Saving Millions of Dollars and Reducing Time to Market with the Right Lyophilization Tools

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This article is organized into three sections. Firstly, we describe the growth of the freeze-drying industry, and the challenges of controlling and scaling-up the freeze-drying process. Following this, we detail the tools that are available for both development and production lyophilizers, and how each of these improve the control of the freeze-drying process. Finally, we discuss the financial incentives of incorporating these tools and explain how they deliver good Return on Investment (ROI).

Growth of the Freeze-Drying Industry

The biopharmaceutical industry continues to grow rapidly, driven by more specialized treatment protocols and the development of complex biological drugs and cell and gene therapies. The biologics market is faced with several challenges, namely: costly active pharmaceutical ingredients (APIs); complex molecules; and challenging lyophilization development cycles.

Recent data indicates that over 41% of biological drug products require lyophilization to retain their native physical structure. In fact, many biological products are unstable in a liquid form and must be freeze-dried to provide long-term stability. Almost all antibody-drug conjugates (ADCs) are lyophilized to ensure the stability of the linker that joins the "payload" to the antibody during storage and transport.

These new products are expensive to develop but have tremendous potential to cure formerly incurable diseases. The lyophilization process is therefore, an essential element, and it must be scalable, to give manufacturers consistency in their product - from initial formulation and development, through clinical trials, to full commercial manufacturing.

In order to achieve quality products consistently, tools must be produced that offer a stable and reliable freeze-drying cycle, and which enable users to understand every phase of the production process.

The Importance of the Operating Space

For optimal product performance, global regulatory bodies strongly recommend a systematic approach to drug manufacturing called Quality by Design (QbD). This methodology requires establishing a design space with sets of operating variables needed to maintain product batch consistency and repeatability. These variables are represented graphically as multi-dimensional points that roughly form a triangle depicted in Figure 1. The limitations of freeze dryer performance or equipment capability form the left side and formulation limitations on the right. Any region below the intersection of these two lines is termed operating space and will result in an acceptable and compliant product. Any deviation to the left or right of the operating space will result in product failure.

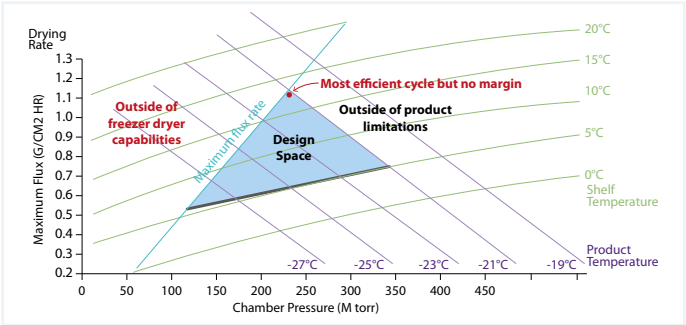


Figure 1: *Operating Space*

Without the proper tools to monitor the process, production personnel do not have a clear indication if their product fits within or outside of the process operating space as illustrated in Figure 2.

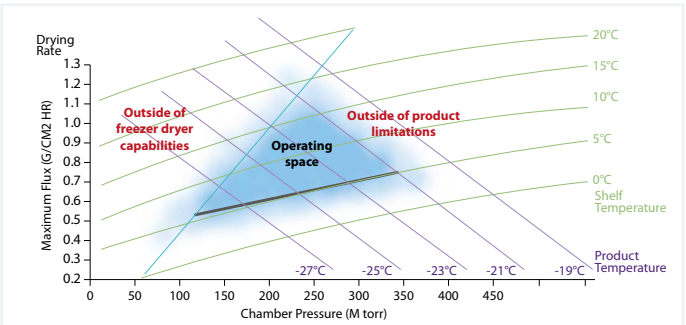


Figure 2: *Production's Traditional View of Operating Space. The blurred area outside of the operating space triangle is a depiction of a small number of vials that product quality may have been compromised.*

The following discussion will explain how the SP Line of Sight™ range of tools solves this issue, and provides real-time data so the production supervisor understands the precise condition of the product through every phase of the freeze-drying cycle.

The Challenges of Freeze-Drying Products

In order to create a consistent, reproducible biopharmaceutical product, the development and implementation of the lyophilization process must be controlled. Common challenges include:

Collapse temperature – The challenge for product development is to understand the product collapse temperature (T_c) and other critical thermal characteristics of the formulation such as the glass transition temperature, T_g' or eutectic temperature, T_{eu}.

Cycle development time – The development of the freeze-drying cycle can require many repetitive runs to optimize the design space with sufficient safety factors to account for process variations that may occur during scale-up.

Melt-back – Excessive heat can cause melt-back when the primary drying phase has ended before the ice at the bottom of some of the vials completely sublimes.

Understanding vapor port limitation – Choked flow condition (vapor port constraint), is when the flow of vapor is impeded by the dryers capability, possibly resulting in the collapse of the cake.

Uncontrolled (stochastic) nucleation – Without nucleants, the purity of the product delays the freezing process beyond its normal freezing temperature. The freeze-drying recipe must continue to lower the chamber temperature until all the vials within the batch nucleate. This super cooling effect creates smaller ice crystals and increases product resistance (R_p), which restricts the vapor path required for drying, resulting in longer product cycles and reconstitution time.

Need for real-time data – In the absence of real-time data, it is challenging to understand and monitor the freeze-drying process.

As the quantity of product increases during product development, scale-up and testing, these challenges intensify. However, with the right tools on the development freeze dryer as well as the production units, these obstacles can be minimized or eliminated.

Proven Tools to Improve the Freeze-Drying Process

The following Line of Sight™ tools help the scientist defines the optimal design space, so the production supervisors can monitor process sensors to ensure product quality attributes compliance during the freeze-drying cycle. They are available for both development lyophilizers and production units.

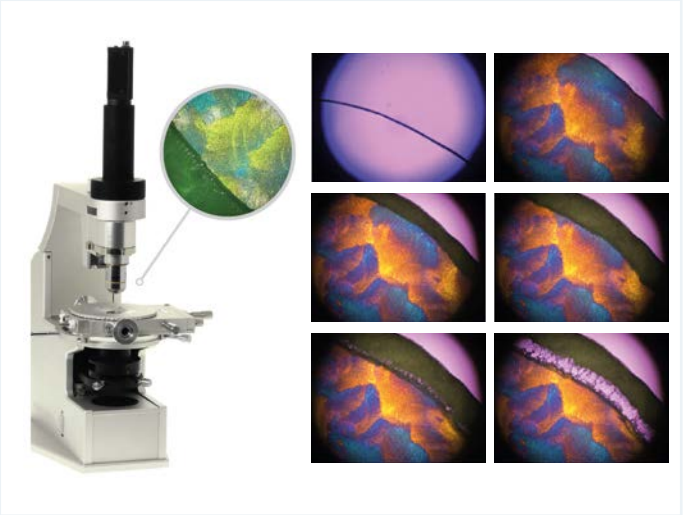


Figure 3: *Freeze-Drying Microscopy (FDM)*

1. The Freeze-Drying Microscope

The freeze-drying microscope (FDM) is essential to understand product collapse temperature and critical thermal characteristics of the formulation.

Every freeze-drying formulation has a critical temperature, which should not be surpassed at any time during the primary drying, in order to prevent product defects. The freeze-drying microscope allows the sample structure to be observed during freezing and drying so the exact point of collapse can be determined. Following analysis, formulations and cycles can be developed that are safe, robust, and cost efficient. Understanding this product characteristic is critical, as freeze-drying efficiency improves by approximately 13% for every 1°C increase in the shelf temperature set point.

2. TEMPRIS* Wireless Sensors

To obtain accurate and reliable measurements, sensors must be properly secured to the bottom center of the vials, however placing traditional wired thermocouples (TCs) and maintaining the sensor position with trailing wires is extremely challenging. Tempris* wireless sensors provide a means to monitor the temperature of a product, in real-time without the need for wires.

Additionally maintaining batch sterility is critical for validation or production batches intended for release to prospective patients. The sensors must be cleaned and sterilized to prevent product contamination. Manually positioning wired thermocouples greatly increases the risk to product sterility. Furthermore, wired thermocouples are incompatible with automatic freeze dryer loading and unloading systems at the production scale.

Tempris sensors have the following advantages:

- Wireless temperature measurement
- Compatible with autoloaders
- Available from development scale to full production
- Battery free
- Sterilizable
- Reusable

Figure 4: *Tempris Wireless Sensor for Product Temperature Measurement*

The wireless and battery free Tempris* sensors can be applied on all scales of lyophilizers, providing the most comparable and consistent real-time temperature measurement.

3. SMART* Freeze-Drying Technology Primary Drying Optimization Tool

The goal of any production scientist is to develop a product that is of a high quality and safe to use while minimizing production time and costs. In short, scientists aim to:

- Optimize freeze-drying cycles in less time
- Eliminate trial-and-error approaches to cycle development
- Infer critical data, such as cake resistance and product temperature, non-invasively

SMART* Freeze-Drying technology is a primary drying optimization software and process analytical technology (PAT) enabling you to jumpstart cycle development using known data that is batch representative.

With patented manometric temperature measurement (MTM) - a technique for measuring pressure increase - SMART-MTM determines freeze-dried cake resistance and product temperature at the ice interface, among other parameters. These attributes are critical to understanding the long-term product stability. SMART* technology can shorten the freeze-drying development process by approximately 10 weeks (as illustrated in Figure 5), by eliminating the trial-and-error approach normally involved in developing new lyophilization cycles. It provides an efficient and robust process which enables experts and novices alike to develop new freeze-drying cycles quickly, while ensuring the highest product quality .

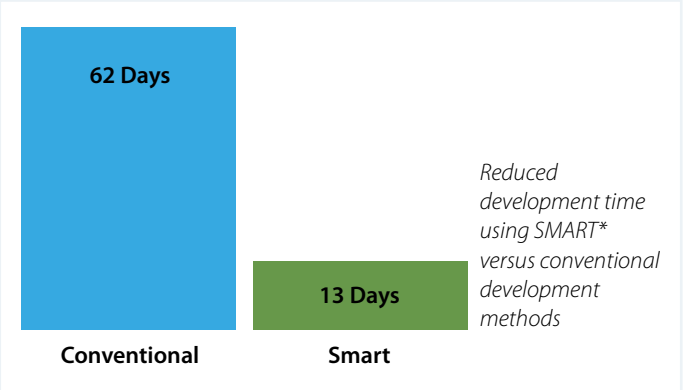


Figure 5: *Comparison Between Conventional Freeze-Drying Cycle Development and Utilization of SMART* Freeze-Drying Technology*

4. LyoFlux* TDLAS Sensors

The LyoFlux* system by Physical Sciences, Inc. is a PAT tool that uses tunable diode laser absorption spectroscopy (TDLAS) to accurately measure water vapor concentration, gas temperature, and gas flow velocity throughout the freeze-drying process. Laser transmitters and receivers are mounted outside the vapor port to prevent interference with vapor flow from the chamber to the condenser. Available on laboratory as well as production lyophilizers, it can be used for numerous applications in designing and monitoring freeze-drying processes including:

- Determination of batch average product temperatures, T_p
- Product temperature at bottom, T_b
- Primary and secondary drying process endpoint detection
- Determination of vial heat transfer coefficients, K_v – the most critical factor in scale-up / down
- Determination of product dry layer resistance to drying, R_p
- Equipment capability limits – choked flow (maximum sublimation rate, dm/dt vs pressure)

Operating Space with Safety Margin

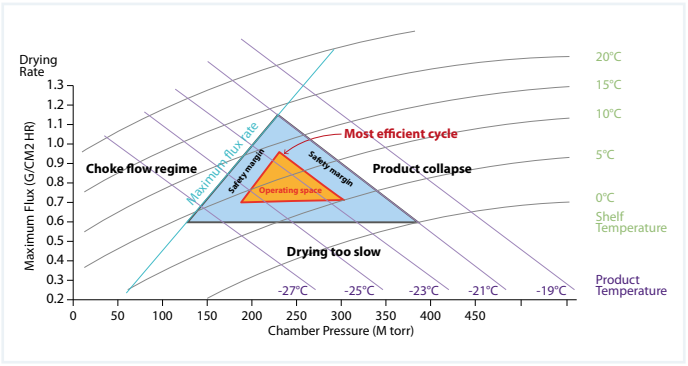


Figure 6: *Graphical design space indicating the optimal cycle with safety margin*

The heat transfer coefficient, K_v, is a critical factor in determining the operating space parameters. K_v is traditionally determined gravimetrically and requires multiple experiments at varying temperatures and vacuum set points. To support the journey to market, K_v determination can be conducted in a single LyoFlux* sensor experiment. By varying pressure over time to obtain the sublimation rate at the respective pressure set points, any disruption of production freeze dryer schedules can be minimized.

Reduction in the number of experiments from at least four to five experiments to just one is a cost saving activity, a saving of three to four folds and minimize operation downtime due to the use of the filling suite and equipment.

For contract manufacturing organization (CMO) or contract development manufacturing organization (CDMO), these tools are an added value for the end users because of the valuable data and product understanding generated by the process.

LyoFlux is a registered trademark of Physical Sciences Inc., Andover, MA, USA and used by permission.*

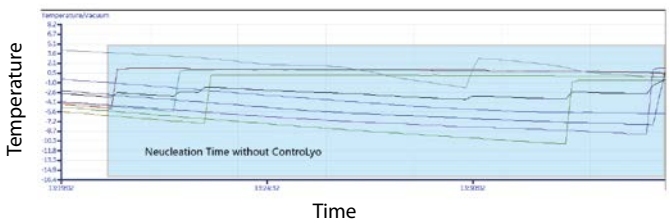
5. ControLyo® Nucleation Technology

ControLyo® provides precise control of nucleation, a freezing process once considered uncontrolled. This is accomplished by over-pressurizing the chamber with nitrogen or other inert gases, while lowering the temperature of the product to the optimal freezing temperature. Following a rapid reduction in pressure, all vials will nucleate at exactly the same time, regardless of their position within the chamber, and without the introduction of foreign material. Controlled ice nucleation offers several advantages, such as:

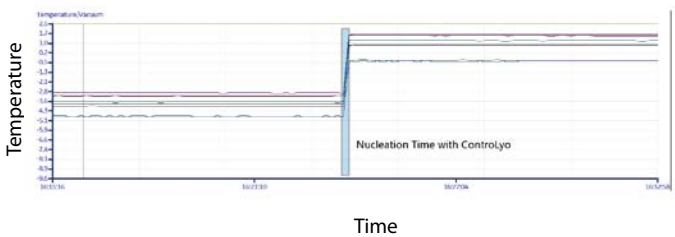
- Delivering a fully homogeneous batch with less quality rejects and higher cake visual quality
- Enabling nucleation at higher temperatures leading to:
  - Larger ice crystals
  - Shorter primary drying time
  - Reduced vial breakage
  - Enabling freezing of high protein concentration formulations

Without ControLyo®, each of the vials in a freeze dryer supercools to a different temperature before nucleating. This freezing process can sometimes take as long as 45 minutes or longer before all vials have nucleated. Smaller ice crystals are formed if the product nucleates at a lower temperature which, in turn, creates smaller pore channels leading to higher product resistance to vapor flow. As a consequence, the freeze-drying cycle time, final product reconstitution time, and product quality inconsistency are increased.

Graph 1 in Figure 7 reflects the extended time required to nucleate all vials within the batch versus the simultaneous nucleation event that occurs with ControLyo® (Graph 2).



Graph 1



Graph 2

Figure 7: *Graphs showing freezing cycles without ControLyo® (Graph 1) and with ControLyo® (Graph 2)*

ControLyo® generates larger ice crystals which increases the sublimation rate, effectively increasing the design space by delivering sublimation cooling to the product and providing a larger safety factor for the working process (Figure 8).

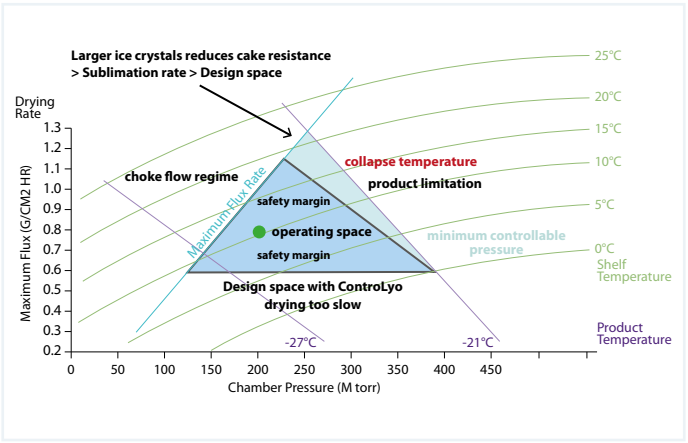


Figure 8: *Increased Design Space with ControLyo®*

The freeze-drying process relies on very precise control of product temperature by controlling the shelf temperature and chamber pressure. Variations in electrical supply, mechanical inefficiencies and mechanical component failure can lead to process excursions that move the product beyond the design space and can result in the loss of product (Figure 9a).

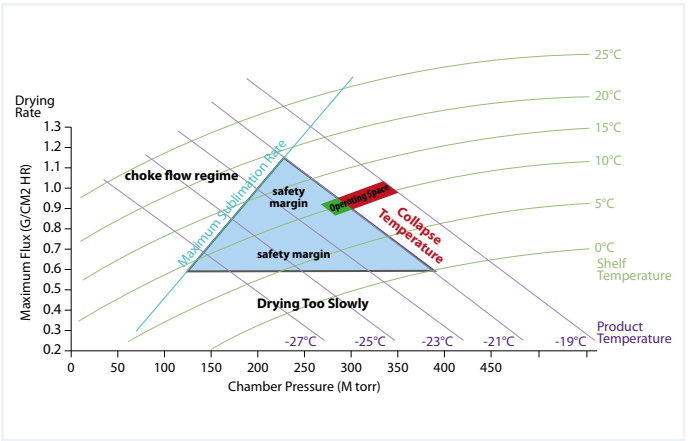


Figure 9a: *Product Excursion without ControLyo®*

With ControLyo®, all the vials will nucleate at the same time, their graphic representation within the design space will be a single point. The added safety margin obtained through ControLyo® minimizes the risk that a similar process excursion will result in product loss (Figure 9b).

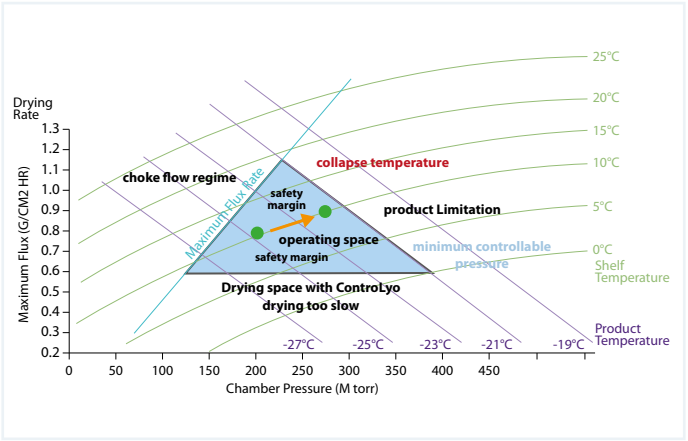


Figure 9b: *Product Excursion with ControLyo® can Minimize Product Loss*

Financial Advantages of Novel Line of Sight™ Freeze-Drying Tools

Line of Sight™ tools provide process reliability and improve product quality and consistency to ensure developers can:

- Be first to market, thereby increasing annual revenue
- Drive down cycle times and develop robust cycles that reduce manufacturing cost
- Replicate production excursions on development freeze dryers that produce product quality data to rationalize release of batches that may otherwise be discarded

Getting to Market First Translates Into Millions of Dollars of Revenue

Using Tempris* wireless sensors, SMART* technology software, ControLyo® Technology and LyoFlux* TDLAS eliminates the traditional trial-and-error process of developing a workable cycle, minimizing the amount of expensive API and saving weeks of development time.

Being first to market can mean millions of dollars in increased revenue. It is estimated that getting to market sooner, translates into customer revenue upwards of $1 million per day, not to mention the financial benefits of being first to patent a novel drug. The Line of Sight™ tools, shortens the time required to optimize the development of production freeze-drying cycles, generating millions of dollars in revenue by bringing a product to market sooner.

Time-to-Market Revenue – An Example

Cycle development without SMART software is typically about 63 days. Aside from the obvious benefits that include a reduction in data errors and patenting a novel drug, adding SMART* software reduces development time to only 13 days (Figure 5), which can improve overall revenue by **$50 million**.

Optimizing Operating Space Produces a Robust Process That Saves Money

The freeze-drying microscope helps create a stable product and an optimized cycle by identifying the precise collapse temperature. The freeze-drying microscope can provide essential thermal characteristics to develop the product isotherms (top right side of the design space triangle, Figure 1) and define the failure limit.

LyoFlux* TDLAS provides the equipment capability by non-invasively measuring the sublimation rate at different shelf and vacuum parameters to define the constraints of the freeze dryer and define the choked flow regime for the lyophilizer (left side of the design space triangle, Figure 1).

ControLyo® Technology expands this operating space by creating larger ice crystals to allow a less complex path for the vapor the escape. This results in a shorter batch cycle with larger safety margins. For every 1°C increase in nucleation temperature, the drying time is reduced by approximately 3% and for every 1 °C rise in shelf temperature set point, the primary drying time is reduced by 13%. This added process control increases yearly production capacity, allowing developers to add additional batches, improve product consistency and reduce downtime.

Cycle Time Reduction Revenue Example

Assuming a batch is seven days long (including two days for clean-up and batch turnaround), using Line of Sight™ tools can save one day per batch, increasing the maximum annual production capacity from 48 batches a year to 57 batches. Based on a conservative revenue estimate of $4 million per batch, this potential increase in capacity of 9 batches per year could increase revenue by **$36 million per year**.

Line of Sight™ Data to Support Batch Integrity

Biologics are complex molecules that are expensive to produce. A typical batch can cost $400,000 and be worth approximately $4 million or more in revenue. In the event of a power outage or other excursion event during the production cycle, the tools on the development lyophilizer can be used to re-create the production excursion with minimal product. By generating the data quickly, there is evidence to prove to quality personnel and regulators that the suspect batch remained within the design space, regardless of the irregularity in that particular cycle.

Saving Batch Revenue Example

Finally, a batch – and therefore revenue – can be saved by controlling the freezing process. ControLyo® freezes all product at exactly the same temperature which represents a single point in the design space matrix. This greatly increases the safety margin to minimize issues with production excursions and increase product homogeneity. Inter- and intra-batch homogeneity is essential to ensure product quality. All Line of Sight™ tools allow you to quickly use your development freeze dryer with minimal API and replicate production issues to support product release with real data rather than subjective assumptions. Assuming this effort results in the release of one additional batch per year and considering our previous value per batch, the increased annual revenue would be: **$4 million per year**.

Summary

The freeze-drying process is dependent on hundreds of critical components functioning at precise times throughout a multi-day cycle. Having access to real-time data from development and production freeze dryers should be justified on product quality and consistency alone.

Regulatory will often ask "why would you not consider using technical features that improve the quality of your product if they are readily available?".

However, the financial advantages of being first to market, having additional production capacity and the opportunity to possibly save an entire batch that otherwise may be discarded, supports the obvious decision to add these Line of Sight™ features to any new freeze dryer acquisitions.

Line of Sight™ tools are now available on new SP freeze-drying equipment as well as retrofittable to some existing lyophilizer installations.

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