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How continuous freeze-drying fits in the paradigm shift from batch to continuous manufacturing

White Paper

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The pharmaceutical industry faces pressure to improve its manufacturing efficiency and product quality as a result of multiple factors:

- the global strain on healthcare budgets
- more personalized product pipelines and needs
- the low manufacturing efficiency of processes today
- a need for more sustainable manufacturing processes
- increased development time and costs of new drugs
- increased competition from generic drug manufacturers

All of these factors have reduced profit margins. On top of these, regulators are calling for better supply chain reliability to avoid “stockouts” on many important drugs.

Continuous manufacturing

Continuous manufacturing principles allow for the replacement of single-source high-volume factories with many decentralized small-footprint manufacturing units. Therefore, continuous processing is gaining momentum as the next generation of flexible and lean manufacturing. Although continuous manufacturing has been successfully implemented in various industries such as food, personal care, petrochemicals, electronics, and polymer for years, pharmaceutical manufacturers have been slow to adopt this approach, and batch processing remains the prevailing production method.

One of the barriers to deploying continuous systems is the need to purchase new capital items and update the infrastructure for continuous manufacturing when conventional manufacturing plants are old and generally depreciated.

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Batch processing

In conventional batch processing, a specific quantity of materials – such as an API (active pharmaceutical ingredient) and excipients – is processed through a series of sequential unit operations to produce the final dosage form. Each unit operation is run using specific settings, and when the predetermined end point of a specific unit operation is reached, the process cycle ends. The intermediate materials are then stored in warehouses until their quality has been assessed in control labs using offline analysis tools. This segmented manufacturing approach significantly delays the material throughput time of a batch manufacturing process and can result in economic losses if the predefined quality standards are not met. Moreover, for high-volume manufacturing, batch failure can severely disrupt the supply chain for the product. That results in subsequent difficulties for the medical profession and leads to patients dealing with stockouts. Situations that are highly criticized by regulators and governments.[1]

In contrast, continuous manufacturing integrates all unit operations into an uninterrupted production train without a start/stop phase at each unit operation. Raw materials are continuously fed into the process, and finished products are continuously removed. Quality assurance during a continuous process requires and enables continuous monitoring and control of critical process parameters, as well as continuous inspection of quality attributes of raw materials, intermediates, and end products through at-line, online, or in-line measurements in the process stream. Deviations can be rapidly detected, and real-time adjustment of process parameters becomes possible through control loops, thereby minimizing material loss. Handling intermediates in a continuous process is not required as raw materials are directly converted into finished products through an integrated process, reducing material throughput time.

Continuous manufacturing usually relies on small-footprint platforms that can be replicated to obtain a higher throughput. Such a scenario provides a much lower risk of catastrophic disruption to the supply chain and greater flexibility in using the installed assets, which can reduce expensive inventory costs.

[1] https://www.politico.eu/article/health-care-pharma-why-is-europe-running-out-of-medicines-and-whats-being-done-about-it/

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Continuous freeze-drying

Over the last decade, the pharmaceutical industry has increasingly shifted its focus from traditional small-molecule drugs to biopharmaceuticals. However, developing and manufacturing the latter comes with several challenges, one of the biggest being their successful formulation. Refrigerated or even frozen transport and storage is the most straightforward solution, but it can be challenging, costly, and energy-consuming – especially in countries with warmer climates. As a result, over 40% of biopharmaceutical drug products are freeze-dried to increase their stability and shelf life, as well as deliver a workable supply chain.

Pharmaceutical batch freeze-drying is a time-consuming, inefficient, energy-consuming, expensive, and poorly controlled process that has been used for over 50 years. However, a continuous freeze-drying technique has been developed to address these issues.

One significant difference between batch and continuous freeze-drying occurs during the freezing, where liquid solution-filled vials are rotated along their longitudinal axis during a so-called spin freezing step (Fig. 1). The liquid spreads over the vial wall due to centrifugal forces, creating a thin, uniform frozen product layer with a higher surface area that is much thinner than the product layer obtained during batch freeze-drying. That produces a sublimation rate up to twenty times higher than conventional freeze-drying methods because of the large surface area, resulting in a much shorter drying time and making it compatible with continuous processing. Furthermore, the applicable cooling and freezing rates are much faster compared to batch freeze-drying. That can be very relevant for certain types of biologics, such as mRNA LNPs.

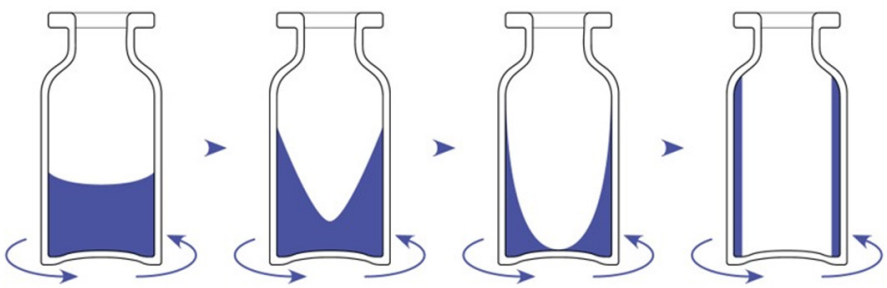

Figure 1: *Illustration of spin freezing – Vials are rapidly rotated to create a thin frozen product layer spread over the entire vial wall.*

The second difference between batch and continuous freeze-drying lies in the drying phase. Infrared (IR) heaters supply heat, and the amount of radiated heat is controlled per vial through continuous in-line non-contact thermal measurements (Fig. 2). That allows each vial to be dried as quickly as possible while guaranteeing end-product quality and eliminating the highly variable and inefficient heat transfer between the dryer cupboard shelf and the bottom of a variably shaped glass vial. The combination of spin freezing and optimized drying conditions potentially reduces drying time by a factor of more than 20 on the unit dose level.vial. The combination of spin freezing and optimized drying conditions potentially reduces drying time by a factor of more than 20 on the unit dose level.

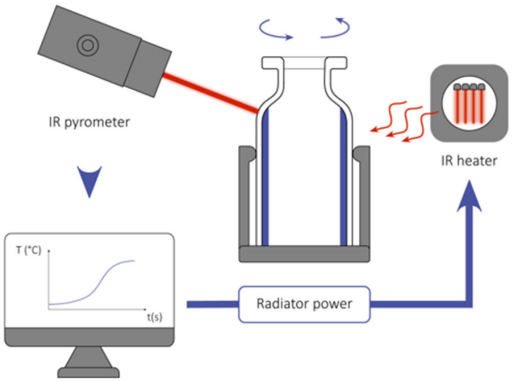

Figure 2: *Illustration of closed feedback loop to control the drying process.*

By transferring the vials to a drying chamber via a load-lock system after spin-freezing, a continuous flow is created. This load-lock system enables fast transfer from atmospheric pressure (spin-freezing) to vacuum (drying). After drying, vials are transferred via a second load lock to a capping and stoppering station, where they are vented to atmospheric pressure, stoppered, and capped (Fig. 3).

Figure 3: *The end product of the spin-freeze drying process*

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The Advantages of Continuous Manufacturing

Regulatory authorities such as the FDA and EMA are facilitating the transition from batch to continuous manufacturing. They have increased support for these processes and have integrated continuous manufacturing into their guidelines: the U.S. Department of Health and Human Services Food and Drug Administration, the Center for Drug Evaluation and Research (CDER), integrated the *"Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry" and EMA/CHMP/ICH/427817/2021, the Committee for Medicinal Products for Human Use, introduced the "ICH guideline Q13 on continuous manufacturing of drug substances and drug products"*

We can anticipate that in the long term, they will favor continuous manufacturing techniques over batch manufacturing.

In addition to the regulatory drivers, there are many reasons to implement continuous manufacturing:

1. **Increased Efficiency:** One of the advantages of continuous manufacturing is increased efficiency, as it streamlines the production process. Production can run continuously, resulting in a higher output or a better match between supply and demand. This increased efficiency can be particularly beneficial when scaling up production to larger volumes because of the significant time and resources that are saved in terms of process development and engineering runs.

2. **Reduced Defects and Waste:** Another advantage of continuous manufacturing is reduced waste and fewer batch losses. Because companies can produce more products with fewer losses (and, therefore, fewer resources), this can result in significant cost savings. Additionally, reducing waste is crucial for companies looking to become more sustainable and environmentally responsible.

3. **Improved Quality:** Continuous manufacturing leads to improved product quality, as the process is more consistent and allows for real-time monitoring and control. That can be particularly beneficial when scaling up production, as these techniques can be implemented on a single vial level, resulting in a smaller defect and rejection rate.

4. **Faster Time-to-Market:** Continuous systems show many advantages in the development of processes. It consumes smaller amounts of material, and the increased control enables faster process development because of a better understanding of the processing steps delivered by the advanced analytical systems. The faster development times enabled by continuous manufacturing can result in faster time-to-market. That, in turn, allows companies to remain competitive and meet customer demands. In addition, a faster time-to-market leads to longer useful patent life and increased revenue.

5. **Flexibility:** Continuous manufacturing is more flexible than batch manufacturing, making it easier for companies to adjust their production processes as needs change. That can be particularly important in scaling up production when companies need to adjust processes to meet customer demands. With traditional batch freeze-dryers, regulations require companies to produce the same volume of vials as the validated protocol stipulates. Moreover, the number of vials placed in the batch freeze-dryer will impact the process settings and overall product quality, which makes it difficult to change the production volumes.

6. **Scalability:** one of the advantages of continuous manufacturing is that it allows for direct scalability from small to large volumes, with little to no engineering or scale-up runs. That is because the production process runs continuously, making it easier for companies to increase their production output as needed. Thanks to continuous manufacturing and individual vial control, it is possible to copy the process settings from small lab-scale devices to large GMP production scales.

Case Study: Continuous manufacturing of monoclonal antibodies

The company simAbs (simabs.com) designed a continuous manufacturing process that consistently produces high-quality Drug Substance of monoclonal antibodies. In this case study, the comparability of a biosimilar antibody produced by continuous manufacturing with its originator molecule was demonstrated.

The manufacturing of monoclonal antibodies (mAbs), is a very complex process and is associated with high production costs. The structure and biological activity of mAbs, as well as other biologicals, is highly sensitive to subtle changes in the manufacturing conditions. Therefore, it is of utmost importance to prove the robustness and consistency of the manufactured product. In order to obtain this crucial information, simAbs performed a case study for the commercially available Trastuzumab (Herceptin®) where they assessed the quality profile of the product manufactured using the simAbs' continuous production platform and benchmarked this to the originator molecule. In this case study, they ran a continuous production process for five weeks during which the produced antibody was directly harvested and processed by a series of multiple purification steps (Figure 1).

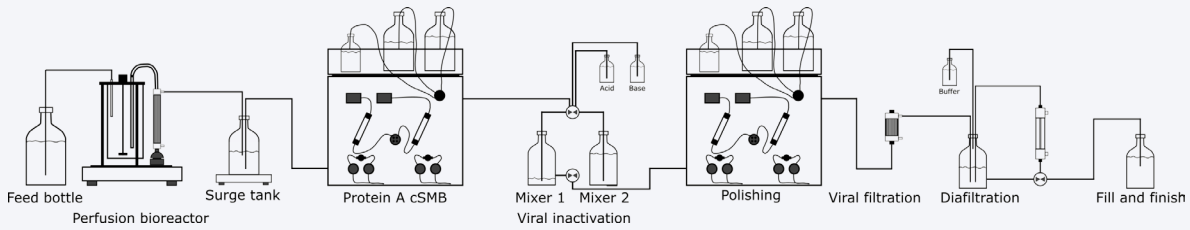

Figure 1: *ICB overview*

In all analyses performed, the antibody generated using the continuous platform had a comparable quality profile during the entire production run. In-depth analyses revealed that the Drug Substance produced by continuous manufacturing even outperformed Herceptin for some quality attributes. One can conclude that the continuous production line is able to meet the current standards in bioprocessing.

It is the intention to extend this study further downstream by applying the lyophilization technology of Rheavita.

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Conclusion

As it leads to increased efficiency, reduced waste, reduced floorspace needs, a faster time-to-market, scalability, and the ability to scale from small to large volumes directly, continuous manufacturing is a valuable investment for companies looking to stay competitive and meet customer demands. Furthermore, the gains in energy consumption during production and the transportation of freeze-dried drug products (as opposed to their frozen counterparts) cannot be ignored. As the demand for (bio) pharmaceuticals grows, companies must consider the advantages of continuous manufacturing and its impact on the bottom line.

The trend towards more personalized medicines will lead to smaller production volumes and require a more flexible production capacity. That need for flexible production capacity can be met by implementing continuous (freeze-drying) processes instead of sticking to existing batch processes.

Contact us to discover how our continuous freeze-drying process can benefit your drug development and production.

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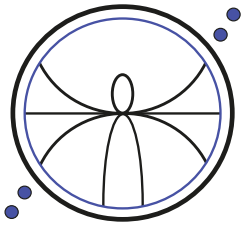

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