Utilization Of Technologies And Process Analytical Tools To Overcome Lyophilization Challenges During Development, Scale-Up And Manufacturing Of Biologic Products

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Abstract

Biologic drugs have shown great promise in curing many life changing diseases, even some that were once thought incurable. However, due to the sensitive nature of biological material it requires specialized development and manufacturing processes. Stabilization by lyophilization is attractive to retain the product's biological activity, structural integrity and homogenous quality, all of which are crucial to the success of the product. This white paper describes the challenges associated with lyophilization of biologic drug products. Using a Quality by Design (QbD) approach with the SP ***Line of Sight™*** (LoS) suite of technologies that provide a data-rich environment, many of these challenges can be overcome. In particular, scaling-up of lyophilization from early development to full commercialization can be streamlined through the use of scalable technologies available within the LoS portfolio. Companies working on biologics need robust processes with proven data to deliver successful products.

Introduction

In a 2018 market report, it was stated that '50% of the drugs in the clinical pipeline are comprised of biologics'[1]. This equates to over 5,000 new biopharmaceutical drugs (including >960 biosimilars and biobetters) currently in clinical development[2]. In 2018, the world biopharmaceutical market revenue is at a rate of approximately $275 billion/year, which is a significant portion of the total $1.1 trillion market for the global pharmaceutical industry[3]. The increase in annual biopharmaceutical revenue is predicted to be ≥12%[3] which will provide significant revenue within the pharmaceutical market over the next five years.

Large biological molecules, typically proteins or antibodies are, mostly, administered parenterally requiring different manufacturing capabilities to standard solid or semi-solid drug formulations. Biologic drugs and antibody-drug conjugates (ADCs) are, not only very expensive to manufacture, but some are not as stable as other formulations or molecules. Preserving their activity during storage and transportation is also very difficult. In addition, the importance of product temperature monitoring cannot be underestimated especially as the process moves to an aseptic environment with larger equipment where a reliable solution to measure product temperature should be considered as part of the development strategy.

To overcome these demands and increase shelf life, the compounds, drug products or conjugates can be freeze-dried (lyophilized). The process of lyophilization lowers the temperature of the product to below its freezing point, before water or other solvent(s) are removed by sublimation using a controlled vacuum. At least 41% of biologic drug products and almost all ADCs are freeze-dried to retain their physical structure. Lyophilization of ADCs ensures the stability of the linker that joins the 'payload' to the antibody, during storage and transport. Freeze-dried biologics can be reconstituted quickly and easily whilst retaining their biological activity.

Each part of the freeze-drying process has a large impact on product quality and integrity. With the advance of technologies and more sophisticated tools, there is a better understanding of how to measure and record parameters that affect the final product and therefore, greater knowledge of the product itself. The US Federal Drugs Administration (FDA) and other regulatory bodies strongly recommend a Quality by Design (QbD) approach to drug manufacturing that assures in vitro product performance. FDA's release of the Process Validation guidance in January 2011 states the need for companies 'to continue benefiting from knowledge gained, and continually improve throughout the process lifecycle by making adaptations to assure root causes of manufacturing problems are quickly corrected'[4]. This shift from a trial-and-error approach to a science-based approach for the lyophilization process provides confidence of in vivo product performance of these biologic drugs.

A QbD approach to optimizing the lyophilization of biologic drugs

Increased growth in the number of biological drugs often serving small target populations, has led to greater demand on developers and manufacturers to improve efficiency with higher yield and

Understanding design space

As part of the QbD approach, a systematic methodology to development is applied beginning with predefined objectives and emphasizes product and process understanding. This is supported by scientific knowledge and quality risk management to establish a design space with defined sets of operating variables needed to maintain batch consistency (Fig 1). These parameters are represented graphically as multi-dimensional points to define sets of operating variables needed to maintain batch consistency. Operation within the design space (operating space) will result in a product meeting a predefined quality.

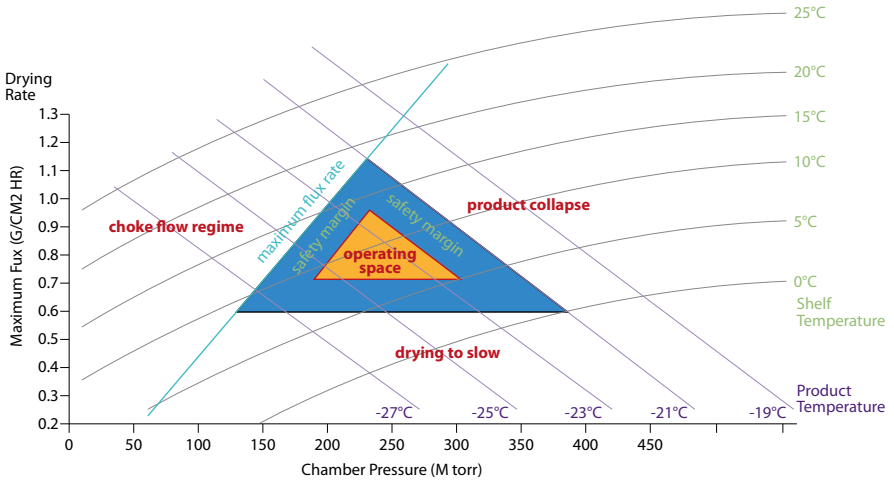


Fig 1. ***The design space of the freeze-drying process.*** *Simplified depiction of a design space – a multidimensional representation of equipment capability limit and product knowledge*

better product quality. Consistency within and between batches is an integral quality parameter based on several properties from physical appearance and structural integrity to biological activity. Parenteral drugs also require a high level of sterility during the manufacturing processes. Shorter development times, improved stability and quality attributes can be achieved within a sterile environment through increased control over the freeze-drying process.

Addressing these challenges begins with having a good understanding of a product early on in its life cycle. Better development of the freeze-drying process from the start will lead to optimal large-scale commercialization and a lower economic burden in the long-term. However, even with this knowledge, scale-up can be an on-going challenge for manufacturers of biologic drugs. Differences in freeze-drying equipment performance and operation can occur between development and production scales, leading to time consuming and costly re-optimizations of lyophilization parameters to achieve successful freeze-drying of the product at each stage.

Part of the QbD approach to drug manufacturing, utilizes Process Analytical Technology (PAT) tools to improve the freeze-drying process so that critical process parameters can be well defined and their impact on product quality appreciated and monitored in a timely manner. Paying particular attention to these parameters will create an optimal design/operating space which will ultimately lead to a reduction in costs.

A suite of tools to scale up lyophilization of biological compounds

Recognizing the inherent challenges of scale-up and the desire for improved results in the development and manufacture of biologic drugs, SP has created ***Line of Sight*** (LoS). LoS is a suite of tools - technologies and equipment - that can be employed at each stage of development and production for increased control, efficiency, quality and consistency in the lyophilization process. This suite of technologies and PAT are built into small-scale freeze dryers through to large scale commercial dryers offering research and production lyophilization professionals a clear, LoS approach to their processes supported by real time data. This approach also ensures the use of technology and methodology from one piece of equipment can be reproduced and compared directly to another.

LoS tools comprise products, such as the LyoCapsule™, a seven-vial development freeze dryer that is suitable for early stage formulation development or cycle development, the SP Hull LyoStar™ 4.0 freeze dryer, a 'go-to work-horse' for cycle development and cycle optimization activities, and the SP Hull LyoConstellation™ range of larger freeze dryers that not only perform cycle development but offer fully aseptic operation. All these dryers can be augmented with data from technologies, such as ControLyo® for controlled ice nucleation, SMART* for accelerated primary drying optimization, the LyoFlux* TDLAS vapor mass flow sensor, which allows non-invasive inference

of critical product and process data, and the wireless Tempris* sensor for product temperature measurement.

Increasing lyophilization process efficiency

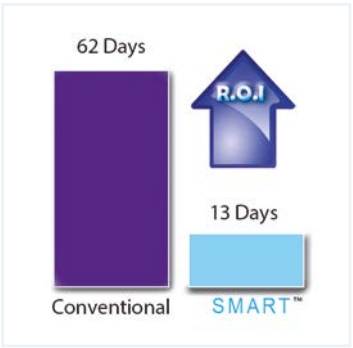
Lyophilization efficiency relies on obtaining a high-quality product with minimum waste (of materials, energy, time, money). The pre-defined set of operating variables that create the design space determine process efficiency. Having a larger design space, or parameters in which to work, increases the probability of executing a successful cycle repeatedly, even in the face of potential problems including unplanned process excursions. LoS enables expansion of the design space for a particular target by understanding how process parameters can impact critical product attributes.

Primary drying cycle optimization tool

SMART freeze-drying technology is a patented PAT tool using the manometric temperature measurement (MTM) technique to determine freeze-dried cake resistance and product temperature at the ice interface. Along with AutoMTM which allows researchers to run their own pre-determined cycle while reporting on critical process and product parameters, SMART technology has been shown to save precious development time and provide relevant product data. In a comparison study with a large pharmaceutical company and two Biotech companies, SMART technology was used to develop an optimized cycle for a single formulation. All three labs reported that they recouped their investment in less than three months with the average development time reduced by 62 days[5]. In addition, scientists were often able to produce a cycle optimized to their specifications after a single experimental run which left time available to conduct further experiments to test for process limits. These results also mean that a formulation can advance into pilot production months faster than the current time frame.

Real-time accurate and reliable product temperature measurement

The LoS suite also provides another product temperature measurement tool which determines temperatures accurately and in real time throughout development, technical transfer and production of a lyophilized product. Traditionally, thermocouple wires have been used to measure product temperatures in freeze-dryers, but these are difficult to position within vials creating unreliable data and issues with sterility. Tempris* sensors enable wireless real-time temperature measurements. Being cleanable and sterilizable, these sensors also prevent any contamination of product when used in pilot or commercial manufacturing. In addition, their wireless property enables them to be loaded in a system protected by RABs (Restricted Access Barriers) or full isolation. Tempris sensors enable greater cost efficiency and time savings with reproducibility and are practical at all stages throughout the entire production process from development to scale up and technical transfer.



Return of investment (ROI) illustration of development effort using conventional method vs. SMART* technology

Accurate measurement of vapor mass flow

Efficient real time monitoring of the lyophilization process and scale-up can be measured by another PAT tool in the LoS suite of technologies. The LyoFlux sensor uses Tunable Diode

Laser Absorption Spectroscopy (TDLAS) technology to measure water vapor concentration and flow velocity from which the temperature can be derived at the ice interface for a specific formulation. LyoFlux enables calculation of process design space parameters for a specific product in as little as three experiments compared to a minimum of 5 or 6 runs traditionally. Using the LyoFlux technology, the maximum sublimation rate to determine the equipment capability can be conducted in one run. Once equipment capability is established for this equipment, the heat transfer coefficient, Kv of the vials to be used for the product can be determined. Again, LyoFlux enables multiple experiments to be performed in a single test by varying the chamber pressure and monitoring the sublimation rate for the respective pressure set points. The LyoFlux can also determine cake resistance during freeze-drying in a vial. This streamlines the use of production freeze dryers and minimizing downtime required to conduct multiple sets of experiments, thus obtaining product attribute and equipment capability data for further analysis of the design space. LyoFlux data may also be used as input to SMART in the place of MTM technology.

LyoCapsule: 7-vial development freeze dryer

Precise control of the freezing point

The degree of supercooling is one of the biggest freeze-drying scale-up challenges. The lower the temperature that the product nucleates, then the higher the degree of supercooling leading to smaller ice crystals. This impacts sublimation rate and product temperature profile resulting in performance differences between laboratory generated cycle and commercial manufacturing generated cycle. Freezing is a stochastic process with nucleation of vials occurring randomly within the dryer at different times and yielding heterogeneous batches and variability in drug product resistance. SP Scientific's ControLyo technology utilizes an inert gas and a series of pressurization and depressurization steps for instantaneous, controlled ice nucleation in all vials in the product chamber at a higher temperature. This minimizes supercooling and yields the largest possible ice crystals. Large crystals create larger cavities as the ice sublimes resulting in less resistance for subsequent drying of internal areas, shortest potential drying time and easier reconstitution of final product. Previous studies have shown that for every 1°C increase in nucleation temperature, the primary drying time is reduced by 3%[6]. In some instances, ControLyo has been shown to reduce the cycle time from 7.5 to 5.5 days which increases productivity and provides economic benefits (unpublished data).

Many new biological drugs are complex formulations with high protein content and high fill volume presenting a significant challenge when freeze-drying. The use of ControLyo can ensure lower product resistance and homogeneity due to sublimative cooling therefore, enabling more aggressive cycles for products and expanding the design space. The added advantage of ControLyo is that it can be fitted, or retrofitted, to any freeze dryers.

Accelerating freeze-drying cycle development with just 7 vials

As the active pharmaceutical ingredients (APIs) of biologics are costly, limited quantities are available for freeze-drying development and optimization. Freeze dryers within the LoS suite include a small-scale dryer, LyoCapsule equipped with the innovative PAT tools and technology that are also incorporated in the SP larger dryers. With the ability to process as few as seven vials, the LyoCapsule uses less material, less resources and less preparation time. This makes it possible to screen more formulations and optimize the drying conditions far better than in larger freeze-dryers. Larger scale development dryers, such as the LyoStar 4.0 or the LyoConstellation range aids further cycle development, optimization, lab scale stability studies and scale-up. The range of LyoConstellation freeze dryers can further be employed for full commercial production of batches ranging from a few hundred to a several thousand vials.

A smooth transition between early stage development and commercialization

The critical parameters that lead to efficient production of a quality product is the same whether it is in early stage

development, clinical stages, pilot batches and commercial manufacturing. However, transferring from one stage to another often requires repeated optimization due to the differences between equipment at each stage.

The LoS suite of technologies consisting of freeze dryers for each stage of product development (LyoCapsule, LyoStar 3, LyoConstellation) is designed to minimize these differences by providing continuity of proven technologies (SMART, LyoFlux TDLAS, Tempris and ControLyo) in each dryer. This approach provides greater confidence in the methodology and meaningful comparison of the results at each stage.

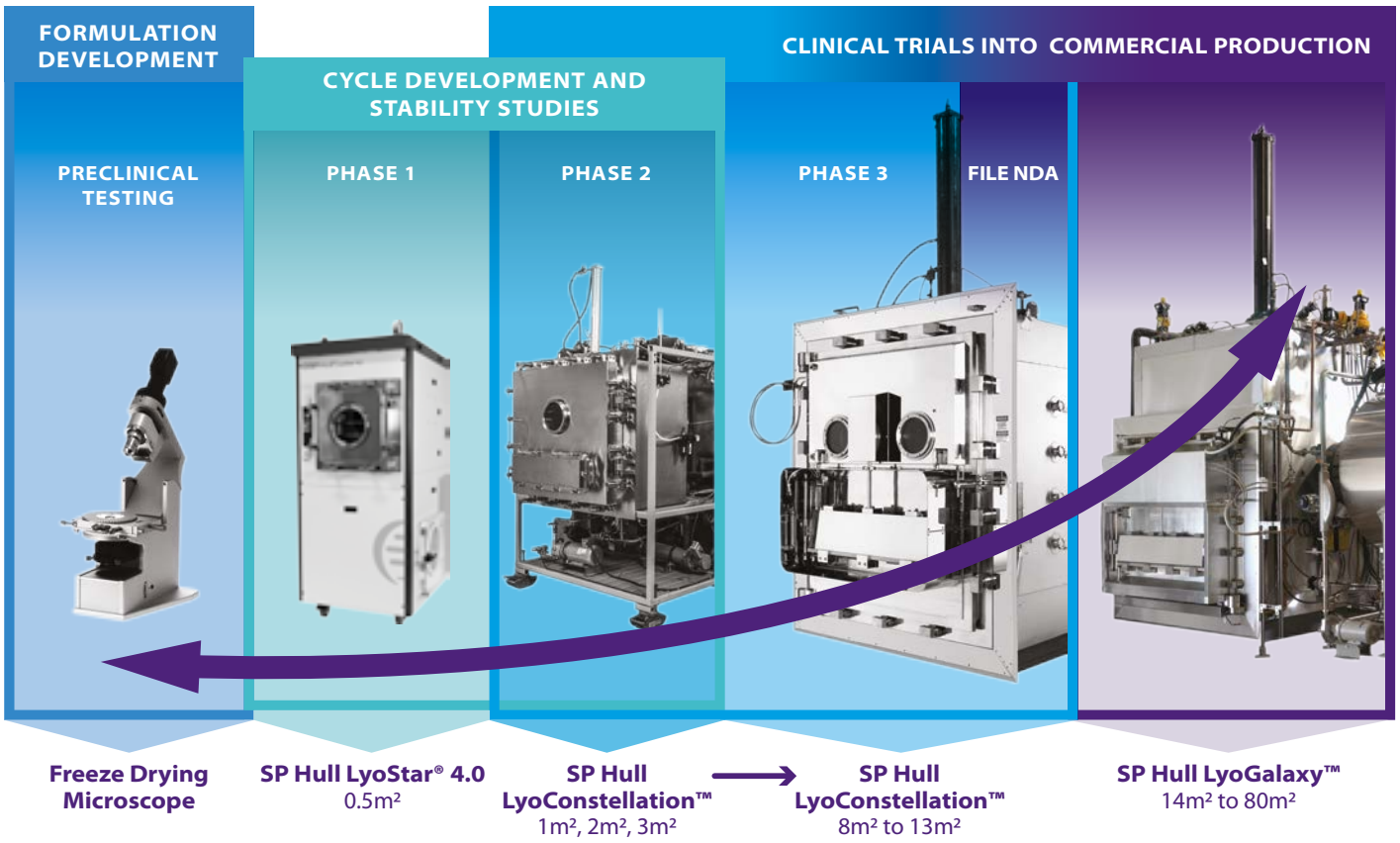
The importance of LoS for scaling up the product lyophilization process has been recognized by several Biotech and Pharmaceutical companies. A scientist at one Biotech company reported "LyoCapsule limits financial risk as it can test more conditions with less API. Using the same technology during scaling-up of product development provides a more comprehensive understanding of the product and increases the likelihood of success over the traditional trial-and-error approach."

Conclusion

Development of biologics such as human growth hormone, insulin, and red-blood cell stimulating agents has carved the path for new treatment modalities and biotherapeutics which can be used to fight against many previously incurable diseases. The scale of this market has increased exponentially with many molecules being evaluated in clinical phases.

Due to their complexity and characteristics, there are many challenges associated with development, manufacturing and distribution of biological products. Stabilization by lyophilization is considered the best way to retain biological activity, structural integrity and homogeneity of the drug product.

A QbD approach to development and manufacturing within a well-defined design space is considered best practice and is expected of by any regulatory agencies. From accurate monitoring of product and conditions through to the entire freeze-drying process, the SP Line of Sight suite of tools support QbD to improve development processes and assure success in



manufacturing. Equipment design and incorporation of LoS technologies increases the flexibility of the operating space, improving batch consistency, yield and product quality.

In addition, the industry has a growing interest in non-invasive measurement of key process parameters and product quality of the lyophilization process. This is driven by the rise of automation as the FDA mandates removal of people from the process to protect the product from the operators, and the development of highly potent formulations to protect the operators from the product.

LoS's range of freeze dryers and innovative technologies enable lyophilization conditions to be optimized at the early stages of product development, provide the product knowledge, and then be transferred to clinical and manufacturing stages smoothly without costly re-optimization at each stage. With the sensitive and aseptic monitoring devices and established technologies, critical lyophilization product parameters can be measured accurately and non-invasively providing a data-rich environment.

The evidence here demonstrates the value that can be gained by optimal biological drug production facilities. By investing in the SP scalable technologies, a product can move through different stages of development to commercialization more efficiently. These technologies provide the same level of product and process knowledge along the way for continued understanding of quality attributes that are affected by the process variables. These efforts streamline the development process and establish consistent product quality for lower long-term economic burden and support of best patient outcomes.

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Footnotes

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