HELIUM LEAK DETECTION TECHNOLOGY SOLVES COLD SUPPLY CHAIN CHALLENGES OF TODAY'S HIGH-RISK PHARMACEUTICALS

By: **Oliver Stauffer**, CEO, PTI Inspection Systems, and **Jeff Morrow-Lucas**, Principal Engineer, Helium Technologies, PTI Inspection Systems

The COVID-19 pandemic has highlighted many of the challenges facing the pharmaceutical industry, among them the importance of distribution logistics. Along with COVID and other vaccines, pharma has seen a dramatic increase in the production of cell and gene therapy treatments, biologics, and other large-molecule products. Many of these require unique storage conditions to ensure the safety and efficacy of the drug, and container performance during the cold chain is of particular concern.

Some of the most novel products are now filled and sealed in combination devices. Since the components must function together, design and distribution considerations are critical to the early design of both the drug and the container. Fill-finish quality and container performance in cryogenic distribution are areas where the industry can improve rapidly, through new container design supported by the most sensitive container testing methods.

Helium leak detection technology is widely available, most everyone in the industry is familiar with it, and it is generally regarded as the most effective means of ensuring container integrity. Yet, many manufacturers still only use it sparingly or not at all because of its complexity compared to less reliable methods. Utilizing helium detection early in development is a sensible solution that companies can apply immediately to make profound improvements in the quality of their drug delivery system design for the complete container life cycle. Doing so will save time and money while raising the standard of safety.

THE IMPORTANCE OF PHASE-APPROPRIATE LEAK TESTING

The bulk of distribution problems stem from manufacturing inconsistencies and tolerance differences in packages that are assembled with a variety of different components. Often, these inconsistencies in dimensions or raw materials stack up to produce containers that introduce risk of closure failure, which can lead to more serious implications down the supply chain. Glass vials and pre-filled syringes may not seal properly at critical fill-finish closure points. These flaws often result from a one-dimensional approach to quality control, such as using imprecise leak detection methods or only validating container performance at time zero.

In some cases, this is due to physical limitations in the manufacturing process that do not allow for effective physical test methods that could identify microbial critical defects. While companies continue to design containers with innovative attributes to manage many common challenges, the concepts underlying the development process do not always encompass a holistic picture of that container's life cycle or the qualities influencing what its life cycle should be.

In the early stages, developers should assess the manufacturing conditions and variables that should lead them to choose the right components, processing parameters, and production settings to ensure they will design and produce a properly sealed container system. Break-free gliding force for syringes is a focus in design but may run counter to closure performance. A substandard fit is likely to introduce oxygen or other environmental contaminants over the container life cycle that would compromise the efficacy of the drug in the barrel. It is critical at this point to use the most precise leak detection approach possible. Methods such as vacuum decay, dye, and bubble testing cannot adequately assess whether the ribs of a plunger fit into a syringe barrel well enough to form a proper seal. Vacuum decay, high voltage, and other testing certainly will be valuable after component selection, when developers proceed with routine leak testing throughout the manufacturing process. However, while it may seem impractical because of its complexity, helium leak detection is the most effective test for component selection in container design.

As the second smallest molecule on the periodic table, helium can expose virtually any opening. This method, therefore, is far more sensitive and will yield a good fit from the start, which should facilitate a more robust manufacturing process and make routine leak testing methods more reliable. On the other hand, utilizing these methods at the wrong stages – like applying vacuum decay early and using helium as a routine testing method – is likely to produce exactly the types of manufacturing and structural inconsistencies leak detection should prevent. The other methods are not as precise and may miss leaks helium would detect in component selection. The complexity of helium testing also makes using it in later stages much more impractical and would increase the probability of false negatives or false positives in routine testing.

Helium testing has been around for decades and there are different ways to do it. Many companies, though, take a manual approach that is tedious and time-consuming. These manual methods also expose developers to the risk of FDA warning letters for lack of compliance with data recording regulations (21 CFR Part 11). In the last 10 years, FDA action letters and warning letters associated with data integrity failures have significantly increased. A large portion of these is for not having the proper data integrity software or data integrity controls associated with high-risk quality control tests. Given that helium testing can be somewhat complicated and subject to a greater degree of regulatory scrutiny, many companies opt for simpler – albeit more antiquated and less precise – methods like dye and bubble leak testing.

Dye and bubble leak testing are nowhere near as accurate as helium, nor can they exploit leaks as small as those detectable with helium testing. Yet, these methods have been grandfathered in and remain acceptable. Regulatory bodies such as the FDA prefer not to issue specific guidance, because they understand that the nature of testing methods and container design is dynamic, and that processes and situations inevitably will arise where an explicit guidance is wrong or cannot practically be applied. However, a testing method should not necessarily be used just because it is allowed. The FDA is leaning on USP 1207 – the industry guidance that says deterministic test methods should be used – but it ultimately is up to container developers to acknowledge this and act accordingly.

SIMPLER TESTING MAKES FOR SIMPLER CHOICES

Today's vaccines and treatments are unique because of their sensitivity to temperature. The inherent demand for cold chain distribution logistics means helium testing is critical to understanding how these drug products operate and how these containers perform under dynamic temperature conditions. At cryogenic temperatures, the physical and mechanical properties of container materials will change and shift, potentially creating unforeseen gaps. Helium is the only method of testing which can be adapted for real-time applications in the -20 to -140 °C range, or even temperatures approaching liquid nitrogen. While many containers used today are being tested with helium, as an industry we also know using the right technology in manufacturing is vital, and we cannot produce enough vaccine fast enough to distribute it to the market quickly enough to get life back to normal.

PTI offers three leak detection systems that, when used together throughout the development process, can ensure more precise detection, faster and in full compliance with FDA and industry standards. For helium testing, the LT150 and LT80 cold chain helium mass spectrometers can accurately test containers in cold chain and cryogenic conditions and generate 21 CFR Part 11-compliant reports in real time. The proprietary algorithm underlying these systems provides information on flow rate, gas concentration, and other factors that help developers identify the exact size of a leak, down to less than 6 x 10-6-millibars-liters per second helium leak rate, a value that has become the standard for maintaining a sterile barrier.

For routine testing, PTI's vacuum decay system can detect leaks down to less than one micron in under one minute, and under five microns in less than eight seconds. With many of the large molecule products on the market, though, vacuum decay may not always work. Those larger molecules do not evaporate, but they also cannot be detected because they often plug the leak. This is where high-voltage testing is effective, as long as it is used on a liquid-filled container. Traditional high-voltage systems are often inefficient or ineffective at leak testing with low-conductivity liquids. PTI's MicroCurrent high-voltage system uses both AC and DC currents, sig-

nificantly reducing the exposure voltage during inspection, thereby maximizing leak detection while minimizing the risk of damaging highly sensitive pharmaceuticals.

When developers have access to fast, accurate testing equipment and apply appropriate test methods at the right points along the development timeline, they can produce better quality products more efficiently. Today's high-risk pharmaceuticals and their containers require a profound depth of understanding about all the conditions to which they will be exposed. PTI's suite of leak detection technologies can help developers of today's most critical treatments bring them to patients, sooner and safer. Visit www.ptiusa.com for more information about these systems.