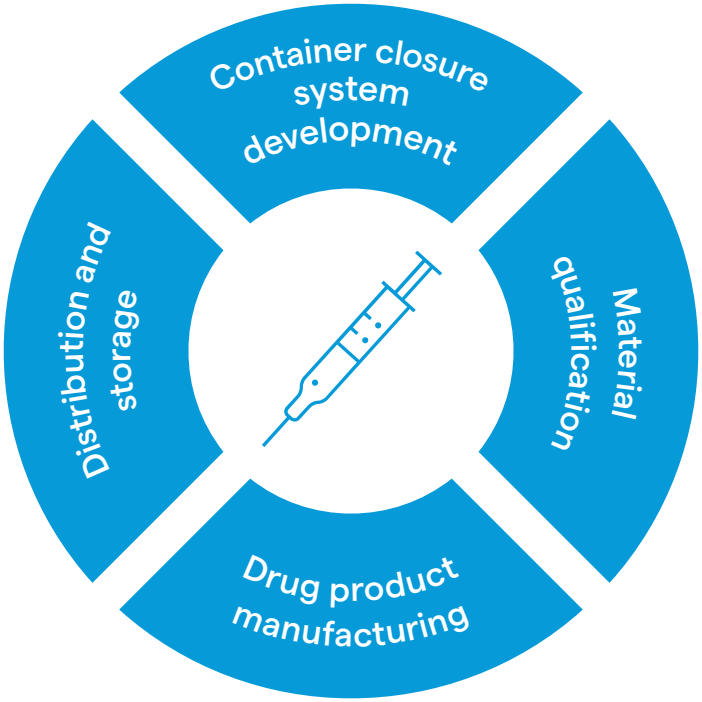

Figure 1. Four key areas of Lonza's approach to maintaining CCI throughout product development.

Container closure system development

A drug product's container closure system plays a significant role in a drug product's final presentation. This system includes all packaging components that, when securely sealed, protect a drug product from contamination and degradation while also maintaining its efficacy and safety throughout its shelf life. Effectively selecting the components that will create a suitable contain-

er closure system for the therapy to be developed requires appropriate methods for CCI testing (CCIT). There are several CCIT methods used in the industry today, including probabilistic methods like blue-dye ingress and deterministic methods, such as oxygen headspace analysis, high voltage leak detection, vacuum decay, and helium leak.

Probabilistic CCIT methods rely on a series of sequential and/or simultaneous events that have a probability of occurring, as opposed to deterministic methods, which follow a predictable chain of events while using controlled and monitored physiochemical techniques to measure leakage. Although there is no regulatory requirement to use one versus the other, the FDA has indicated it looks favorably on objective quality metrics data, such as that produced by deterministic methods; the agency has stated that this type of data may lead to higher levels of safety, efficacy, delivery, and performance.[3] At Lonza, our go-to method for the DPS team is helium leak, which is currently the most sensitive deterministic physical CCIT method that can provide a good correlation to microbial CCIT.[4]

CCIT also requires an appropriate leak test fixture. We utilize two fixtures that are Lonza proprietary technologies: one for vials, shown on the left side of Figure 2, and one for prefilled syringes (PFS), shown on the right side of Figure 2.

The PFS fixture allows testing on both sealing areas, with one hand on the rigid needle side and the other on the plunger side.

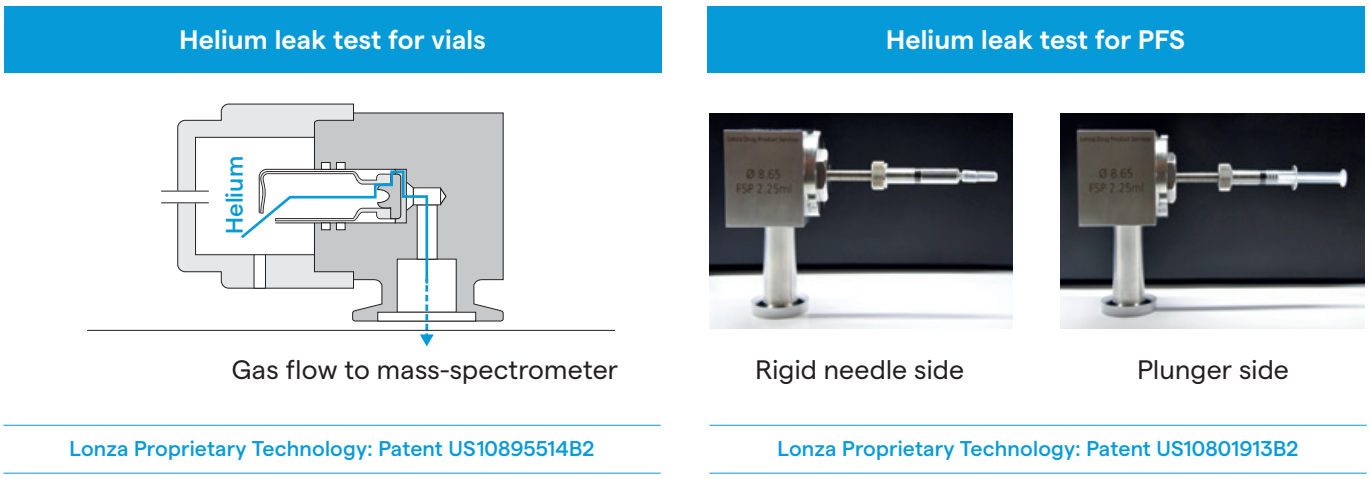

Figure 2. Our proprietary technologies used for the helium leak test of vials and PFS.

After the right method and fixture are selected, the next step is to define acceptance criteria. During early-stage development, We use maximum acceptable leakage limit of 10^(-7) mbar/s. This threshold is acknowledged in scientific literature and regulatory guidance [USP 1207] as sufficient to exclude any microbe contamination of the tested containers. In the qualification or stability stage, typical regulatory expectations are to use a test that detects pinholes as small as 20 micrometers. Laser-drilled micro-holes, capillaries, and/or copper wire can be used to create artificial holes for leak testing.

This complete analytical development enables characterizing the performance of the container closure system. The key attributes of a vial container closure system that contribute to CCI are its land seal and valve seal, which are the two sealing areas between the stopper and the vial (Figure 3).

The following factors must be taken into consideration when testing these seals:

- Component fit
- Impact of temperature and transportation
- Manufacturing conditions
- Manufacturing parameters

Figure 3. For vials, two sealing areas between the stopper and the vial ensure CCI.

For the component fit, the focus is on the crimping of the vial. As a result of the crimping process, the stopper is compressed against the vial. This can be measured by the force the stopper in the compressed state applies on the vial, which is called the residual seal force (RSF). Figure 4 shows how a high RSF versus a low RSF will affect the sealing between the stopper and the vial, ultimately affecting the tightness of the container closure.

The measurement of RSF in combination with helium leak tests is the industry best practice for safeguarding CCI.

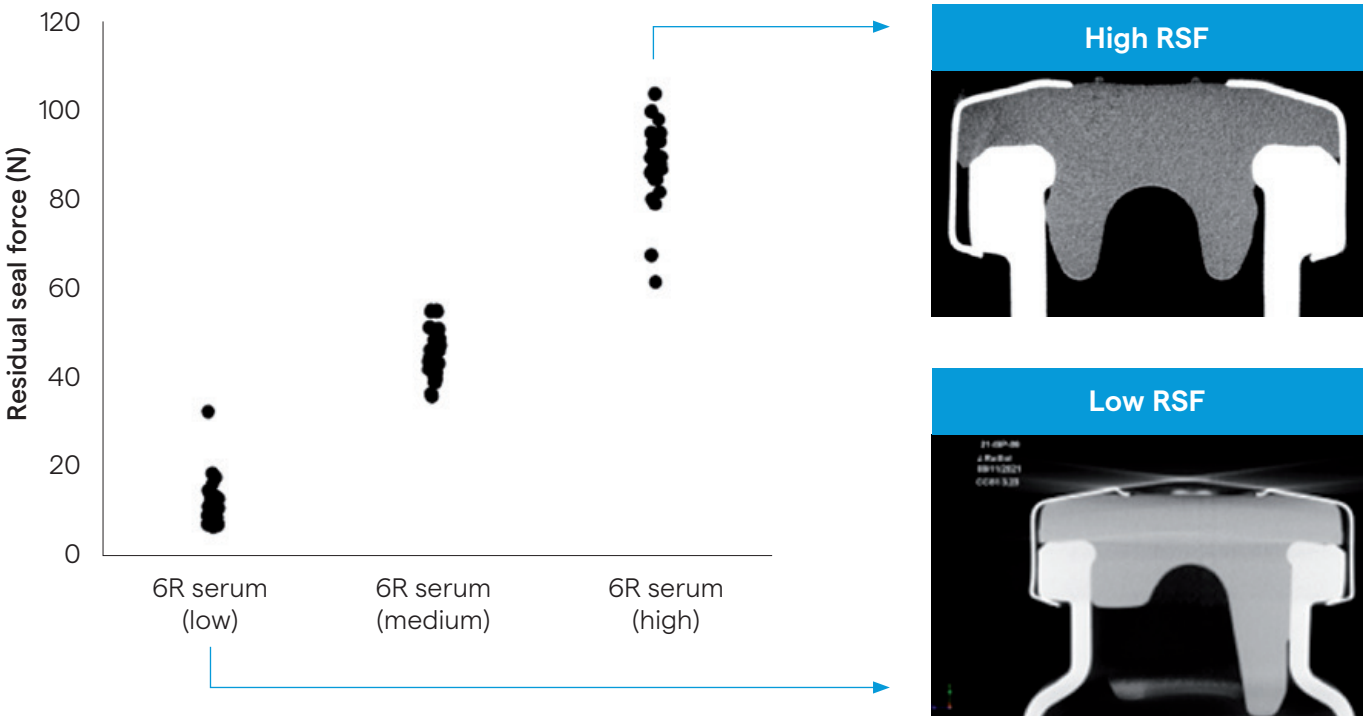

Figure 4. Comparison of high and low RSF measurements.

Some products present specific challenges to maintaining a CCI with a vial. For example, a well-known defect with lyophilized products is that the stopper may lift after it is secured in place. The EU GMP Annex 1 requires that this phenomenon be tested prior to crimping, which calls on the establishment of acceptable sensitivity for detecting lifted stoppers.[2] We have developed dedicated testing for this issue.

Products that require storage and transportation at low or even freezing temperatures, such as mRNA modalities and/or lipid nanoparticles, also present CCI challenges, as a vial may not be as secure at low temperatures as it is at room temperature. In these cases, the residual seal force range, which will ensure the container closure system remains tight at the intended storage condition, might be reduced. To address this, we have developed a proprietary technology that enables advanced testing techniques for CCIT down to temperatures as low as -80°C.

Figure 5. Summary of the critical elements in vial container closure development.

The key attributes of a PFS container closure system that contribute to CCI are the sealing of the rigid needle side (RNS) and the sealing of the plunger (Figure 6, next page).

Like a vial container closure system, the component fit, impact of temperature and transportation, manufacturing conditions, and manufacturing parameters must be taken into consideration when selecting a PFS container closure system. In addition, important attributes of a PFS container closure system are the plunger position and the air gap size, as the plunger can move alongside the barrel. Plunger position and air gap size can be measured using optical measurement. Due to the shape of the syringe barrel, the sealing interface between the plunger and the syringe barrel may change. When the plunger is deeply inserted, the barrel narrows and may squeeze the plunger ribs. When the plunger is too close to the flange, the barrel inner diameter may vary and affect the sealing with the plunger. Therefore, CCI measurements should be performed for

both plunger positions to ensure tightness can be maintained over the entire plunger position range. The impact of plunger movement must also be tested, as it can move during transport or due to interactions with delivery devices such as autoinjectors. Our approach is to characterize this movement and verify it does not exceed a predefined maximum acceptable displacement.

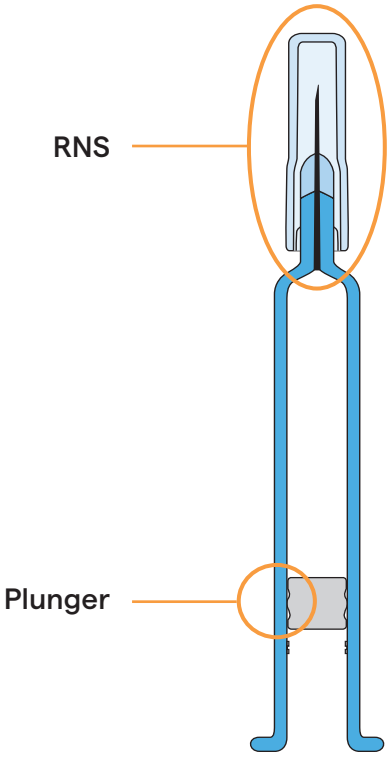

Figure 6. The RNS and plunger seals are key attributes of a PFS container closure system.

A key consideration for defining maximum acceptable plunger displacement for a PFS container closure system is the concept of sterile zone length, which is defined as the distance between the first and last rib of the plunger. We use optical measurement for this test. The plunger movement will then be evaluated under worst case conditions and should not exceed the sterile zone length. Air movement that leads to RNS displacement in a PFS container closure system is also something that must be monitored and tested. This displacement can happen when production of the PFS is moving from one station to another during the manufacturing process. To control this at Lonza, our DPS team developed methods to define the maximum acceptable RNS displacement that still ensures CCI. This data is used to define functional specifications for the PFS presentation of our customers' drug products.

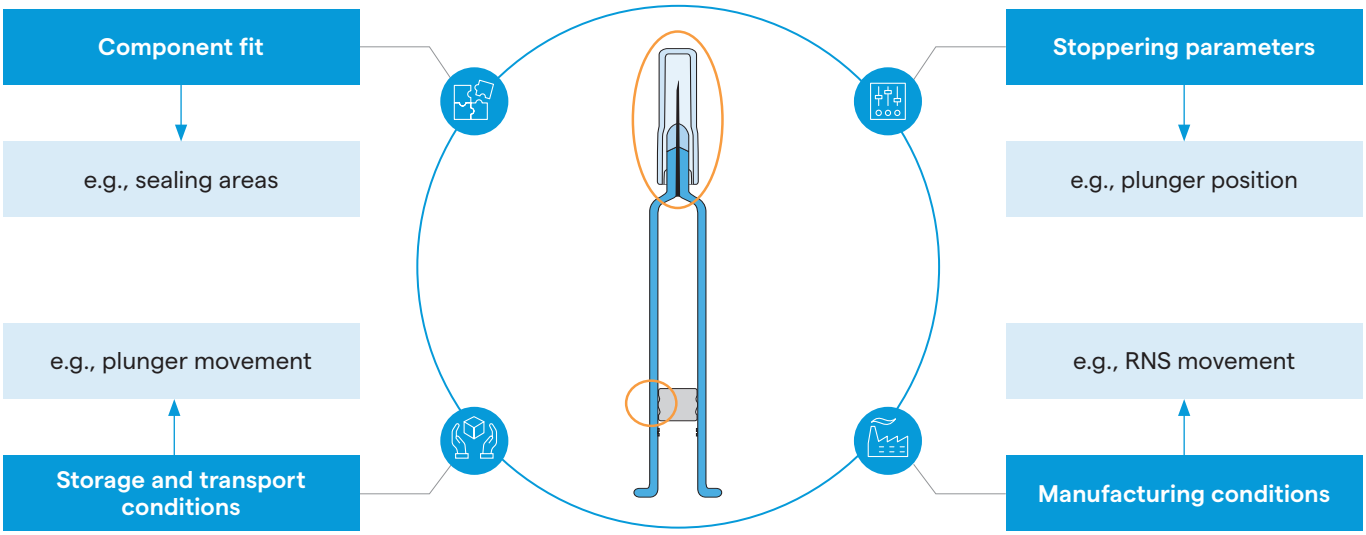

Figure 7. Summary of the critical elements in PFS container closure development.

The second key area of our holistic approach to maintaining CCIT during a product life cycle is material qualification.

Material qualification

Ensuring robust material components and characteristics is another important element of quality control, as this will further help minimize the risks of contamination and/or degradation of a drug product. One example of the critical material attributes in a container closure system includes the vial and plunger diameter, as both are major contributors to the valve seal. The key contributors to the land seal are vial height, stopper thickness, cap thickness, and cap skirt length (valve and land seals shown in Figure 8).

Once these aspects are identified, the next step is to evaluate the design of the components and the capability of our supplier to maintain consistent quality of critical material attributes. For the caps, we will look at whether it is a single or multiple die processing as well as how the aluminum and plastic parts are bound together. For the stopper, the team considers the mold tooling qualifications and the achieved dimensional capability. There must also be established in-process controls to ensure consistent production, which comprises certificate of compliance (CoC)/certificate of analysis (CoA) reviews and regular material qualification and incoming release testing.

For vials, our testing plan includes direct and indirect dimensional controls. The goal is to avoid performance testing (i.e., CCIT) during incoming control. For PFS, the same approach will be executed: first identifying the critical material attribute and then verifying that our supplier ensures consistent quality. Regarding the testing plan, some performance testing (CCIT, RNS Removal Force) may be considered as the barrel, needle, and RNS are purchased assembled. The supplier can therefore commit to a performance level on this subassembly.

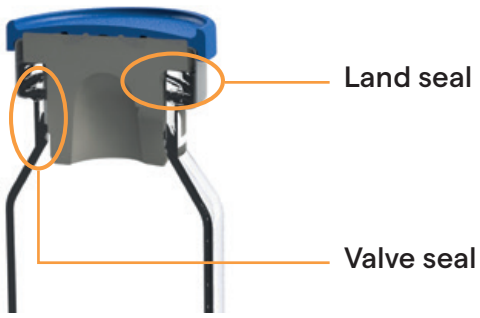

Figure 8. Sealing areas for a vial container closure system

Drug product manufacturing

The analytical panels used for filling equipment qualification are dependent on the primary packaging. For vials, our DPS team will perform CCIT by helium leak and visual inspection for crimping defects. Although these tests do provide valuable insight, they do not offer a full understanding of the crimping process, so the team also performs residual seal force measurement to identify and optimize suboptimal processes. PFS testing includes CCIT on the manufacturer container and then measuring the plunger position to ensure it is within the defined specifications. The same applies to plunger movement, which is tested under the pressure standards defined by the American Society for Testing and Materials (ASTM).

Distribution and storage

As a result of the thorough development and qualification process explained above, the performance of a container closure system, which is expected to maintain product sterility and quality throughout its shelf life, should already be well understood. Nevertheless, stability testing provides an opportunity to confirm efficacy of the work done up to that point using this holistic approach. Stability testing also generates the necessary CCI data required by regulatory agencies in the CMC package.

A common practice is to utilize a sample size for CCIT that is similar to the size used for sterility testing. However, it has become increasingly difficult to defend this to regulators who prefer a risk-based justification. Leveraging on the comprehensive data package and on the use of sensitive testing methods, a limited sample size can be demonstrated sufficient to mitigate the low residual risk. In addition, CCIT cannot be included in characterization in accelerated conditions as the higher storage temperature does not stress the container closure system like it stresses the drug product. To ensure long-term CCI data is available at the time of IND application submission, a better approach is to generate drug product-agnostic data (e.g., on empty vials) ahead of the program. Indeed, such platform data is far more representative of the performance of the drug product than any storage at higher temperature. It is important to note that some countries will combine the requirements for CCIT and sterility. Our standard approach generates the most efficient data to enable a seamless clinical development in most countries. When preparing for launching commercial product, the approach is then tailored to the regulatory requirements for the country where the drug is intended to be marketed.

It is also necessary to assess potential impacts to CCI during shipping, such as the effect of:

- Air pressure on plunger movement in a PFS container closure system during air transportation
- Low temperature variations from the environment or from the dry ice packed in the tertiary package
- Any shocks/vibrations

Other real-world studies representing worst-case conditions can also be conducted at this stage. However, best practice – and that of our DPS team – is to adopt the comprehensive science- and risk-based approach outlined above, which helps mitigate risk during early development to prevent issues later in the product life cycle.

Benefits of our holistic approach to CCI for our customers

Our holistic approach to CCI is a key asset for ensuring we achieve a consistently high level of quality across our portfolio of therapies as well as meet the expectations of our customers. Indeed, some critical concerns apply to every drug program: time-to-clinic or time-to-market, drug substance usage, and regulatory/technical risks.

By building our data platform up front, we are able to skip the container closure system development phase and equipment qualification activities that impact our customers' timelines. Moreover, because our platform data is generated without drug substance, this highly valuable and limited resource is spared. Finally, using a unified approach across customer programs allows us to collect frequent feedback on its validity and efficiently mitigate regulatory/technical risk for our customers.

Our data-driven platform can also be extended to support the requirements of specific therapies. For example, mRNA drugs are currently stored at temperatures as low as -65°C +/-15°C. Having developed proprietary techniques, we are completing container closure system development activities with CCIT data down to -80°C, ensuring the components and crimping process we recommend are suitable for this modality.

For PFS presentations, our data platform covers every project-agnostic aspect of container closure integrity. In addition, tailored studies are systematically integrated into every program to encompass the unique needs of each project. An example is the specification for plunger position, which depends on the intended dose and drug viscosity, as these affect fill weight capability. Since PFS are meant to be included in a delivery system such as an autoinjector, we typically perform these additional studies prior to the first GMP batch in parallel to the technical fills that enable initiation of autoinjector development. For that, we combine dedicated technical filling and analytical capability with proprietary techniques to optimize time-to-market. Finally, use of surrogate solutions limits the impact of drug substance availability on the analytical scope, thus enabling a more thorough characterization of technical and regulatory risks.

These examples highlight not only the various challenges manufacturers can face when it comes to maintaining CCI during product development, manufacture, and delivery but also the need to work with an experienced CDMO utilizing a holistic approach that focuses on quality and risk mitigation from the beginning, ultimately enabling successful clinical and commercial launch. With With our strong in-house expertise, we can develop your standalone container closure system project and/or biologic product, with confidence, for clinical or commercial purpose with flexible entry points as needed.

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