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VERIFYING THE CONTAINER CLOSURE INTEGRITY OF CUSTOM PRIMARY PACKAGING

Dr Alex Vasiev
Manager of Device Development
T: +44 1223 736237
E: alex.vasiev@ovalmedical.com

Connor Everett
Intellectual Property Engineer
T: +44 1223 736236
E: connor.everett@ovalmedical.com

Steven Hay
Senior Industrialisation Engineer
T: +44 1223 736253
E: steven.hay@ovalmedical.com

Oval Medical Technologies
Unit 3, Enterprise 3930
Cambridge Research Park
Beach Drive
Waterbeach
Cambridge
United Kingdom

www.ovalmedical.com

In this article, Alex Vasiev, PhD, Manager of Device Development, Connor Everett, Intellectual Property Engineer, and Steven Hay, Senior Industrialisation Engineer, all of Oval Medical Technologies, explore the challenges of verifying the container closure integrity of custom primary packaging.

For more than a decade, Oval has been developing proprietary primary drug containers (PDCs) that are specifically optimised for integration with its autoinjectors. Oval's PDC designs are therefore the result of a thorough understanding of all the functions, considerations and requirements that this integration entails. As a result, its containers use several unique design features which differentiate them from other market offerings both in terms of form and function. This is what allows the company to produce autoinjectors which are strong, compact and consistent in both delivered dose and needle-insertion depth.

While bespoke primary packaging features offer advantages in autoinjector performance and design flexibility, they also create challenges in container closure integrity

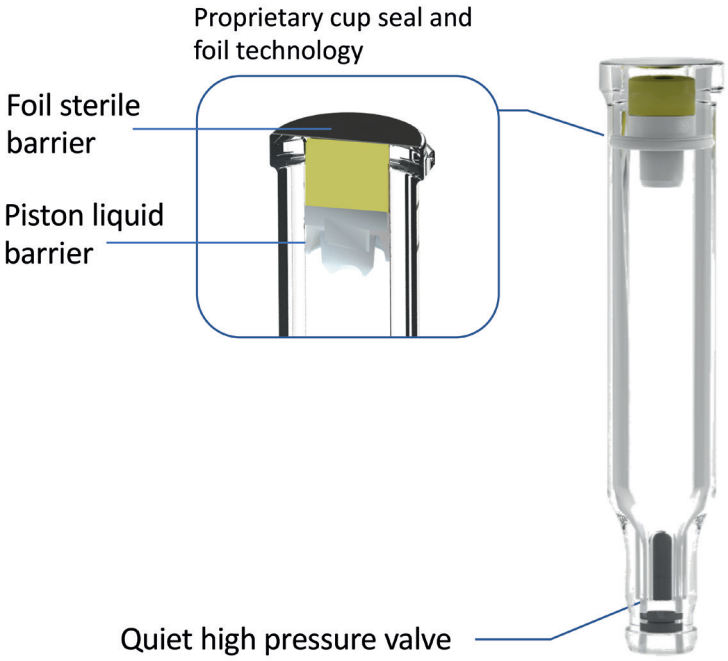

Figure 1: Illustration of seals and CCI interfaces present in Oval's ArQ Bios high viscosity primary drug container (1 mL).

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"CCI is a critical aspect of any primary packaging system. Patient and consumer health and safety is the principal reason why testing methods are put into place for its verification."

(CCI). For this reason, Oval has established a multidisciplinary industrialisation team to provide in-house expertise in the commercialisation of devices and primary packaging. This has allowed it to develop both research and development (R&D) tools for CCI feature optimisation and 100% in-line CCI inspection during manufacture.

This article explores some of the CCI features that are present in Oval's proprietary PDCs, the means by which they are optimised during the development phase and how they are tested in production.

UNIQUE CONTAINER ARCHITECTURE

Although control over the form of PDCs offers unparalleled design flexibility, there is a need to balance novelty with manufacturability and validation. Nowhere is this more apparent than in the ArQ Bios PDC for high-viscosity drugs (Figure 1).

Cup Seal And Foil Technology

Delivering high-viscosity formulations through small-gauge needles requires the generation of very high pressures within the container. It is imperative that the plunger operates effectively at these pressures, ensuring low glide force whilst preventing leakage past the seal. Traditionally, the plunger also provides a sterile barrier in storage. This is a challenge for rubber stoppers, where a low glide force and effective sterile seal present conflicting requirements.

Rubber stoppers have a large contact area which allows them to seal effectively. However, the Poisson's ratio of most rubbers approaches 0.5 – making them virtually incompressible. When a rubber stopper is subject to a high pressure within the container, much of the applied delivery force is translated into proportional friction with the container wall. To overcome this challenge, Oval has developed a high-pressure cup seal which decouples the sterile and liquid barrier functions from one another.

The piston design consists of a high-density polyethylene (HDPE) self-energising seal. The lubricious nature of HDPE, and the limited contact area it has with the container, act to reduce glide force. CCI is then maintained by a layer of aluminium foil, induction welded across the back of the container to form the sterile barrier. Process optimisation of the induction welding process, and therefore container closure integrity testing (CCIT), is critical.

High-Pressure Valve

The release of a high-force delivery spring in an autoinjector, as it impacts the plunger at the start of drug delivery, can cause a significant level of frightening noise and haptic feedback for a patient.

For this reason, the front of the ArQ Bios PDC incorporates a proprietary hydraulic valve release mechanism. The valve enables quiet and gentle activation of the device, even when the drug is pressurised to 300 bar. The activation is performed by a sliding contact between a seal and the fluid path. While advantageous for the patient, the incorporation of additional seals and moving parts creates additional challenges for container closure. This makes an in-house capability in CCIT invaluable for developing and optimising these types of novel designs. The process of optimisation can include a variety of changes to component design, material and fit, as well as the arrangement and surface finish of tooling.

CONTAINER CLOSURE INTEGRITY

CCI is a critical aspect of any primary packaging system. Patient and consumer health and safety is the principal reason why testing methods are put into place for its verification. CFR Title 21 part 211.94[1] stipulates that container closure systems must provide adequate protection against anticipated external factors that can cause deterioration or contamination of the drug product, both in storage and in use.

For common CCIT methods, such as dye ingress, the expectation from US regulatory agencies is that it should be capable of detecting defect sizes ≤ 20 µm in diameter. This defect criterion is applied to routine test methods and is an expected positive control.[2] Is this leak threshold sufficient when ensuring CCI? Recent updates to USP 1207.1 define a maximum allowable leakage limit (MALL) rather than a physical defect size for CCIT methods.[3] The reason for this is that there is a large difference in the leak sizes which correspond to compromised sterility in the literature. Some researchers found that metal cans left to cool in an E. coli challenge media required leaks > 5 µm for contamination to occur.[4] Others exposed glass vials to challenge media containing P. diminuta and E. coli, and omitted samples with airlocked leaks. Of the remaining samples, only those with leaks of ≤ 0.2 µm diameter demonstrated sterility.[5]

This discrepancy can be attributed to the variety of methods in which bacterial ingress can be inhibited. Most bacteria require a liquid medium through which to travel and will not cross a leak in the absence of a continuous fluid path or in the presence of adverse differential pressure. Bacteria can also be excluded by size. There are therefore numerous factors that influence the outcome of microbial challenge testing:

- Fluid driving force (wicking or differential pressure)
- Fluid properties (surface tension, viscosity)
- Material properties (hydrophobicity)
- Leak geometry (length, tortuosity, diameter)
- Size, shape and motility of the microbes in question.

The size exclusion approach is a common method adopted in sterile barriers. Most sterilising grade filters rely on tortuosity and a narrow pore size distribution to exclude particles of a certain size in moving fluid, described by a "rating". The current 0.2 µm sterilising grade filter rating is based on the discovery in the 1960s that Brevundimonas diminuta could pass through the 0.45 µm rated filters standard at the time.[6]

"When developing primary packaging, it is preferable to assume the worst case; i.e. the presence of pinhole defects with ideal shape and minimal length."

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When developing primary packaging, it is preferable to assume the worst case; i.e. the presence of pinhole defects with ideal shape and minimal length. To facilitate the exclusion of bacteria, a critical leak diameter is defined as being ≤ 0.2 µm.

CONTAINER CLOSURE INTEGRITY TESTING

Leak detection guidelines specify that container closure testing methods should use analytical detection techniques which are appropriate to the method and compatible with the specific product being tested. Oval uses a combination of high-sensitivity methods during development and high-throughput methods in production when establishing the CCI of its proprietary PDCs.

Tracer Gas CCIT

A high-sensitivity sniffer test is used to characterise the CCI interfaces during container development and process optimisation. The sensitivity of this technique allows the critical seal geometry, influence of production variability and material selection to be evaluated and optimised to produce a reliable and stable sterile barrier.

The CCI interface being tested is placed between a test and an accumulation chamber. A tracer gas is introduced to the test chamber around the specimen. If a leak is present, the tracer gas concentration within the accumulation chamber will rise (Figure 2). The tracer gas concentration depends on the leak size, type of gas, pressure difference and temperature. The increase in tracer gas concentration can be approximated by the relationship:

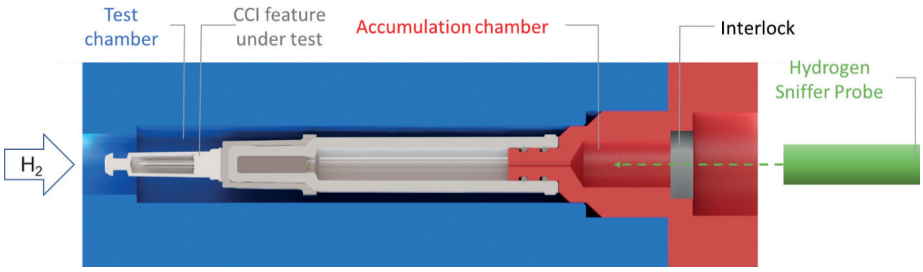

Figure 2: Illustration of a tracer gas CCI fixture. Gas is supplied to the test chamber. If a leak is present, the gas concentration will increase in the accumulation chamber.

$$\frac{\Delta m}{\Delta t} = \frac{q_L M}{RT} \quad where, q_{L,gas} = \Delta p c_{gas} A$$

Where: $\Delta m/\Delta t$ is the rate of mass change, $q_{L,gas}$ is the leak rate, M is the molar mass, R is the gas constant, T is the temperature, Δp is the driving pressure gradient, A is the orifice area and c is the speed of sound within the gas.

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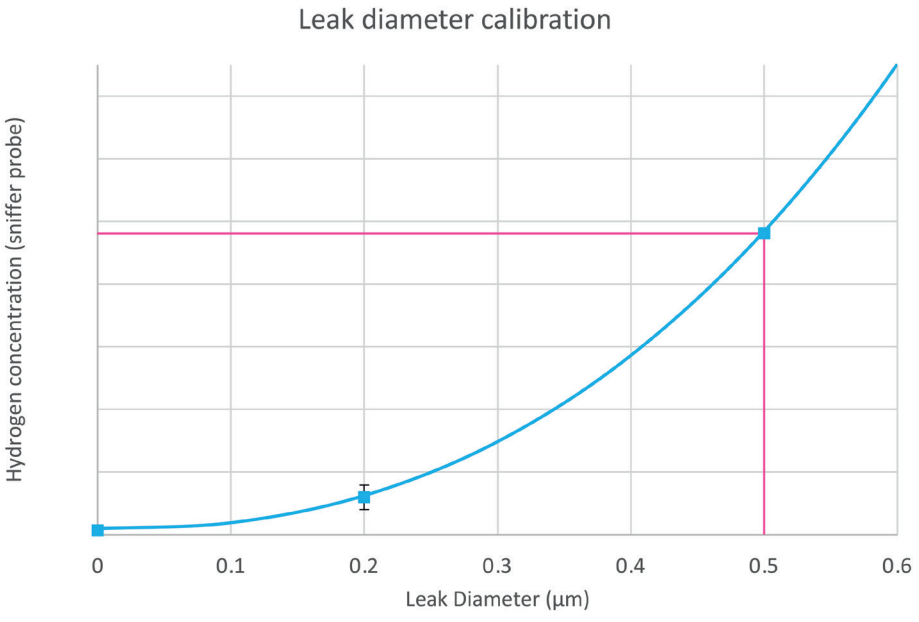

Figure 3: Graph showing a typical calibration curve for hydrogen a sniffer test fixture. Error bars: 1σ (n=5).

Helium and argon are often used as tracer gases. The small size of helium atoms, and the high speed of sound in helium, result in a threefold increase in sensitivity compared with air. Argon does not undergo chemisorption, giving it specific uses depending on the environment. Both these options are costly, with hydrogen offering a sustainable and cost-effective alternative. Because hydrogen is flammable, Oval uses a tracer gas mixture of 5% hydrogen/95% nitrogen (non-flammable concentration). The hydrogen gas is highly mobile, filling volumes and passing through leaks quickly. It also does not stick to surfaces as much as helium, reducing background interference from large leaks or residual gas in tested fixtures.

A microelectronic hydrogen sensor probe containing a thin film of palladium (Pd) is used to detect hydrogen concentration in the accumulation chamber. When hydrogen molecules reach the Pd surface, the former dissociate into elemental hydrogen which is occluded by the film, forming palladium hydride. This produces several physical effects, including a rise in electrical resistance proportional to the ambient hydrogen concentration. The reaction is reversible, the hydrogen atom desorbs from the Pd film surface when ambient hydrogen concentration decreases.

The sniffer probe is introduced into the accumulation chamber before the test to set a baseline and again after a fixed time interval to take a reading. A rise in hydrogen concentration (ppm) is detected if a leak is present. The probe reading is calibrated to the defect size using engineered leaks of a predefined size. This allows a calibration curve to be produced (Figure 3). A solid (blocked) control sample is used to determine a baseline value for the fixture.

Any CCI interface needs to be optimised to compromise on the needs of different design features. A component can have several conflicting functional requirements, such as pull off force, friction and the integrity of the sealing interface.

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The design of the seal geometry in a needle shield is provided as an example. An equivalent leak size of ≤ 0.2 µm is used as an acceptance criterion. Initial geometry optimisation leads to an improvement in the efficacy of that CCI interface, whereas other changes which aid manufacturability or address other, non-CCI related functional improvements can have unintended consequences. Learning from the effect of previous design iterations allows the designer to find an optimum solution (Figure 4). The ability to establish CCI efficacy at an early stage of development offers several advantages:

- Provides useful feedback to designers during development
- Helps separate important design features from those which are less effective
- Provides insight into batch-to-batch variation and process capability.

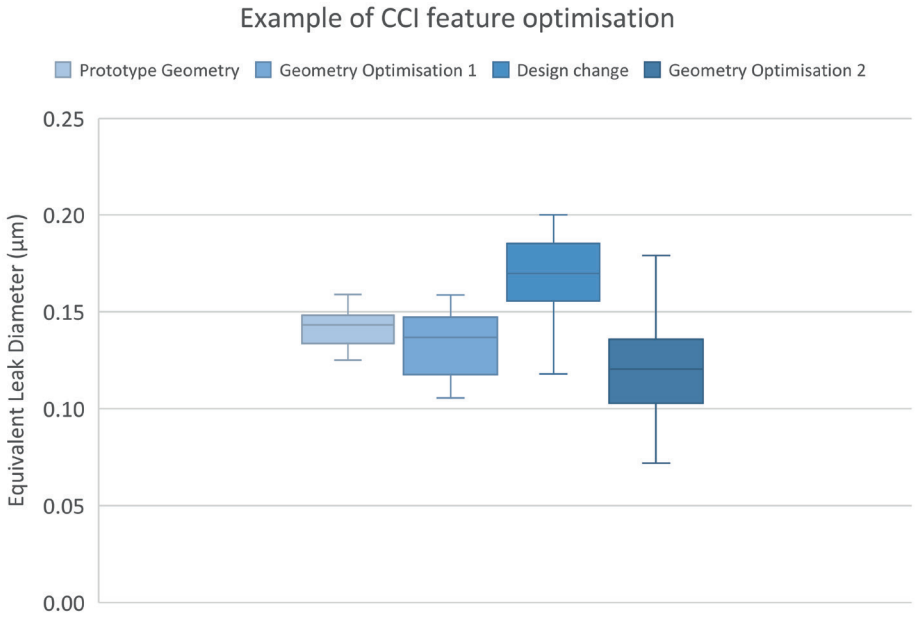

Figure 4: Boxplot showing an example of CCI performance optimisation using hydrogen leak testing. Tests performed at room temperature (23±5) °C and (50±25) % relative humidity (left to right: Plots 1-3 n≥10, Plot 4 n=30).

Real-World Variability

The calibration curve is the product of idealised defects. Actual leaks tend to present in a variety of shapes and flow paths. Care needs to be taken when interpreting the results and outputs of a test:

- Tortuous leak paths can reduce the flow rate of tracer gas, reducing the leak rate. These tortuous paths also tend to inhibit the migration of bacteria
- The presence of multiple smaller leaks can produce a larger combined flow path which may increase the leak rate without ever compromising the sample sterility
- Seals can deform and deflect due to the slight pressurisation during the test. This can cause leak paths to deform in ways that do not reflect normal conditions, exaggerating or masking the true leak size.

Hydrogen leak testing does not require pressurisation, as the test is conducted at low (0.1 bar) gauge pressure. This avoids unintentional deformation of the seals. The test method, like any gas-based leak detection method, would fail a component which had a multitude of smaller leaks, resulting in false positives (critical leak detected but not actually present). This makes the test a worst case, providing an appropriate impression of the quality of an interface.

Vacuum Decay (In-Line) CCIT

While hydrogen leak testing offers excellent sensitivity, it is slow and cannot be applied to Oval filled containers in-line due to the number of CCI interfaces present (need to access both sides of the seal). EU GMP regulations also stipulate that containers such as Oval's, which are closed by fusion, should be subject to 100% integrity testing.[7] A more rapid method is therefore required for in-line testing.

To achieve this, Oval uses a non-destructive vacuum decay system. The system creates a vacuum around the sample whilst monitoring chamber pressure over a short cycle time. The use of negative pressure prevents contamination being forced through any defects which are under the threshold of detectability. It also prevents the pressurisation of sealing interfaces which could mask potential leaks.

Qualification of this approach requires the creation of positive and negative controls which are tested together with the filled PDCs. Positive controls are created by laser drilling calibrated holes (calibration of leak flow rate and hole diameter) in a sample to mimic leak defects. Negative controls (free from leaks) are created by

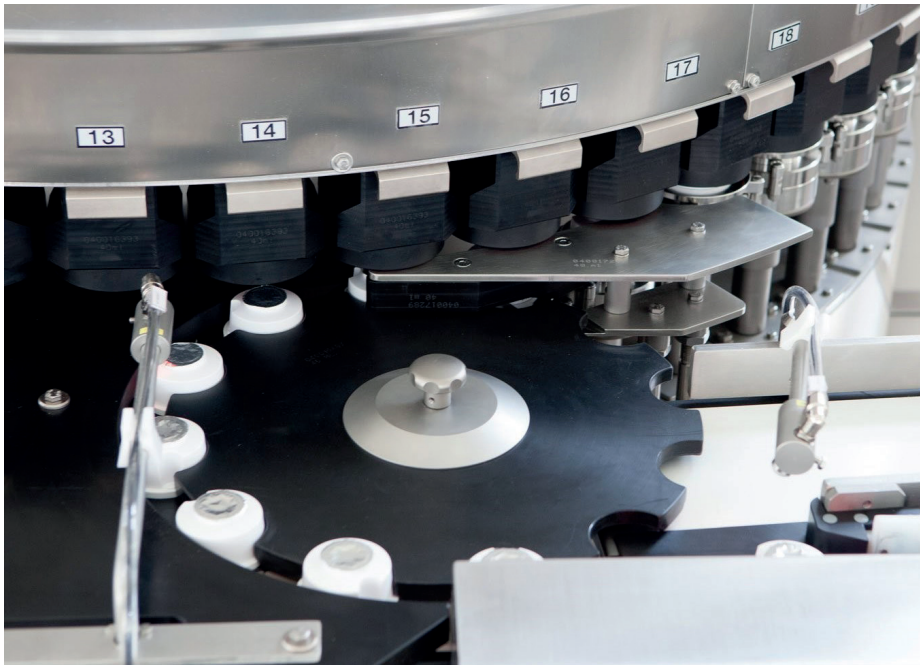

Figure 5: Image of an in-line vacuum decay CCIT method used during production. Photo courtesy of Bonfiglioli Engineering Srl.

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precision machining a solid form of the PDC. Acceptance criteria are also set such that all negative controls pass while all positives fail. A lower and an upper limit of detection are also established, followed by relevant validation processes. Validation is essential to prove test accuracy, repeatability and detection limit.

Oval uses a 5 µm positive control for in-line testing; this is an industry standard and the performance limit for CCIT at higher throughputs. The 5 µm leak diameter threshold is considered appropriate in production because the component design itself is optimised using the more sensitive technology of hydrogen leak detection, as previously discussed. In addition, none of the sterile CCI interfaces in Oval's PDCs are in contact with the formulation, which mitigates the risk of a liquid path facilitating bacterial ingress.

Two pressure readings are taken after fixed time intervals, following pressure stabilisation. If the difference is greater than the threshold determined from positive controls, the container has a leak. If the value meets expectations, the container closure is integral. Leaks manifest as sharper vacuum decay profiles as they allow air inside the container to equilibrate the vacuum generated outside. Oval's system uses proprietary technology which helps to overcome the challenge of differentiating between micro and macro leaks (Figure 5).

CONCLUSION

The development of this expertise has allowed for the efficient optimisation of the sterile seal geometries in Oval's primary packaging. Control of this critical aspect of Oval's PDCs allows for implementation of features to suit the needs of a particular formulation and autoinjector architecture, with confidence that they will not impact on the demands of CCI.

The ability to perform 100% inspection of PDCs in-line helps guarantee patient safety when manufacturing a commercial drug delivery device at scale. The proprietary technology facilitating this is just a small part of the expertise offered by Oval's in-house industrialisation team. It is adapted specifically to meet the needs of commercialising Oval's novel primary packaging.

> "The ability to perform 100% inspection of PDCs in-line helps guarantee patient safety when manufacturing a commercial drug delivery device at scale."

ABOUT THE COMPANY

Oval Medical Technologies is a drug delivery company whose patient-centric autoinjector platforms enable pharmaceutical companies to deliver a wide range of drug formulations for both subcutaneous and intramuscular injection. Oval's flexible, robust drug delivery platforms can be tailored precisely, providing unprecedented scope for pharmaceutical companies to address the needs of current patient populations and develop and market new products. With its patented integrated primary drug container technology at their core, Oval's devices are safe, reliable and easy to use in their target patient populations. The company is certified to ISO 13485 (2016).

ABOUT THE AUTHORS

Alex Vasiev, PhD, is an engineer with a wide range of experience in medical and biomedical R&D gained in academia and consultancy. Before joining Oval in 2019, his primary focus was the interface of engineering, physics and biological systems. In the space of drug delivery, Dr Vasiev has developed everything from smart hydrogel microcarriers to patch pumps, inhalers and several high-viscosity autoinjectors. As a Manager of Device Development, he is responsible for leading technical teams and device development programmes at Oval. He graduated with an MEng in mechanical engineering with aeronautics, and a PhD in biomedical engineering from the University of Glasgow (UK).

Connor Everett is an Intellectual Property Engineer at Oval and manages its innovation and intellectual property portfolio, maintaining and curating all the proprietary knowledge within the company. His broad knowledge of the biomedical space allows him to assist in the design and development of Oval's novel autoinjectors, as well as associated systems and processes, such as container closure integrity testing. Mr Everett joined Oval after graduating with an MEng in biomedical engineering from Queen Mary University of London (UK).

Steven Hay has been with Oval for the past three years. As a Senior Industrialisation Engineer, he has worked on the industrialisation of Oval's PDCs and autoinjector devices. He focuses on PDC and device assembly, fill/finish, and subsequent test and inspection processes. Mr Hay has previously worked in the medical devices sector, having held roles in process engineering management, process development and new product introduction. Prior to joining Oval, he managed the process engineering team for a point-of-care medical monitoring and diagnostic device company – and has broad prior experience from the auto catalyst and optical data storage industries. Mr Hay graduated from Anglia Ruskin University (Cambridge, UK) with a BEng in mechanical and manufacturing engineering.

REFERENCES

1. *"CFR – Code of Federal Regulations Title 21". US FDA, part 211.94.*
2. *Hughes PF, "Aseptic Processing of Biological Products: Current Regulatory Issues". Presentation at WCPB 2016 conference, pp 26–28.*
3. *"USP<1207> Package Integrity Evaluation: Sterile Products". US Pharmacopeial Convention, 2018.*
4. *Gilcrist J et al, "Helium Leak Test for Micron-Sized Holes in Canned Foods". J Food Prot, 1985, Vol 48 (10), pp 856–860.*
5. *Kirsch LE, Nguyen L, Moeckly CS, "Pharmaceutical container/closure integrity. I: Mass spectrometry-based helium leak rate detection for rubber-stoppered glass vials". PDA J Pharm Sci Technol, 1997, Vol 51(5), pp 187–194.*
6. *Meltzer TH, Jornitz M, "The sterilizing filter and its pore size rating". Am Pharm Rev, 2003, Vol 6, pp 44–52.*
7. *EU GMP Annex 1, section 8.18.*

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