



BIO•PHARMA

S E R V I C E S

— THE POWER TO MAKE® —

CRITICAL FACTORS OF FILL FINISH MANUFACTURING FOR LARGE MOLECULES



With the explosion of the large molecule (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 (mAbs), which are anticipated to have worldwide sales of over \$240 billion by 2025.

However, with this expanding market comes some considerable challenges for drug manufacturers due to the fragile nature and instability of these large, complex molecules. As compared to small molecules, large molecules generally require special handling procedures for the bulk drug substance, formulation, and sterile filtering and filling of the final drug product, which is forcing changes at nearly every level of the manufacturing process.

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HANDLE WITH CARE

Large molecule properties and protein functions 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 change or impair functionality, which is why preservation of structure during fill finish operations is of utmost importance. 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 structure and hence not only its behavior but also its stability. Unlike small molecule drugs, large molecules 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 specific temperatures of 2-8 °C, -20 °C, and -80 °C must be on hand to ensure a therapeutic protein is kept at its optimal storage temperature.



Additionally, temperature-controlled units for intermediate storage need to 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 irreversible protein damage and ultimately millions of dollars of lost product. Through carefully planned and executed risk-mitigation strategies, considerable losses in both time and product no longer available for patient treatment 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 key 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 and downtime. In addition, large molecules can be susceptible to shear forces, which can cause conformational changes or protein aggregation that may affect activity and solubility. Therefore, rotary piston pumps are not preferred in the filling of large molecules as they have an increased potential to damage these fragile proteins due to their mechanism of action.

Because of the handling challenges presented by large molecules, the preferred filling system is a peristaltic pump. Through continuous external pressure, a peristaltic pump moves the large molecule through tubing. The large molecule is only in direct contact with the tubing and is not exposed to internal parts of the pump. Another significant benefit of peristaltic pumps is that they

offer gentle, low-pressure pumping, which is preferred due to the sensitive nature of the large molecule 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 generally exceeds 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 pumps. This alleviates dosing variation typically seen with viscous or high-concentration products.

Once a large molecule 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 visual inspection. If a manufacturer does not have properly-qualified and skilled operators to perform these manual inspections, they may not be able to distinguish between inherent product properties and extrinsic particulate defects. High-concentration large

molecules may have inherent, visible protein attributes. Inspectors who are properly trained can identify whether this is inherent to the product or an extrinsic defect. Having operators who are properly trained, qualified, responsible for inspecting large molecules on a daily basis is another safeguard to ensure the stability of the large molecule product.

A CDMO 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 CDMO must be capable and adaptable in completing fill finish on lower-volume products.

For those CDMOs 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. It is necessary for these CDMOs 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.

Overall, the future of the biopharmaceutical industry and the ability to successfully develop large molecules 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, Ajinomoto Bio-Pharma Services has invested significant resources to build manufacturing platforms that specifically

protect the integrity of large molecule products. Our goal is to provide clients with the confidence that their high-value investment is protected from beginning to end. By selecting a CDMO that possesses extensive large molecule experience and a structure that meets your stage of production, you will find yourself more prepared for the ebbs and flows of drug product fill finish.



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