

Whitepaper

Pioneering innovation in pharmaceutical lyophilization



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Executive summary

Lyophilization, or freeze-drying, is increasingly critical in pharmaceutical manufacturing, particularly for the stability and viability of sensitive biopharmaceuticals and vaccines. As these complex formulations continue to play a pivotal role in modern healthcare, the industry faces the challenge of maintaining their efficacy throughout storage and distribution without reliance on extensive cold chain logistics.

The process of lyophilization involves meticulously controlled stages — freezing, primary drying, and secondary drying — that require precision to ensure the final product's integrity. Despite its benefits, the technique presents significant challenges, including the need for high energy consumption, sophisticated equipment, and specialized knowledge to manage the freeze-drying cycle effectively. Furthermore, as the demand for biopharmaceuticals grows, the industry must scale up these processes efficiently while adhering to stringent regulatory standards.

This whitepaper examines lyophilization as a strategic solution to these challenges, providing insight into the following considerations:

- The pivotal role of lyophilization in enhancing the stability and accessibility of sensitive pharmaceuticals, enabling global distribution without stringent cold chain requirements.
- Detailed analysis of the lyophilization process stages, emphasizing the importance of precision in freezing, primary drying, and secondary drying to ensure product integrity.

- The expanding market demand for lyophilization services offered by CDMOs, driven by advancements in biopharmaceuticals and the critical need for regulatory compliance.
- The value of strategic CDMO partnerships in advancing drug formulation and lyophilization process optimization, enabling the pharmaceutical industry to meet global health challenges with innovative solutions.

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Enhanced stability and accessibility through lyophilization

Innovation in the biopharmaceutical industry has led to the development of many types of drug substances that are remarkably effective as therapeutics yet inherently unstable when exposed to environmental factors, such as air, moisture, and temperature fluctuations. Lyophilization, commonly known as freeze-drying, has emerged as an essential technology to address these challenges. It not only safeguards the therapeutic efficacy of medications but also prolongs their shelf life, which is crucial for ensuring that these lifesaving treatments are delivered in their most active and potent form to patients, regardless of distance or location.

Through lyophilization, drugs are rendered more stable by converting them into a dry form that is less prone to degradation, thus retaining their potency over extended periods and under various storage conditions. This technology is particularly pivotal for vaccines and biologics, playing a critical role in sterile fill-finish processes and making these vital treatments more accessible, especially in regions where there is a critical need, but cold chain logistics are not feasible.

By meticulously removing water content without altering molecular structures, lyophilization prevents many potential biological and chemical reactions that could otherwise compromise drug quality. Consequently, it enables the storage and transport of sensitive medications at ambient temperatures, eliminating the need for cold chain infrastructure, packing materials, and expertise, which can be a game-changer for delivering advanced therapeutics to remote and under-resourced areas. The versatility of lyophilization also extends to a broad spectrum of pharmaceuticals, from established biologics to novel personalized treatments like cell and gene therapies, underscoring its role as a cornerstone of modern drug delivery systems.

Overview of lyophilization process stages

Lyophilization, a tightly controlled freeze-drying process, is executed in three primary stages: freezing, primary drying (sublimation), and secondary drying (desorption). Each stage is critical to the integrity of the pharmaceutical product, demanding thorough characterization studies to achieve unparalleled product quality.

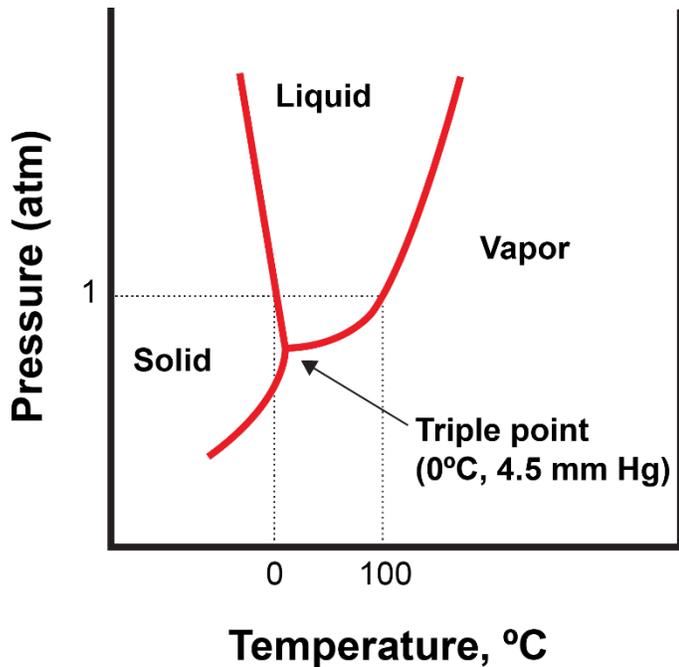
Stage 1: Freezing. In a specially designed lyophilization chamber, the liquid drug is cooled at specific rates below its critical temperatures — either the eutectic or collapse point — to form a solid matrix that will allow the vapor to be removed during drying steps. The careful design of this freezing process sets the stage for successful drying, as the structure of the “frozen cake” directly affects subsequent processing steps.

Stage 2: Primary drying (sublimation). Within the controlled environment of the chamber, pressure is decreased, and heat is introduced to prompt sublimation, transforming ice directly from solid to vapor without passing through a liquid phase, expelling the bulk of the water content from the product to be then captured on the condenser coil system.

Stage 3: Secondary drying (desorption). The final drying phase escalates temperatures to drive off water molecules still bound to the drug substance and excipients in the cake, completing the dehydration process and securing the stability of the drug substance.

The process relies fundamentally on the principles depicted in the water phase diagram (**Figure 1**), which maps the states of water under varying temperatures and pressures, including the triple point where solid, liquid, and vapor phases coexist (a temperature of 0 °C and a pressure of 6.11 mbar). Understanding the triple points for materials in a drug formulation is vital for tailoring the lyophilization parameters to the unique requirements of each drug formulation, thereby safeguarding its potency and efficacy.

Figure 1. Phase diagram for water



Throughout each phase of lyophilization, precise control of chamber temperature and pressure is indispensable to achieve optimal quality of the final dried drug product, underscoring the need for bespoke settings for each specific drug entity. Considering that every lyophilization cycle is unique, formulation and process conditions must be customized for each drug substance.

Recent advancements in lyophilization technology have helped improve its efficiency, scalability, and quality in pharmaceutical applications. Innovations such as improved automation, rigorous monitoring, and sophisticated control systems now facilitate the processing of even the most delicate therapeutic substances and complex vaccine formulations, ensuring high-quality outcomes at scalable volumes.

Growth trajectory of the lyophilization services market

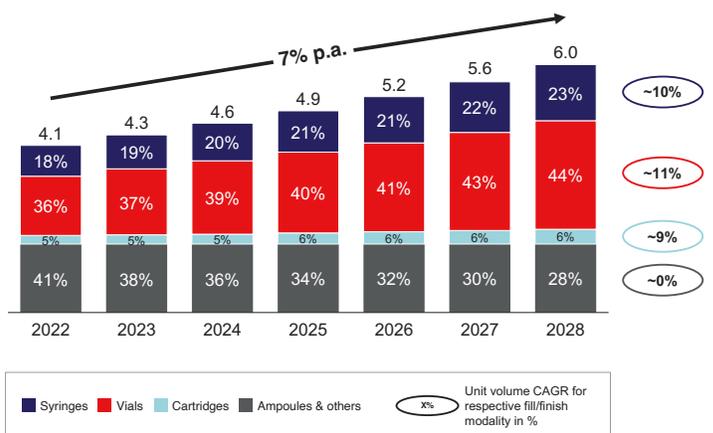
The demand for fill-finish services provided by contract development and manufacturing organizations (CDMOs) is on a notable upward trajectory. Market analyses forecast a growth from approximately 4 billion units in 2022 to an estimated 6 billion units by 2028,

underscoring the expanding role of CDMOs in this domain (**Figure 2**). In 2022, vials accounted for 36% of packaging formats, trailing only slightly behind syringes at 41%. Current trends, however, indicate a shift: The demand for vials is surging, projected to represent 44% of total units by 2028, with syringes diminishing to less than a third at 28%.

This surge is paralleled by an increase in the lyophilization of vials, with around half of all vials currently undergoing this process. This demand is expected to intensify, spurred by the proliferation of both traditional biologics and a burgeoning pipeline of emerging therapies advancing through the clinic to commercialization. Consequently, lyophilization capacity is anticipated to expand significantly.

Additional drivers for demand growth for lyophilization CDMO services include evolving regulatory frameworks that streamline the approval process and an increasing reliance on CDMOs by biopharmaceutical companies. These companies are turning to CDMOs for their expertise in formulation and process development, leveraging this partnership to accelerate the journey from laboratory development to commercial viability and patient accessibility.

Figure 2: Projected annual volume of doses per modality¹



Overcoming lyophilization hurdles to optimize quality

Developing optimal lyophilization processes is no easy task. Several challenges must be navigated to ensure the production of freeze-dried drug products of the highest possible quality. The primary concern is to lyophilize heat-sensitive substances without compromising their integrity. Processes must not only be robust and reliable to deliver uniformity from laboratory to full-scale production, but they should also safeguard against contamination to preserve sterility — all while minimizing energy consumption and environmental impact.

Recent innovations in lyophilization have been developed to ensure the success of complex lyophilization processes:

- **Thermal protection:** The deployment of specially formulated stabilizers and protectants defends against heat-induced degradation, critical for the preservation of delicate molecules during freeze-drying.
- **Analytical precision:** Cutting-edge analytical methods facilitate a thorough examination of a drug's chemical and physical attributes, leading to the formulation of stable drug products through accelerated stability testing.
- **Process control:** The incorporation of process analytical technology (PAT) tools, alongside intelligent sensors and sophisticated algorithms, affords real-time monitoring and precise control over the lyophilization cycle, meeting exacting quality standards.
- **Scalability and adaptability:** Scalable platforms and modular designs enable seamless scaling from small clinical batches to larger commercial quantities while maintaining high-quality output, showcasing the process's adaptability to changing demands.
- **Automation:** State-of-the-art lyophilization equipment, featuring automated loading and unloading mechanisms, boosts efficiency. These machines are designed with optimized

shelving to ensure uniform heat distribution and to accommodate diverse vial sizes, guaranteeing consistent quality treatment for each unit.

- **Sterility and contamination control:** Advanced lyophilizers equipped with isolator technologies, along with automated vial capping systems, significantly reduce contamination risks, further ensuring the sterility and integrity of the final product.
- **Energy efficiency:** Energy-efficient lyophilizers with energy recovery systems contribute to a greener production by curtailing energy use and diminishing ecological footprints.

Ensuring compliance and control in lyophilization

Optimizing lyophilization processes is only one part of the equation; ensuring that these processes comply with stringent regulatory standards is crucial for delivering pharmaceutical products that are safe, effective, and of the highest quality.

Adherence to regulatory guidelines is non-negotiable. Organizations must rigorously follow the current relevant guidelines set forth by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), such as Annex I and ICH Q8, which cover many aspects of pharmaceutical freeze-drying — from process control and equipment to product quality.

The importance of thorough process validation cannot be overstated. Comprehensive documentation that verifies consistency and replicability is a cornerstone of regulatory compliance. Employing a quality by design (QbD) framework ensures that lyophilization processes are not only efficient but consistently yield high-quality results since they have been designed on a thorough understanding of the process.

Effective quality control is achieved by implementing rigorous quality checkpoints throughout the lyophilization cycle. These controls are supported by extensive testing at each process stage, ensuring the product's uniformity and integrity from start to finish. Modern analytical techniques, backed by robust

statistical methods, are essential tools in maintaining this high level of quality control, assuring that each product meets exacting quality and safety benchmarks.

Furthermore, to meet regulatory requirements for product stability and sterility, advanced lyophilization technologies must be utilized. These technologies facilitate adherence to the highest standards of safety and efficacy for the final drug products to protect patient health.

Detailed lyophilization process development

Lyophilization process development is a complex endeavor, demanding a highly focused and strategic approach. Such meticulous development is crucial for crafting freeze-drying processes that ensure the sterility and stability of water and temperature-sensitive drug substances.

Development commences with pinpointing the optimal formulation. The pre-formulation phase involves a rigorous screening of excipients to establish those that bestow stability and enhance the solubility of the drug substance. A diverse range of buffers, surfactants, co-solvents, bulking agents, and cryo-/lyoprotectants are scrutinized. Design of experiment (DoE) techniques, coupled with stability studies, aid in determining the precise quantity of each excipient to ensure long-term stability and performance.

The next phase involves cycle optimization, in which the freezing and drying steps are fined-tuned to obtain optimal product quality (appearance, final water content, stability, reconstitution time) and process efficiency (reduced drying temperature and time). Sophisticated modulation of freezing conditions facilitates control over nucleation and ice crystal formation, enhancing product uniformity. Techniques such as differential scanning calorimetry and thermal gravimetric analysis provide the thermal characterization data critical for this phase.

Application of advanced PAT is pivotal in enabling real-time monitoring of critical parameters, further refining the process. Manometric temperature measurement,

among other analytical methods, is deployed to ensure accurate end-point determination and consistent batch-to-batch quality.

Throughout each stage of development, a commitment to detail and deep-seated expertise is indispensable. It is these qualities that underpin the successful development of lyophilization processes that are not only efficient but also yield products of exceptional quality.

Case study: Streamlining the scale-up of a sensitive small molecule antibiotic

Thermo Fisher Scientific's lyophilization expertise was put to the test with a small molecule API known for its sensitivity to common pharmaceutical process conditions, such as oxygen exposure, contact with stainless steel, heat, and moisture. Previously successful on a smaller scale, the challenge was to optimize and scale up the process for commercial production while maintaining the delicate balance required by the compound's reactive nature.

The initial production process involved intricate steps, such as nitrogen sparging to mitigate oxygen exposure and the measurement of dissolved oxygen to avoid oxidation. Additionally, the presence of sodium hydroxide in the formula created pockets of high pH, necessitating a precise control of the solution's acidity. The process also demanded stringent hold times for quality control, which presented risks for batch integrity and called for additional validation procedures.

Thermo Fisher's solution was a collaborative and dynamic approach to process optimization involving tight coordination between operational and quality control teams. Detailed batch records and a bespoke operator training guide were developed to ensure flawless execution. Direct engagement with the client facilitated swift, informed decision-making onsite.

The result of these efforts was a robust, scalable process that led to the successful completion of three validation batches, signifying regulatory compliance and readiness for commercial scale-up. This enhanced process was not only effective but also replicable, allowing for its adoption at another production site, establishing a dual-source capability for the small molecule's commercial launch in 2020.

Effective lyophilization is an essential enabler of pharma industry innovation

Efficient lyophilization processes that increase the stability of sensitive and complex pharmaceutical drug substances are central to increasing patient access to many of today's advanced therapeutics and vaccines. Freeze-drying helps ensure maintenance of drug effectiveness across varying storage and transport conditions and enables the distribution of sensitive medications around the world, including to remote locations lacking cold chain management infrastructure.

References

1. Adapted from Markets & Markets Fill Finish Manufacturing Market Global Forecast 2022
2. [“How sterile pharma manufacturers can grow capacity without capital investment.”](#) McKinsey & Company. Mar. 2023

Recent technology innovations, including automation, energy-efficient solutions, advanced monitoring and control systems, and extensive formulation development and cycle optimization expertise are enabling implementation of lyophilization processes with significantly greater efficiency and scalability. These capabilities must also be supported by a commitment to regulatory compliance and quality control, with strict adherence to stringent pharmaceutical standards around the world.

Strategic partnerships have been instrumental in driving innovation in drug formulation and lyophilization process optimization. Looking ahead, these collaborative ventures in research, development, and quality improvement will remain instrumental in the evolution and enhancement of lyophilization processes, further empowering the industry to meet health challenges with innovative solutions.

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