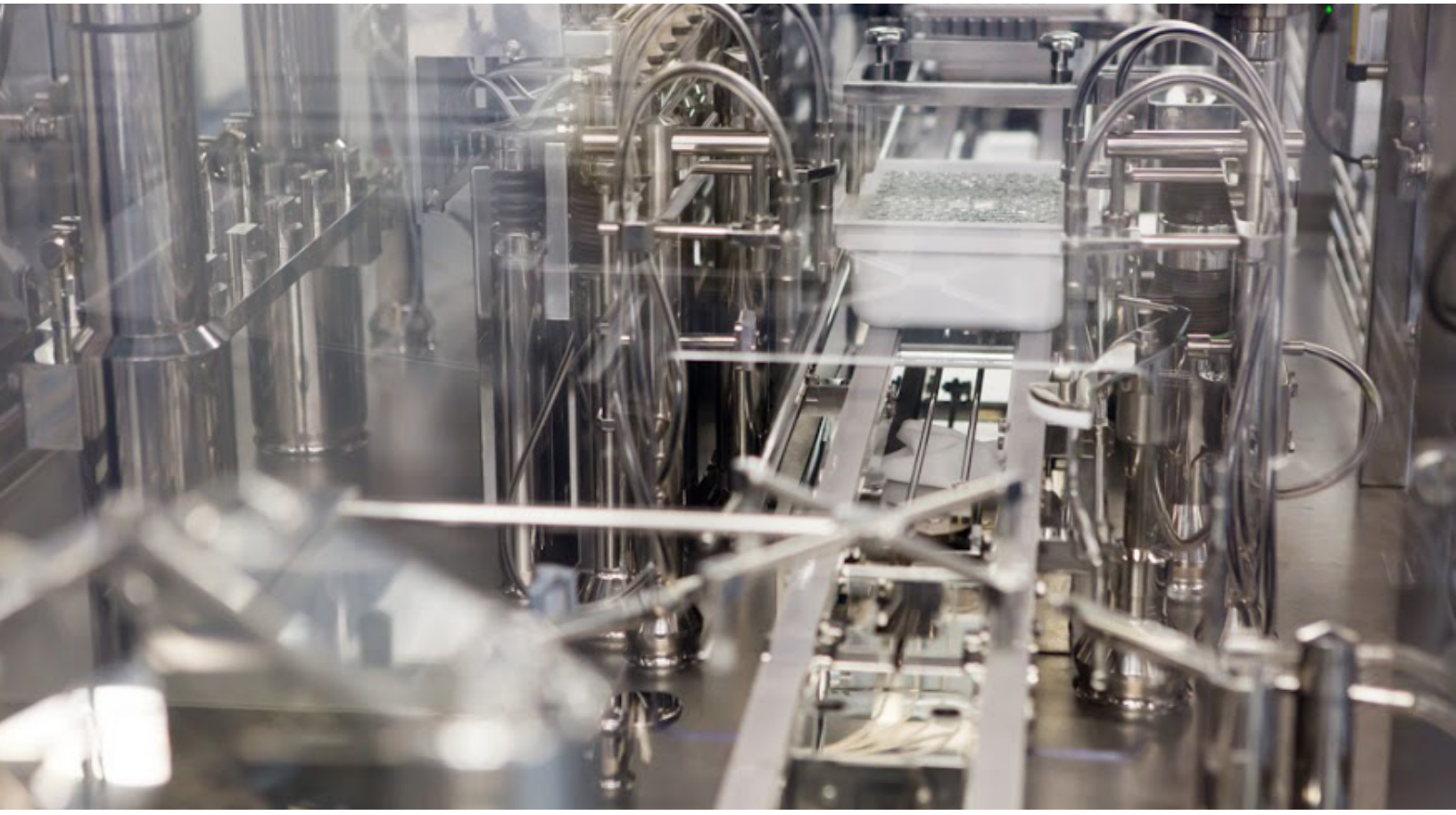
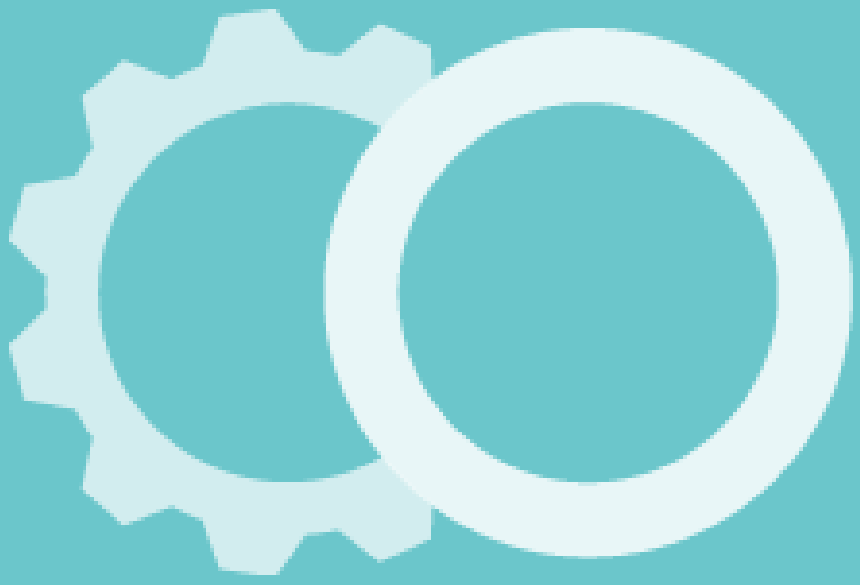
ALTHEA

THE POWER TO MAKE®

CRITICAL FACTORS OF FILL FINISH MANUFACTURING FOR BIOLOGICS



With the explosion of the biologics market, which now accounts for an estimated 20% of all pharmaceutical sales, the industry has entered a new era of drug development. This growth — 10% to 15% each year — is being driven by monoclonal antibodies, which are anticipated to have worldwide sales of nearly $125 billion by 2020[1]. However, this burgeoning market comes with some considerable challenges for drug manufacturers, due to the fragile nature and instability of these large, complex molecules. Specifically, their need to be handled differently than small molecule drugs is forcing changes at nearly every level of manufacturing. The bulk drug substance, formulation, and sterile filtering and filling of the final drug product all require special handling procedures.



HANDLE WITH CARE

The properties of a biologic and the function of its protein are directly dependent on both the nature of the manufacturing process and the preservation of the protein's 3D structure. Proteins that have been misfolded (or altered) can function differently, which is why it is imperative to preserve this structure during fill finish operations. For this reason, a sterile manufacturer must be aware of the innate properties of proteins and the external factors that can affect an individual protein's behavior and stability. One key area is proper handling. Unlike small molecule drugs, biologics are extremely sensitive, and therefore require specific handling procedures throughout the manufacturing process, starting with receipt of the incoming bulk drug substance (BDS).

End-to-end cold chain infrastructure and traceability are also critical to maintaining the quality of BDS and subsequent drug product. Temperature-controlled units that can maintain temperatures of 2-8° Celsius, -20° Celsius, and -80° Celsius must be on hand to ensure a protein therapeutic is kept at its optimal storage temperature. Intermediate storage should be available in the case of extended hold times or multi-day filling processes. If a temperature excursion occurs at any point, it could mean millions of dollars of lost revenue. Through carefully planned and executed risk-mitigation strategies, considerable losses in both time and money can be avoided.

PERISTALTIC VS. PISTON

Historically, rotary piston pumps have been the go-to technology for liquid filling and are well established in biopharmaceutical production processes. While they are known for being robust, reliable, and highly accurate, one drawback is that internal parts of the pump come in direct contact with the fluid moving through it. This makes piston pumps much less efficient and more costly in a multi-product facility due to the required cleaning validation. In addition, biologics can be susceptible to shear forces, which can cause a protein to aggregate, as well as cause conformational changes that may affect activity and solubility. Therefore, rotary piston pumps may damage fragile proteins due to their mechanism of action.

Because of the handling challenges presented by biologics, the preferred filling system is a peristaltic pump. Through continuous external pressure, a peristaltic pump moves the biologic through tubing. This is the only part of the pump exposed to the biologic. The most significant benefit of these pumps is that they offer gentle, low-pressure pumping, which is preferred due to the sensitive nature of the biologic product. And because of single-use tubing, a peristaltic pump offers the ability for a quick changeover between batches, thereby mitigating the risk of cross-contamination and eliminating the need for cleaning validation.

While the accuracy of a piston pump still trumps that of a peristaltic, one way to address this is to ensure the use of properly-sized tubing. Shearing and other effects that can lead to protein degradation can be avoided by pumping viscous solutions through small diameter tubing. This reduces the total number of rotations a peristaltic pump must make to deliver the product dose. Using properly-sized tubing for the specific product also mitigates dripping that may occur at the fill nozzle, due to low surface tension or higher viscosities. In addition, rigid teflon lines can be used to replace a majority of silicone lines that make up the filling apparatus. Pliable silicone tubing will be utilized through the pumps to deliver the dose, but the rigid teflon lines reduce the expansion and contraction of the fill tubing when dosing with peristaltic.

This alleviates dosing variation typically seen with viscous or high-concentration products.

Once a biologic product has been dispensed into vials or syringes, it must be visually inspected. In both the U.S. and Europe, this is most often achieved through manual inspection. If a manufacturer does not have properly-trained, skilled operators to perform these manual inspections, they may not be able to distinguish between inherent product properties and extrinsic particulate defects. High-concentration biologics may have visible protein attributes. Inspectors who are properly trained can identify whether this is inherent to the product or an extrinsic defect. In addition, improper handling of a biologic product during the inspection process can lead to problems. Having operators who are properly trained and qualified to handle sensitive products and who are responsible for inspecting biologics on a daily basis is another safeguard to ensure the stability of the biologic product.

A CMO READY FOR THE FUTURE

The biopharmaceutical industry has traditionally focused on developing blockbuster drugs. However, over the past several years, a new era of drug development has unfolded, and personalized medicine and orphan drug designation are now driving manufacturers to pursue niche markets, resulting in smaller batches. In order to serve this market, a CMO must be capable of completing fill finish on lower-volume products. For those CMOs positioned to produce larger batches, using the same equipment to produce small volumes is not cost effective. Controlling hold-up volume during manufacturing also becomes an issue with larger set-ups. These CMOs are then required to make adjustments that reduce the loss of product at all steps, such as proper filter selection, fill set selection, and proper intervals for dose verification. Finally, it is more difficult for large support staffs to adjust to change and remain flexible in scheduling and timing, which becomes imperative when trying to get the throughput necessary to be profitable.

Overall, the future of the pharmaceutical industry and the ability to successfully develop biologics are both dependent on a manufacturer's ability to preserve the native state of a biologically active protein. This becomes especially important in fill finish, where there are a significant number of manipulations necessary to complete the process. Therefore, a controlled environment equipped with the expertise and experience needed to ensure the safe handling of high-value therapeutics becomes incredibly important. Since its founding, Althea has invested significant resources to build manufacturing platforms that specifically protect the integrity of large molecule biologics. The goal is to provide clients with the confidence that their high-value investment is protected from beginning to end. By selecting a CMO that possesses a structure that meets your stage of production, you will find yourself more prepared for the ebbs and flows of drug development.

Reference

1. www.bptc.com/sites/default/files/articles/ecker-2015-the_therapeutic_monoclonal_antibody_market-rprnt.pdf

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