

Aseptic Processing and Cleanroom Technology

Robert Lee, President, and James S. Drob, Director of Manufacturing Operations, from the CDMO Division of Lubrizol Life Science Health (LLS Health) discuss the importance of cleanroom technology being fit for purpose in aseptic processing and how changing R&D pipelines have led to a rise in the number of companies outsourcing their sterile product manufacturing to CDMOs.

The cleanroom technology market is a growing segment of the manufacturing industry that is expected to expand from a value of \$3.87bn in 2019 to \$5.04bn by 2025.¹ One of the main drivers of this growth is an increase in sterile drug products, such as injectable biologics and ophthalmic formulations. Market data shows that over half of clinical stage projects are injectables, and programs for eye diseases have doubled in the past five years alone.² This pipeline will continue to drive demand for sterile cleanrooms and aseptic manufacturing services well into the future.

More than just cleanroom technology, producing drug products in a sterile environment requires a unified organisational effort. This includes having well-trained personnel, robust quality infrastructure, and the proper manufacturing equipment and processes to ensure a consistent product. The complexity of establishing and maintaining all these elements often leads pharma companies to outsource their aseptic processing requirements. This is especially true for small or virtual companies who can more efficiently progress into clinical and commercial production with the right CDMO partner.

Challenges in maintaining a cleanroom environment

Ensuring sterility is extremely challenging, and careful planning is needed at every stage of processing to negate the serious risk that contamination poses. Injectable and ophthalmic drug products present an increased risk of infection or harm due to the way that they bypass the body's natural defences. Because of this, regulatory

requirements around aseptic processing are strict and constantly evolving.

Operator responsibility

All individuals operating in a cleanroom environment need to be suitably trained, well-disciplined, and very careful. The objective of the aseptic manufacturing process is to eliminate any opportunities for contamination, and this begins with the operators. After all, contamination arrives most often from the humans involved in the process. To this end, a gowning qualification to ensure proper gowning techniques must be carried out and forms part of a well-orchestrated routine to minimise contamination risk from the moment operators enter a cleanroom environment.

A risk assessment should take place while defining the optimal manufacturing process for each project. As a project progresses from R&D into clinical and commercial production, the process may change, and new assessments may be needed. For example, many products start with manual hand-filling of small batches of clinical trial material before moving onto semi-automated and then fully automated high-speed filling lines to support registration batches and commercial supply. These stages have different steps, equipment, and may even take place in different cleanroom environments, which must be factored into the risk assessment.

The risk of cross-contamination

Cleanrooms require a controlled environment, and multi-product facilities that work with several different client APIs have processes in place to eliminate the risk of cross-contamination. Environmental Monitoring (EM) activities, including the regular collection, evaluation, and interpretation of data regarding the air, surfaces, and personnel in the cleanrooms, are essential. The risk of cross-contamination can be managed and simplified by using disposable pre-sterilised components. The use of single-use technology avoids the need for cleaning validation, which must be carried out when using stainless steel or reusable equipment and adds time and cost to any project.

Achieving sterility: The differences between aseptic processing and terminal sterilisation

There are four routes of administration that require sterility: injection, ophthalmic, inhaled, and otic. Producing drug products for these routes of administration requires either terminal sterilization or aseptic processing.

Terminal sterilisation involves manufacturing and packaging the product in a cleanroom environment, then subjecting the drug product and its packaging to a sterilization process, such as heat, steam, chemical, or irradiation.

For some drug products, such as biologics or certain active pharmaceutical ingredients (APIs), terminal sterilization is not possible, often due to the sensitivity of the product or its formulation components. If it is proven that terminal sterilisation cannot be applied to a drug product, then aseptic processing is an option.

Aseptic processing utilises pre-sterilised components for the drug product, container, and closure system. The product must also be packaged in a sterile environment.

Aseptic processing must occur within an ISO 5 (Grade A) cleanroom, while terminal sterilisation typically occurs in a minimum of an ISO 7 (Grade C) space.

Techniques to demonstrate sterility

Aseptic processing is one of the most challenging pharmaceutical processes, and manufacturers need to follow strict processes to demonstrate sterility. Validation of any new aseptic process is essential, and three consecutive media fills or aseptic process simulations (APS) are needed to ensure that a process is truly sterile. Media fills are performed to show sterility assurance across the totality of the process, which means trained personnel, equipment, packaging components, and all manufacturing steps. Any issue during an APS means the entire process may need to be re-validated, costing time and money. A good CDMO performs media fills proactively and maintains validated fills that allow client projects to progress more efficiently

During media fills, sterility is challenge by exposing a microbiological growth medium to product contact surfaces, such as equipment, container closure systems, critical environments, and process manipulations. This is done to ensure that after incubation, quality personnel can more easily detect microbial contamination during processing. The results of this exposure are then interpreted to gauge whether there is potential for the drug product to be contaminated during actual operations.

As previously mentioned, carrying out extensive non-viable and viable EM of the facility is fundamental to ensuring sterility, with close attention paid to the critical areas of operation. EM for viable particles includes methods for isolating bacteria, yeast, and mold in the facility, which involves monitoring the air, members of staff, and surfaces for any microbial contamination. For personnel, this process will involve being plated after critical steps, such as aseptic connections, and upon exiting the cleanrooms.

The changing face of aseptic processing

There is a common perception that there is a sterile manufacturing capacity shortage in the pharmaceutical industry. While sterile filling lines exist for many marketed products, these lines are often inaccessible for new drug developers or not appropriate for the products that are coming to market today.

Much of the existing cleanroom capacity remains geared towards high-volume production and is most suited to manufacturing the blockbuster products of old. In contrast, many of the products coming through the R&D pipeline are lower volume biologics and precision medicines aimed at meeting the needs of complex and sometimes rare diseases. This is driving the demand for greater flexibility in aseptic processing facilities, including the ability to handle smaller batch sizes with speed and manage product changeovers swiftly. This is leading to the adoption of single-use technologies that remove the need for time consuming validation between product batches.

Most biologics are considered complex and introduce unique challenges when it comes to setting up and managing cleanroom environments. Because they cannot be terminally sterilised, most biologic drug products require an aseptic

process. Equipment trains for biologics often incorporate formulation steps such as mixing/blending or filtration prior to an aseptic fill. Having ample processing space in the cleanrooms is critical for these activities. When performing aseptic filling into primary packaging, considerations related to temperature, shear, and oxidation must also be taken into account. And finally, aseptic lyophilization, which is carried out in an ISO 5 (Class A) environment, introduces its own set of challenges.

With a shortage of flexible, smaller batch manufacturing capacity in the sector, CDMOs have made substantial investments in recent years to meet this need. For example, modular facilities are on the rise which allow greater flexibility by containing movable equipment and equipment trains.

LLS Health is addressing this need in our FDA-inspected commercial manufacturing facility, which builds upon our decades of experience as a development and clinical manufacturing partner. Our facility was designed to have no minimum batch sizes and features modular, ISO 7 processing space and utilities to accommodate a wide range of formulation steps. We also offer aseptic filling of vials and bottles along with lyophilization in an ISO 5 cleanroom environment. This facility was designed with the next generation of pharmaceutical products in mind – including ophthalmic products, biologics, and the growing field of precision medicine.

Summary

In short, there are many challenges that need to be overcome to ensure therapies that need to be sterile, safe, and scalable. For the growing injectable and ophthalmic product pipelines, demonstrating sterility is an important task that needs careful attention. As complex products and aseptic filling become more common, flexible cleanroom space will continue to be in demand. CDMOs with trusted teams and media fill strategies, such as LLS Health, will enable companies and products of all sizes to get to market and usher in the next generation of healthcare.

REFERENCES

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Dr. Lee is responsible for product and business development along with providing strategic direction. Before joining LLS Health, Rob held senior management positions at Novavax, Inc., Lyotropic Therapeutics, Inc., and Imcor Pharmaceutical Co. He holds BSs in Biology and Chemistry from the University of Washington and a PhD in Physical Bioorganic Chemistry from the University of California, Santa Barbara. Rob has published more than three dozen articles and five book chapters plus holds 11 issued patents and 15 provisional or PCT patent applications. He has over 30 years of experience in pharmaceutical research and development of both therapeutic drugs and diagnostic imaging agents. Rob maintains strong academic ties, including an appointment as Adjunct Associate Professor of Pharmaceutical Chemistry at the University of Kansas in the early 1990s, serving as a reviewer for both the International Journal of Pharmaceutics and Journal of Pharmaceutical Sciences, and serving on the Editorial Board for the Journal MOJ Bioequivalence & Bioavailability, The Scientific Pages of Nanotechnology, and The Journal of Analytical and Pharmaceutical Research.

Jason Steele

Jason works with LLS Health's CDMO clients to design projects that meet their needs, leveraging his experience providing agile, cost-effective solutions that emphasize our customer-centric approach. His initial focus has been on building relationships with LLS's aseptic manufacturing clients and working with customers with the end goal in mind – getting to market. Jason had over 10 years of pharmaceutical experience with a focus in sterile drug product manufacturing.