UNDERSTANDING THE SCIENCE BEHIND LIQUID LEAK AND MICROBIAL INGRESS MECHANISMS AS THE FOUNDATION FOR SINGLE-USE CONTAINER CLOSURE INTEGRITY (SU-CCI)

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This presentation describes a scientific approach to establishing a relation between liquid leakage and microbial ingress mechanisms in single use plastic containers and developing the appropriate physical integrity testing methods and specifications.

With the expansion of Single Use Systems (SUS) in all process steps of commercial manufacturing, integrity failure can significantly impact drug safety, availability and costs. The use of closed systems in cell & gene therapy can support the reduction of production costs when moving the manufacturing process from class B to class C or even D environment. More significantly, in very critical autologous applications, like e.g. CAR–T cell therapy on terminally ill patients, a single bag integrity failure can result in the loss of the only possible batch, followed by the death of the patient. As current approved sterility test methods take longer than the shelf-life of the cell preparation, additional integrity testing for risk mitigation can help to support the final cell product release before injection to the recipient. A combination of an integrity test of the bioprocess containers with a quantitative, real-time PCR of a product sample (e.g. on mycoplasma) can provide a strong indication that the cell preparation has not been contaminated.
During lentivirus production, operator safety is of great concern as the components are derived from viruses that target human cells, and feature an inherent risk for insertional oncogenesis. Assuring that the virus is contained by technical means is favorable to relying on organizational or personal means, such as use of safety equipment and personal hygiene, as it should present lower risk.
Consequently, there is an increasing industry scrutiny on SU CCI, raising the need to develop good science behind liquid leakage and microbial ingress and appropriate physical integrity testing technologies.

The authors will first review the emerging industry association initiatives and introduce an integrated quality by design (QbD), material science and process control approach as the prerequisite to SU-CCI.
The presentation will then describe how applying good science can help determine the maximum allowable leakage limit (MALL) under which no product leakage and no bacteria ingress occur with SUS under various fluids and process conditions. The understanding of liquid leakage and bacteria ingress mechanisms also enables the validation of robust liquid leak tests and microbial aerosol challenge which are both correlated to the detection limits of physical integrity testing methods.

The authors will conclude with the development of highly sensitive deterministic integrity testing technologies, such as gas tracer detection and pressure decay, which are able to detect the MALL determined during the scientific study. The Helium based Supplier Integrity Test (SIT) for instance is able to control the finished products with a detection limit of 2µm and is correlated to both, liquid leakage and microbial ingress, under all tested process conditions.

Audience take home messages:

- QbD, QRM, Process Control and Quality Control ensure CCI along the entire production cycle
- Understand the science behind SUS films' behavior and the determination of the Maximum Allowable Leakage Limit (MALL)
- Integrity testing technologies can detect the MALL in all parts of complete SUS assemblies at both the supplier and point of use and can be correlated to a bacterial challenge
- Use of closed systems in combination with an appropriate integrity assurance strategy can support cost reduction and risk mitigation for product release in cell & gene therapy applications.