Putting Fill-Finish Customization Into Your Line of Sight

Tackling the challenges of small batch manufacturing in fill-finish programs

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The biopharmaceutical industry continues to grow rapidly, driven by more specialized treatment protocols and the development of new and more complex treatments, such as Antibody-Drug Conjugates (ADCs) and cell and gene therapies. The fill-finish manufacturing market is predicted to be worth an estimated $4.47 billion by 2022,[1] and this growing biological sector of the market typically has smaller batch sizes and is more efficiently filled with smaller, slower speed, quick changeover, filling lines. These lines are often isolated to provide containment as well as sterility to protect the product from contamination as well as the operators from exposure to the product. The final product can be delivered as a sterile liquid, powder, or suspension, and supplied in vials, syringes, or cartridges. Strong product development tools and versatile small batch aseptic filling lines are critical to shorten "time to market" and therefore are becoming increasingly important.

During manufacture, recent data shows that over 40% of biological drug products require lyophilization (freeze-drying), a percentage that is increasing. Many biological products can be fragile in a liquid form and must be freeze-dried to provide stability. Therefore, it is critical to have the correct tools to shorten the freeze-drying development time and optimize the reliability of the freeze-drying cycle. The filling lines may be designed for slower speeds, which is more suited for the smaller batch sizes, but must match or surpass the rigorous quality standards of high-speed lines. These new products are expensive to develop but have tremendous potential to cure, formerly incurable diseases. Therefore, we must produce a stable and reliable process while minimizing the risk from particulate and bacterial contamination, and comply with extensive regulatory scrutiny.

Consequently, there is a growing need for a complete package of rapid product development tools and scalable, good manufacturing (GMP) compliant, aseptic fill-finish production lines optimized for small batch applications. This article discusses the development and manufacturing challenges, and highlights the key considerations required when evaluating product development tools, selecting equipment, and optimizing small batch fill-finish lines.

The role of lyophilization in fill-finish manufacturing

Lyophilization (summarized in Figure 1) substantially increases product stability and shelf life. Consequently almost 50% of the injectable products in clinical trials, or approved for the market, are lyophilized so biopharmaceutical manufacturers need advanced, sterile systems for lyophilization.[2] Moreover, the lyophilization process must be scalable, giving manufacturers the ability to reproducibly freeze-dry their product at every stage of development – from initial formulation and development, through clinical trials, to full manufacturing.

A critical step in the fill-finish manufacturing process, lyophilization removes water from the product after it has been frozen. Modern lyophilization systems utilize an inert gas and pressurization and rapid depressurization to create instantaneous ice nucleation throughout the product, massively improving heterogeneity, and therefore quality. During drying, the chamber is placed under a vacuum, allowing the ice to change directly from a solid to a vapor without passing through a liquid phase. Process control during freeze-drying is imperative to the product integrity.

Figure 1: *An overview of the lyophilization process*

Today, fill-finish manufacturing demands scalability and flexibility – especially for small batches of specialized therapies. Small batch manufacturing does not run efficiently and cost-effectively on conventional, larger production lines, therefore necessitating scalable, lyophilization platforms where the product - irrespective of development stage - can be manufactured under sterile, GMP compliant conditions.

High quality and consistent lyophilization – from development to production

There are many key challenges throughout the lyophilization process that need to be considered in order to create a consistent, reproducible biopharmaceutical product. For example, excess heat can cause melt-back, where the primary drying phase has ended but some of the vials still have some ice at the bottom, and there could also be choked flow, where the flow of vapor is impeded by the dryer's capability to deal with the mass flow. As lyophilization scale increases during product development and testing, these challenges also mount.

To meet this need for consistent, scalable, and cost-effective lyophilization throughout the development and manufacturing process, SP has developed Line of Sight™, a suite of lyophilization systems that incorporate Process Analytical Technologies (PAT) to automate, control, and support the lyophilization process. Line of Sight brings scalable technologies to small batch biopharmaceutical production by providing a data rich manufacturing platform at any scale throughout the development of a biopharmaceutical product (Figure 2). This provides control, efficiency, quality, and consistency throughout the entire fill-finish process.

Precise control is critical

The foundation of Line of Sight is ControLyo®, SP's lyophilization technology that provides precise control during the freeze-drying process, and available in every SP lyophilization system. Perfect for easily maintaining control and reproducibility throughout scale-up, ControLyo is present in SP's LyoStar™ 3 system for formulation, stability and cycle development studies, through to the LyoConstellation™ platform, designed for later stages of product

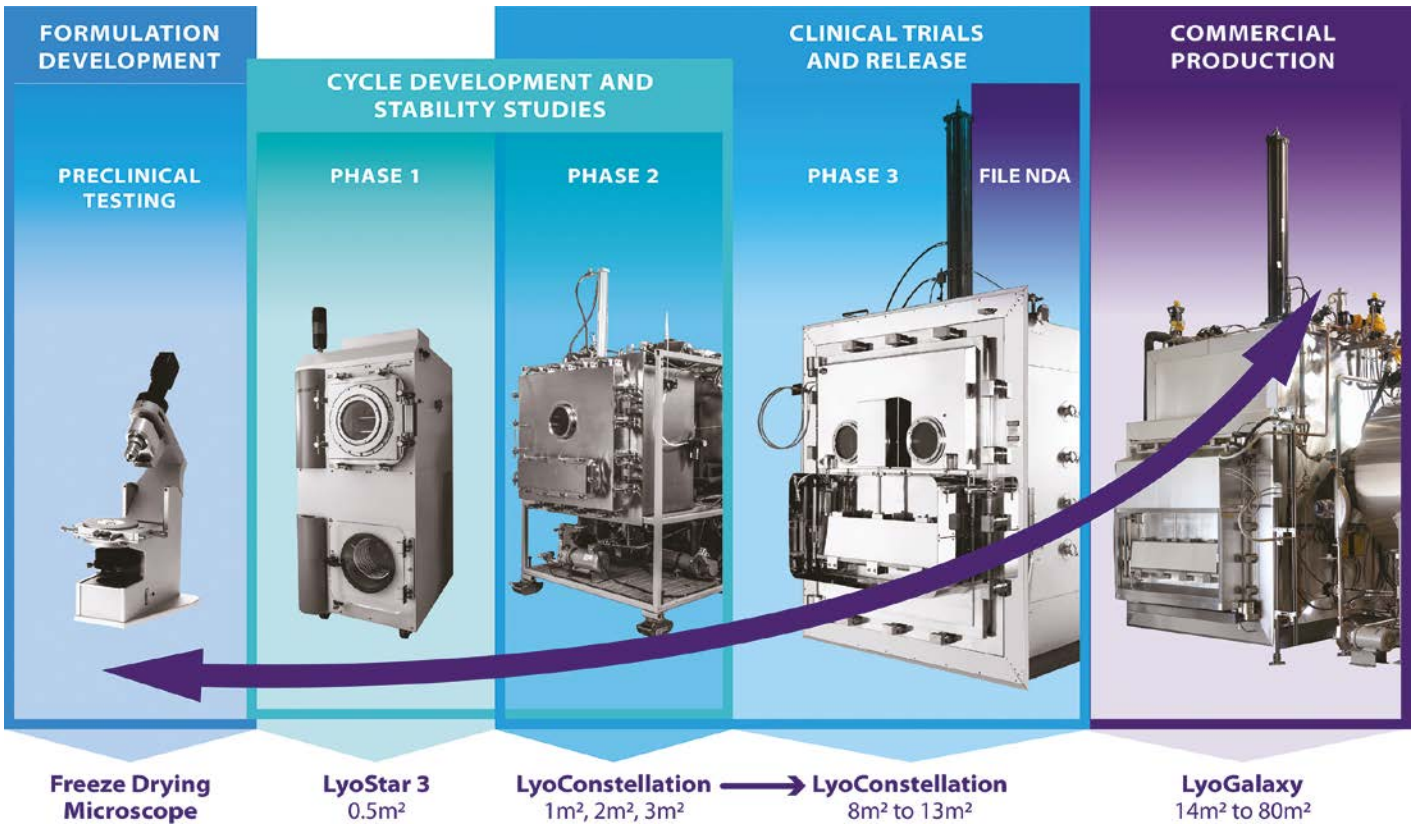

Figure 2: *Line of Sight™, a suite of SP lyophilization systems that ensure scalability in biopharmaceutical product freeze-drying. ControLyo® provides precise control during the freeze-drying process, and is available in every SP lyophilization system.*

development to full commercial production. ControLyo ensures that every vial, irrespective of scale, shelf location or tray position, experiences the same environmental conditions at the same time.

Other Line of Sight PAT tools include LyoFlux® tuneable diode laser absorption spectroscopy (TDLAS) which accurately measures water vapor concentration and gas flow velocity throughout the freeze-drying process, and Tempris® wireless sensors that measure the temperature in every sample loading module.

These Line of Sight technologies are available for every SP lyophilization system guaranteeing that freeze-drying throughout product development, and irrespective of scale, can be repeated and tracked. By tightly controlling the freezing process, the technology improves product quality, shortens drying times, and requires no formulation change or introduction of foreign material into the vials. This guarantees consistency and reproducibility from "pilot to production", considerably lowering development time and cost.

Because SP's Line of Sight lyophilization systems are extremely data rich, they are also capable of salvaging a production batch that experiences an unexpected deviation in the GMP process. SP's lyophilization technologies and equipment can identify the deviation, highlight where best practice can be restored, and (where possible) rescue the impacted batch. Again, this can lead to substantial cost-savings for the manufacturer.

Dependable fill-finish – essential for product quality and speed to market

Fill-finish is the final stage before the product is packaged, shipped and administered to the patient. At this point, biopharmaceutical products are potent and extremely valuable having been through the labor- and cost-intensive production stages of upstream processing, cell culture or fermentation, and downstream purification. Efficient fill-finish is therefore a crucial step in the biopharmaceutical manufacturing process, as bad practice and product loss at this stage will be extremely costly.

As patient treatments move away from entire population therapies in favor of the targeted treatment of smaller (personalized) patient populations, the biopharmaceutical industry is transitioning to smaller aseptic batch manufacturing processes. For example, in oncology, personalized treatments such as antibody drug conjugates can have their stability dramatically improved by freeze-drying. Their development through product characterization, cycle optimization, and manufacturing scale up can be extremely time-consuming and expensive, so it is essential that the fill-finish process is efficient and minimizes product loss.

Challenges in fill-finish manufacturing

Ensuring sterility

In an environment where patient safety is imperative, sterility is the most important challenge in fill-finish manufacture. Any breach in sterility can cause microbial contamination and impact drug purity, placing the batch at risk. More importantly, if the contamination is not identified before release, it can harm the patient and elicit a product recall. Since both the risk to patient and the complexity of the fill-finish process are so high, fill-finish manufacture is subject to extensive scrutiny and inspection, regardless of batch size and production scale. To ensure sterility, and regulatory compliance, the entire fill-finish process requires highly specialized equipment capabilities and manufacturer support.

The filling process

Accuracy, inline process control, monitoring and issues such as mis-dispensing are all factors that must be addressed in the filling process. One common challenge is the "splashing" that can happen with high-speed filling, and when a solution is added to a product at a high velocity. Liquid on the vial sidewalls can also occur if the filling needle drips during the movement of the vial, or if the filling needle is not centered properly, as the solution will not be added directly to the center of the container.

Splashing can create product loss and contamination on the fill line, but more importantly, it can affect container-closure integrity (CCI) as residual product is left around the neck of a vial. CCI may cause breaches in sterility and/or changes in the active pharmaceutical ingredient, both of which can be highly hazardous to patients. Splashing can also affect the final solution volume in the vial, and can create cosmetic defects in the final freeze-dried product. As well as preventing splashing, modern filling systems need to be highly accurate. If an incorrect solution volume is added, this will substantially impact dosage and drug concentration, again risking patient health and treatment success.

Precise filling and vial movement control systems can minimize these challenges, reducing or eliminating splashing and filling with dependable accuracy. Sensors ensure the nozzle is positioned centrally, plus automated control systems can regulate the filling

volume and speed, and reduce the velocity of the final amount of solution as it is added. Additionally, the filling speed of the last volume of solution can be carried out using different nozzles with independent servo control, preventing splashing to ensure every container is filled accurately, regardless of scale.

Containment and regulatory compliance

As discussed, the inadvertent introduction of contaminants at any stage of the fill-finish process can have fatal consequences. Fill-finish manufacturing is therefore held to the very highest regulatory standards, independently defined and inspected by the Food and Drug Administration (FDA). To meet these standards, irrespective of manufacturing scale, biopharmaceutical fill-finish production integrates safeguards and monitors aseptic practices to minimize contamination, maximize efficiency and accuracy, and generate full electronic auditable data. By ensuring batch quality and consistency, the huge fiscal- and time-cost of batch rejection can be avoided.

Regulatory requirements require extensive monitoring and data collection with inline process-controlled instrumentation at every stage of the aseptic biopharmaceutical fill-finish manufacturing process, which labor-intensive, manual processes struggle to achieve. Automation also supports sterility assurance because these are closed systems. In addition to ensuring environmental control throughout the entire process, critical for GMP, closed automated systems also reduce the number of personnel required on the cleanroom manufacturing line, minimizing the risk of contamination. Accordingly, automation, where possible, has become the industry standard.

Versatility – the essential requirement for small batch production

The emphasis on speed to market is also addressed by SP's "Versa-Lines" equipment optimized for biopharmaceutical manufacturing at any scale. The Versa-Line concept is driven by three fundamental principles: compactness; standardization; and flexibility.

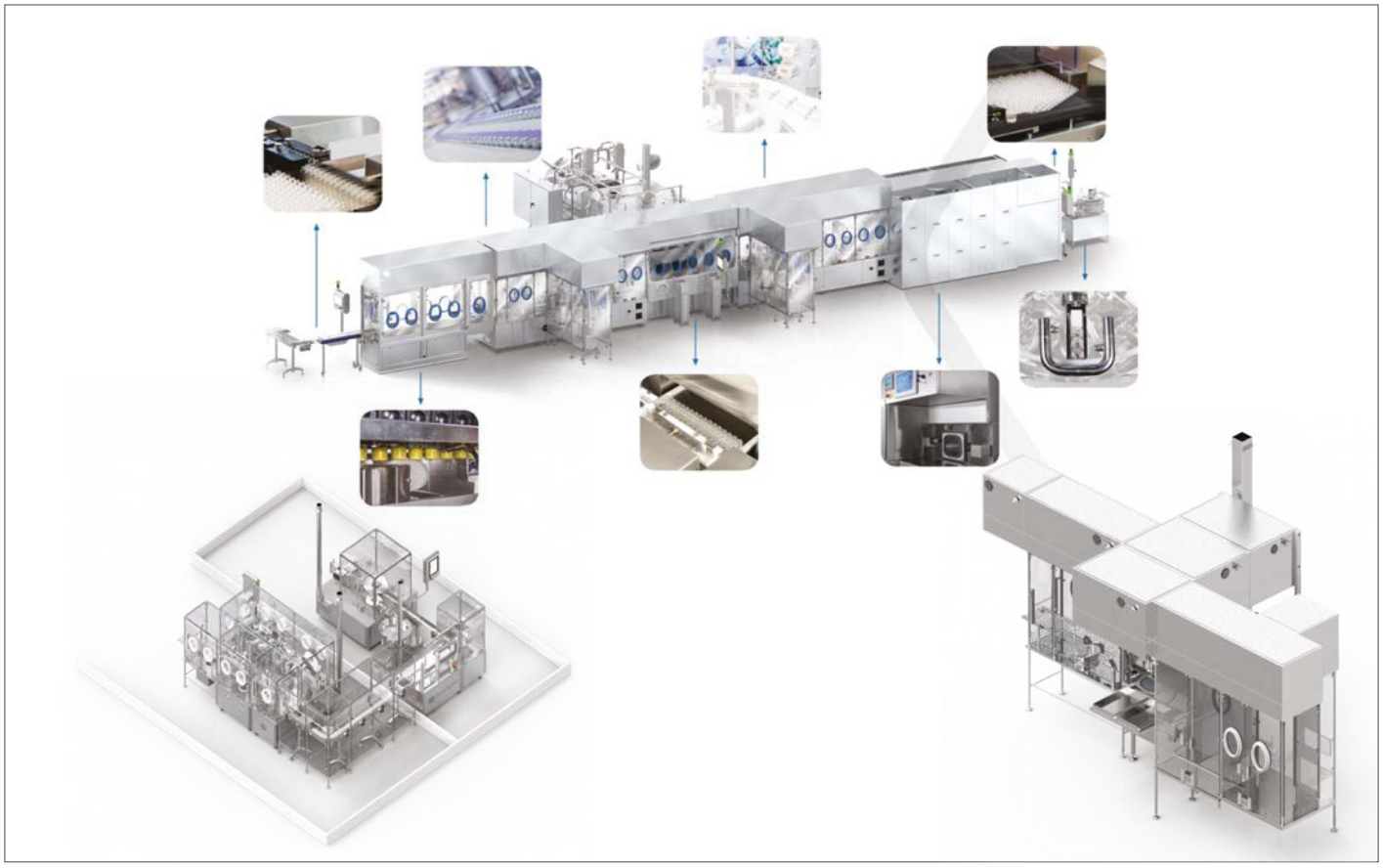

Figure 3: *An overview of SP's Versa-Line approach highlighting how the compact, flexible units offer customization throughout the entire aseptic fill-finish manufacturing process*

Smaller footprints

As discussed, small batch manufacturing does not run efficiently on standard, higher-speed production lines. Even where changeovers are possible, they are time-consuming and complicated. In contrast, every SP Versa-Line component is compact and has a small footprint to ensure the minimal occupation of cleanroom space. This compactness enables quicker, and more straightforward changeovers during fill-finish production, as, for example, SP's filling/ stoppering and capping modules can be used for both sterile and non-sterile studies.

Consistently standardized

SP Versa-Line modules have been standardized, so that every piece of equipment required for the fill-finish process has a modular, standardized footprint, and therefore production lines can be customizable based on room design and space. Moreover, each SP Versa-Line component only requires operator access from one side, saving cleanroom space, reducing personnel on the manufacturing line, and lowering costs. The filling and stoppering module can accommodate liquid or powder filling into vials or syringes by simply exchanging change parts.

Standardization supports easy isolator installation and restricted access barrier systems (RABS) adaption, which regulate the environment, and reduce the risk of contamination during aseptic processing. Critically, standardized modules safeguard the establishment of best practice, rapid set-up, reliability, a shorter lead-time, and a shorter time to production.

Completely flexible

SP Versa-Lines also offer complete flexibility and provide full control for small batch fill-finish manufacturing. The modular, standardized footprint of each piece of equipment means that the entire Versa-Lines suite can be integrated to create a complete manufacturing line, or be customized to suit any user (Figure 3).

SP ensures that the design and set-up used for every client starts with the end goal in sight. For example, one product may require a complete Versa-Line suite incorporating a vial washer, a depyrogenation tunnel, a filler, an automatic loading/unloading system, a lyophilization system, a capper, an external vial washer, and a tray loader. In contrast, a different user may use pre-sterilized glass and only need a de-nesting module for ready to use components, a filler and a capper. The same line could also be used for syringe or cartridge production. SP Versa-Lines enable every possible combination of equipment to be custom installed to perfectly support specific manufacturing requirements and ensure that sterility, reliability, and cost-efficiency are the cornerstone of every small batch aseptic fill-finish production line.

Summary

The biopharmaceutical industry is evolving from large-scale, single product manufacturing to specialized, targeted therapeutic production lines. To manufacture these products requires added control over the development, scale up and production processes minimizing product waste and contamination risks. Moreover, these operations need to minimize product development time, demanding reliability and scalability.

SP's Versa-Line approach meets these needs by ffering complete and dependable aseptic fill-finish manufacturing solutions, with an expert team that supports the customer from concept through installation, to education and ongoing support. SP Versa-Lines are compact, modularized units for every step of the fill-finish process and include Line of Sight lyophilization systems with integrated PAT tools. Together, these provide flexibility and customization at every scale of biopharmaceutical manufacture and underpin a considerable return on investment driven by patient safety, regulatory compliance, and speed to market.

References

[1] Fill Finish Manufacturing Market by Product (Consumables (Prefilled Syringes (Glass, Plastic), Vial), Instruments (Systems (Stand alone, Integrated), Machine Type (Automated, Manual))), End User (CMO, Biopharmaceutical Company) - Global Forecast to 2025, MarketsandMarkets™ INC., (2020)

[2] Kasper, Winter and Freiss; Recent Advances and Further Challenges in Lyophilization, Eur J Pharm Biopharm 85(2): 162-9 (2013)

Video

The SP modular Versa-Line fill-finish system and Line of Sight™ freeze dryer tools, technologies and equipment provide product development and congurable full line solutions. Specializing in small batch applications, the Versa-Line incorporates quick delivery standard modules for vial washing, depyrogenation tunnel, lling and stoppering, freeze dryer and freeze dryer loading systems, capping, external vial washers and trayloaders.