



WHITEPAPER

# High Containment for Lyophilization

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# A Brief History of Lyophilization

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Lyophilization is an important concept in today's pharmaceutical and biopharma industries, but it's actually a years-old process that dates all the way back into the late nineteenth century.

Lyophilization transforms drug products and substances from a liquid to a stable solid by removing water or other solvents. It works based on a simple principle of physics called sublimation. Sublimation is the process of transitioning a substance from a solid to a vapor state without passing through an intermediate liquid phase. Drug developers have been interested in this technique for years as it can extend the shelf life of both small and large molecule drugs.

Freeze drying as an industrial process began as early as 1890 by Richard Altmann who devised a method to freeze dry tissues (either plant or animal), but went virtually unnoticed until the 1930s.<sup>[1]</sup> A major milestone for freeze drying then occurred during World War II, with the need for significant amounts of blood plasma and penicillin to treat the wounded in the field. Because of the lack of refrigerated transport, much of the supplies ended up spoiling before reaching their patients, thus the freeze-drying process was developed as a commercial technique. The freeze-dried blood plasma and penicillin were then rendered chemically stable and viable for transport without refrigeration. In the 1950s–1960s, freeze drying began to be viewed as a multi-purpose tool for both pharmaceuticals and food processing.<sup>[2]</sup> Nowadays, almost every pharmaceutical and biopharma lab in the world are using lyophilization in their daily processes. Some of the typical pharmaceutical products that would undergo lyophilization include bulk pharmaceutical/biopharmaceutical ingredients, protein, collagen, peptide, oligonucleotides, chemical API, enzymes, and mAbs.

# Advantages & Disadvantages of Lyophilization

Given the adverse effects of heat and water on long-term storage of materials, lyophilization is often the best solution for drug products. Besides increasing shelf life, freeze-drying products also reduces their weight and volume, which can cut down on storage and shipping costs. Lyophilization can also remove the need for refrigerated transport, as the freeze-dried products are more stable at room temperature. From sample stability and purity to increased shelf life and reduced costs, lyophilization is a convenient, safe, and efficient method for long-term storage of drug products and substances. Let's take a look at some of the advantages and disadvantages of lyophilization, according to the FDA<sup>[3]</sup>:

## Advantages of Lyophilization

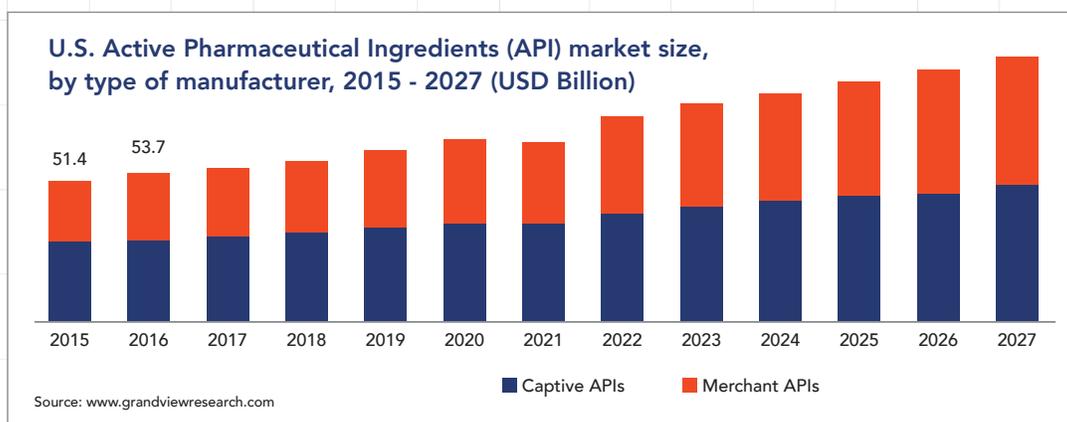
- *Removing water without having to heat the product excessively*
- *Dissolution of reconstituted product (rapidly and easily)*
- *Enhancing the stability of a dry powder as well as the product stability in a dry state*

## Disadvantages of Lyophilization

- *Handling and processing time*
- *Expensive and complex equipment*
- *Sterile diluent needed upon reconstitution*

# Market Landscape

Over the past decade, pharmaceutical and biopharmaceutical CMOs have seen a huge shift in their manufacturing schemes, from producing lower quantities of a single API or drug product to now an increased demand for larger amounts of multiple types of APIs and drugs processed all under one roof. These changes have affected nearly all layers of organizations within the industry, including the manufacturing processes and the need for complex equipment trains in order to remain competitive to this new demand.



As the market for contract manufacturing continues to grow, so does the need for larger amounts of Highly Potent Active Pharmaceutical Ingredients (HPAPIs) and drug products. Suppliers are starting to find the growing market extremely attractive for investing in new containment facilities and associated equipment. CMOs who offer commercial-scale highly potent drug manufacturing services are expanding their capacities even more to keep up with the demand. Likewise, HPAPI producers have increased their capacities as well.

Over the next decade, the HPAPI drugs market is expected to see an enormous growth due to all of the upcoming patent expirations. Also, there is an increasing trend of pharma companies coupling with a single partner who can provide HPAPI development and manufacturing services all in one location, thus reducing the overall time and drug development costs.

# HPAPI Lyophilization Trends

The ever-expanding market is leading to an overall limited outsourcing capacity especially for lyophilized HPAPIs and drug products. Many cancer drugs are being classified as highly potent, cytotoxic compounds. The growth in the oncology segment is, therefore, driving demand for HPAPIs. Market estimates project the value of the global HPAPI market to be expanding at a CAGR of 8.5% to exceed \$28 billion by 2024.<sup>[4]</sup>

Some of the emerging trends and growth drivers in the lyophilization space are:

- More complex drug formulations that are not stable in liquid form
- Growth in Oligonucleotides and Peptides, which degrade in liquid form
- Rising demand for highly potent lyophilized products
- Technological advancements in lyophilization containment strategies
- Growing demand for superior products with longer shelf life and stability

According to BCC Research, 16% of the top 100 pharmaceutical drugs are lyophilized and 35% of biologic drugs are lyophilized.<sup>[5]</sup> With more than 30% of the FDA-approved parenterals lyophilized and soon more than half injectable drugs to require lyophilization, there is a ton of room for further standardization and expansion of freeze-drying processes in highly potent products and materials.<sup>[6]</sup>

The rising demand for freeze drying of highly potent materials from research scale to commercial production is definitely something to look forward to if you're a CMO, but with that also comes an increased demand for proper containment measures and prevailing issues, such as covering overall costs, increasing operator safety, and protecting the quality of the final product. ILC Dover is a world leader in the innovative design and manufacturing of single-use flexible containment systems for lyophilizers. Let's take a look at some of the benefits of a flexible system and how ILC Dover can easily retrofit isolation to existing equipment, or even provide custom solutions for your new lyophilization process.

# Single-Use Solutions for Lyophilization Containment

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Lyophilization of highly potent products has been a challenge for manufacturers as the industry grows. The ability to maintain operator safety throughout the entire process has created new demands to guarantee protection from contamination of personnel and the lyophilized product, and to assure final product quality. Whether using pilot scale lyophilizers for R&D purposes or commercial systems, the operator's ability to handle the vials and trays can potentially create multiple issues that arise during production, including risks of potential exposure and even product loss if mishandled during the transfer process. Traditional solutions using hard wall isolators that are usually very costly, difficult to maintain and clean, and require multiple operators to work simultaneously which often causes ergonomic issues for the team.

All of these problems with traditional hardware can be addressed with single-use containment and retrofitting onto existing equipment has never been easier or more cost effective than now.

# Protecting People, Product, and Environment with Flexible Isolators

As many already know, isolation technology is a requirement when dealing with highly potent products, but there are many challenges to providing sufficient containment when working with lyophilizers and their processes. Whether your company is using traditional hard wall or single-use systems, isolators protect the product from cross-contamination while also protecting the operators and surrounding environment from any HPAPI particles during the transfer process. Any upset conditions with highly potent materials can pose major risks of cross-contamination, operator safety, and the environment in general.

ILC Dover's solution is using single-use flexible isolators during lyophilization, which can adapt to any system typically without re-qualification, can be easily managed during operator activity, thus providing much better ergonomic benefits to production teams, and also has much lower associated costs related to capital expenditure and maintenance.



# Cost Savings and Reduced Cleaning Validation

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There has been a growing idea that single-use isolators will always result in a lower capital cost to purchase, install, and maintain when compared to traditional hard wall isolator systems, which is entirely correct. But the idea goes on to say that purchasing the actual consumables, or the single use components of the single-use isolator, will eventually add up and the cost benefit will diminish over time, which is entirely inaccurate! The fact is that not only is there a dramatic cost avoidance and savings, but the ongoing costs of operating with single-use isolator systems have even further costs saving overtime.

For example, sophisticated cost modeling programs by BioPharm Services Ltd. and BioPlan Associates are used to evaluate the entire project considering all of the cost components.

The main drivers of the cost components usually include labor, cleaning time, cleaning materials, and handling of liquid waste materials. The downtime of the equipment during cleaning is also considered as a major impact. In most cases it has been found that analyses will result in the value proposition for using a single-use option over traditional hard wall systems in every scenario.

As a different approach, Allergan has been known to use the ROHSEI cost model to evaluate the return on investment for implementing a containment solution in a pharmaceutical process. ROHSEI was a program developed by a collaboration of Fortune 500 companies to give their safety teams a tool to make a business case for changes and improvements needed. The Allergan model is specific only to containment strategies and the variables can be changed for a single-use or hard wall system resulting in the expected ROI.

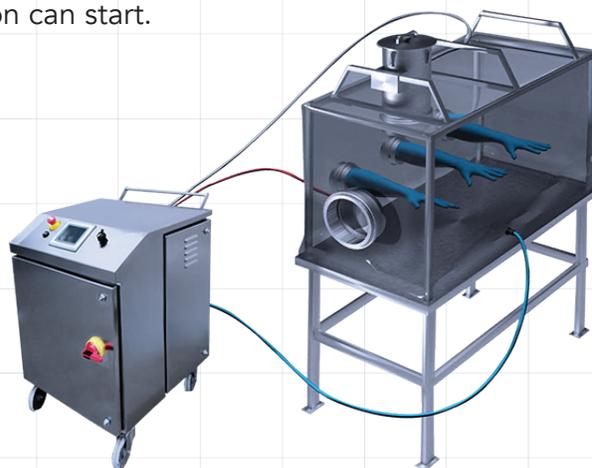
**In all of these cases, it is seen that single-use systems offer the best value.**

# Lyophilizer Solution Examples and Containment Designs

When thinking about the transfer technology associated with single-use systems for lyophilization, ILC Dover has solutions to address all transfer needs, such as flexible pass box systems, rapid transfer ports (RTP) for efficiently transferring materials in/out of the flexible isolator, bag in/bag out (BIBO) systems allowing for multiple transfers of large materials, split butterfly valves for aseptic transfer of small amounts of materials, and even the Beta Bag system for transferring large amounts of materials in an aseptic environment if needed.

The single use isolator is a real advantage when preparing for a production batch. Each isolator is a complete assembly and combined with the transfer system can be integrity checked in a simple way before use. One of the challenges with all isolator technology is the risk of a failure in a glove. The risk of a tear or puncture is the same with durable and single use isolators since they use the same glove materials and thickness. On the other hand, durable isolator gloves can fatigue from use based on the tasks that are performed and the chemical attack from cleaning. This causes for on-line testing of the gloves to assure integrity, wasting time from production to do these tests. Gloves used with single use isolators are integrated at the factory and integrity tested. A quick standard test at assembly of the single use isolator will confirm production can start.

From small-scale R&D lyophilizers requiring adaptable isolation systems to large-scale cGMP operations requiring isolation coupled with Grade A or B environments, there are cost-effective solutions for every facility and team.



# Single-Use Products are the Most Sustainable Option

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With the continuous growth of single-use systems in pharmaceutical and biopharmaceutical processes like lyophilization, it has been growing even faster than the projected CAGR for each of those markets. The main reason this is happening is because most of the new processes are using single-use systems and many of the existing processes are converting over to single-use systems as well.

This emerging trend is based on an evaluation of costs and risks. From a cost standpoint, it has already been mentioned that detailed studies have been done to prove that single use systems reduce the overall costs for cleaning stainless steel systems including labor, generating cleaning water, solvents or detergents requirements, and handling the toxic waste materials. The risks have also been mentioned but really should be highlighted. When a product contamination occurs, it can be more costly than just a lost batch or production time. The issues associated with product recalls and corrective issues are significant. Any effort to reduce the risk of a contamination is significant.

Focusing on the bigger picture, the ever-increasing use of plastics has raised concerns on sustainability and environmental impact. It may not seem intuitive, but recent life cycle analysis (LCA) reports show that single-use products have a much greener footprint than using stainless steel products. In the recently published *The Green Imperative* by authors and the Bio-Process Systems Alliance (BPSA) Sustainability Sub-Committee[7], it was found that "On average, SU facilities are more ecofriendly than traditional (durable) facilities in 18 distinct categories of environment pressures". This study was specific to a Biopharma facility and not just a unit operation, but the point is taken that an LCA is important to understand the complete picture of the value of a single-use system.

The bottom line is that flexible containment solutions for your lyophilization process means increasing your overall profit. Minimizing cross-contamination to ensure product integrity and maximizing containment to ensure operator safety are all sustainable features of single-use isolation technology that your company deserves well into the future.



## BEYOND BOUNDARIES™

ILC Dover is a world-leader in the innovative design and production of engineered flexible protective solutions, for pharmaceutical and biopharmaceutical, flood protection, personal protection, bulk packaging, and aerospace industries. Our customers will attest to our relentless dedication to high value products, advanced technology, and responsive service, as our visionary solutions have improved efficiency while safeguarding people, product, and infrastructure in hazardous conditions through flexible protective solutions since 1947.

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