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Mission: Control™

Technology Backgrounder - ***LINE OF SIGHT®***

Line of Sight® **suite of freeze-drying equipment, with scalable lyophilization technologies and process analytical technology (PAT) tools**

LINE OF SIGHT ENABLED

Technology Backgrounder - *LINE OF SIGHT®*

Enabling Lyophilization Scale-Up from Formulation to Full Commercial Production

SP Scientific *Line of Sight*® is a breakthrough concept comprising a suite of freeze-drying equipment with scalable lyophilization technologies and process analytical technology (PAT) tools. Line of Sight has been designed for both pharmaceutical developers and manufacturers to help them achieve their drug commercialization objectives.

Line of Sight technologies have been developed to provide the tools for a more successful scale-up of a lyophilization process from formulation through to full commercial production. This ensures superior product quality and uniformity and creates a data rich environment across all sizes of freeze-drying systems.

The next step forward in lyophilization, the science of freeze-drying, is being developed for pharmaceutical applications by use of enhanced technological capabilities, improved process and product understanding, and by implementing ***Line of Sight*** enabled freeze-drying equipment.

A Growing Market Demand

Biologics - complex biological drugs - targeting unique and often more complex types of diseases are now the "go-to" treatment for many patients with life threatening illnesses. A bespoke or [more] "customized" approach to treatment has been proven to deliver higher success rates thereby driving widespread development and approval of these drug products to serve the patient specific population needs. With successful clinical trials, the pressure to bring these drugs safely to the larger population is creating greater competition within the industry. Today, more than 41% of biological drug products are freeze-dried to retain their physical structure. In addition, almost all antibody-drug conjugates (ADCs) must be lyophilized to ensure the stability of the linker that joins the 'payload' to the antibody during storage and transport. This number is growing quickly.

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.

As part of the QbD approach, a systematic methodology to development is applied. This begins with predefined objectives and emphasizes product and process understanding, supported by scientific knowledge and quality risk management, to establish a design space with defined sets of operating variables needed to maintain product batch consistency. These are represented graphically as multi-dimensional points in relation to equipment limitation and critical product attributes. It is common for an inner area of the design space to be designated as the nominal manufacturing conditions for a successful production cycle (the operating space).

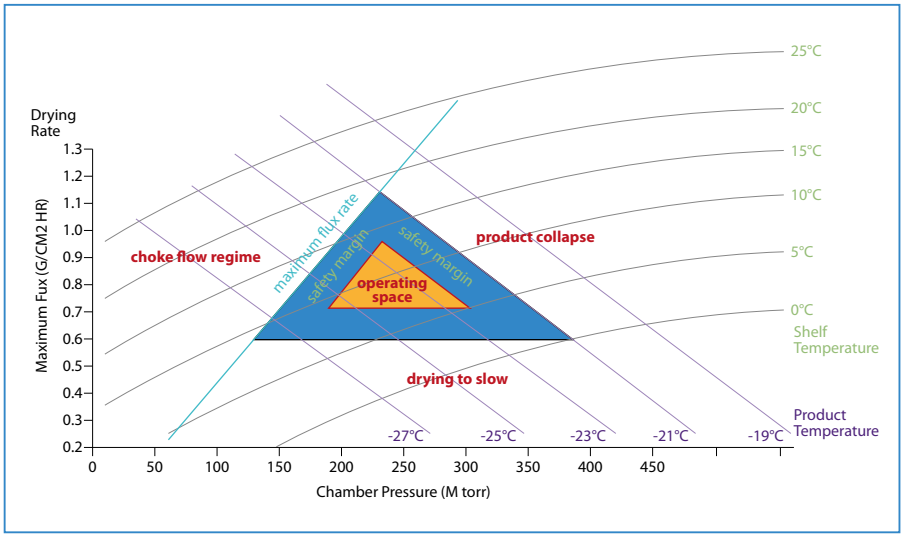
Operation within the design space will result in a product meeting a predefined quality. Having a larger design space or parameters in which to work increases the probability of executing a successful cycle, even in the face of potential problems occurring, including unplanned process excursions.

Quality by Design (QbD)

Expanding The Design Space

- Formulation optimization to improve final product robustness, homogeneity and quality
- Provides more process space for completion of a successful cycle
  - More room to maneuver in the event of an unplanned event eg power outage
  - More data enables proof of batch integrity
- Ensures greater success of cycle, less waste, less rejects
- Enables the most effective and efficient cycles to be developed

The real advantage for the researcher is that with more data, the furthest reaches of the design space can be mapped. Therefore, should a lyophilization process deviation occur, the manufacturer can utilize the known data to confidently demonstrate whether the batch was within a safe space and if so, allow the batch to be released.



The illustration depicted above is a simplistic view on how equipment design and the use of complementary technology such ControLyo® Nucleation Technology can expand your design space. The equipment design addresses the equipment capability curve to the top left by allowing higher sublimation rate and minimizing choked flow. Controlled freezing using controlled ice nucleation technology reduces the product resistance which allows a higher sublimation rate, lower product temperature due to sublimative cooling and so expands the top right curve.

Addressing early stage development challenges with scarce and costly active pharmaceutical ingredients (API) is another drug commercialization hurdle to overcome. ***Line of Sight*** technologies enable the development of the lyophilization cycle with just 7 vials of API using the LyoCapsule™ freeze dryer.

Every additional trial provides more data to expand the understanding of the products characteristics. Compared to traditional approaches using a full shelf in a larger freeze dryer (typically 200+ vials), development using a LyoCapsule freeze dryer uses less API, requires less preparation time and therefore jumpstarts your lyophilization development. Critically these advantages are delivered with the same level and quality of data to support process and product understanding for product life cycle management.

Line of Sight enabled technologies enable drug manufacturers to bring parenteral products safely and quickly to market with confidence by enhancing the product and process knowledge, substantiating the process with comprehensive data, and demonstrating process control and knowledge at every step. Beyond the design space, real time data is the key proof for a process well under control. A well characterized manufacturing process supported by real time data, makes a manufacturer's drug product submission more compelling from the regulatory perspective and demonstrates a higher degree of understanding of the process and product. More importantly, within an expanded design space, users can adopt a more flexible approach to the development and manufacturing process, implement continuous process improvement and maintain integrity within the boundaries of that design space.

The key to managing product quality is to understand what process parameters are required to reproducibly manufacture the product consistently. This is the same whether it is in development environment, technical transfer or commercial manufacturing. Use of scalable technologies across all the different equipment capacities required to develop a commercial cycle enable the user to demonstrate a QbD compliant approach. The FDA encourages users to have line of sight between the technologies used at every step so there is confidence through a meaningful comparison of results at each stage.

Visit **www.sp-lineofsight.com** to hear Dr Kevin Ward, Ph.D, Director of Research and Development at Biopharma Process Systems Ltd discuss the expansion of design space.

Visit **www.sp-lineofsight.com** to hear Dr Alexandra Braun, Ph.D, Leading Scientist at GILYOS GmbH, discuss key benefits for development of a freeze-drying cycle with just 7 vials of API.

Introducing the *Line of Sight* Technologies and Lyophilization Equipment

SP Scientific is leading the way in the development and manufacture of complete aseptic vial fill-finish lines. Drawing upon decades of experience and expertise – SP Scientific has assembled the most comprehensive lyophilization range available today covering cycle development, stability, pilot and clinical batch production to full aseptic manufacturing and commercial production batches. Uniquely the SP Scientific freeze dryer range has been strategically developed using a ***Line of Sight*** approach enabling expansion of the design space in cycle development and scale up/scale down. This approach enables you to use the same freeze-drying technologies from R&D right through to production.

Read more below about both technologies and lyophilization equipment now offered by SP Scientific.

Line of Sight - Delivering Continuity of Technology and Operations

SMART™ Freeze-Drying

Primary Freeze Drying Optimization Tool

- Optimize freeze drying cycles in less time
- Eliminates trial and error approach to cycle development, shortening cycle development time
- Infers critical data such as cake resistance and product temperature non-invasively

SMART technology is a primary drying optimization tool enabling you to jumpstart cycle development using known data, and importantly cuts down the experimentation process. With patented manometric temperature measurement (MTM), a pressure rise measurement technique, it determines freeze dried cake resistance and product temperature at the ice interface among other parameters. These attributes in turn are critical in understanding the long-term product stability. SMART eliminates the trial-and-error approach normally involved in developing new lyophilization cycles, enabling experts and novices alike to develop new freeze-drying cycles quickly, while ensuring product quality and efficient and robust process.

AutoMTM is another mode of operation of SMART freeze-drying technology. AutoMTM allows researchers to run their own pre-determined cycle and still collect and report the critical process and product parameters calculated by SMART. This technique is a valuable tool for understanding how an existing freeze-drying process can be further optimized.

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

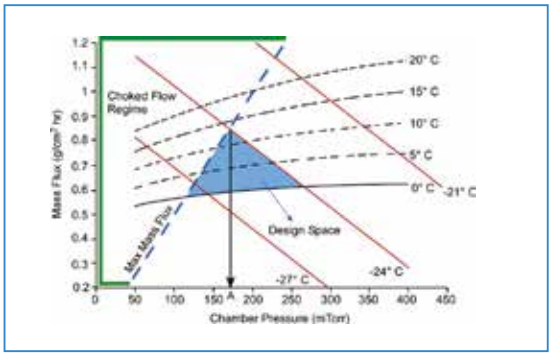
LyoFlux® TDLAS Sensors

Freeze Drying Monitoring and Control Sensor

- PAT tool for process scale-up and process control
- Assess freeze-dryer equipment capability limits
- Continuous, non-intrusive monitoring of lyophilization processes
- Water vapor, concentration, flow velocity (*v*), and water mass flow (dm/dt) measurements
- Applicable to laboratory, pilot and production scale freeze dryers

The LyoFlux sensor uses Tunable Diode Laser Absorption Spectroscopy (TDLAS) technology in a very specific way enabling it to be used for numerous applications in designing and monitoring freeze-drying processes including:

- Determination of batch average product temperatures
- Product temperature at bottom, T_b
- Product temperature at ice interface, T_p
- Primary and secondary drying process endpoints detection
- Determine vial heat transfer coefficients, Kv – 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)



Graphical design space generated using data obtained from LyoFlux sensor measurement and simulation. Image supplied by kind permission of Physical Sciences Inc.

The use of a LyoFlux sensor enables development of process design space, specific for the formulation in as little as three (3) experiments. As an example - Kv determination, which is pressure dependent, 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. This streamlines the use of production freeze dryers, minimizing downtime associated with the use of production equipment to conduct multiple sets of experiments in order to obtain the data for equipment capability or Kv experiments. Traditional gravimetric methods require filling the vials and weighing these filled vials pre- and post the freeze-drying process to determine mass loss during sublimation. This time consuming measurement had to be repeated at different pressure set points to obtain the dependency of the Kv value over pressure ranges. Traditionally, Kv has been measured in commercial dryers only by the most forward thinking companies because of the huge amount of labor and laborious system time required.

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

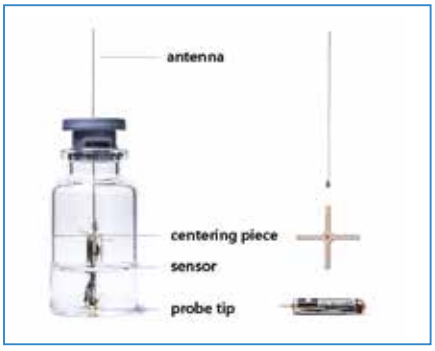
TEMPRIS® Sensors

Wireless Temperature Measurement for Lyophilization

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

Using TEMPRIS wireless sensors for real time product temperature measurement is highly attractive to users faced with finding practical ways of making sometimes challenging temperature measurements in large commercial freeze dryers. Traditionally wired thermocouples have been used but these are difficult to position accurately within the vials so may not provide users with the most reliable data. In addition, they are incompatible with automatic loading and unloading systems available with modern commercial freeze-drying equipment.

In order to get accurate and reliable measurements, sensors must be properly secured to the bottom center of the vials to be measured. Placing these sensors and maintaining these sensors at the prescribed location is a scientist or engineer's nightmare. There is no guarantee that once the sensors are placed in the vials, they remain centered as installed. Additionally, use of thermocouple wires is widely reported as a limitation for accurate positioning of sensors within freeze dryer batch and shelf locations. Another challenge of employing thermocouple wires is to maintain batch sterility so that remaining products can be used for product stability studies, or as a validation batch, for potential release to prospective patients which is an approach common to most high value products. Therefore, sensors will be required to be cleanable and sterilizable to prevent any product contamination.



Tempris wireless sensor assembly for product temperature measurement. Image supplied by kind permission of iQ-mobil solutions GmbH.

The wireless and battery free Tempris sensors can be applied on all scales of freeze dryers and thereby provide the most comparable and consistent data for this parameter in real time. They can be deployed throughout development, transfer and production of a lyophilized product, even in combination with automatic loading systems. This enables greater cost efficiency and time saving with high product quality and usable in all scales throughout your entire production process.

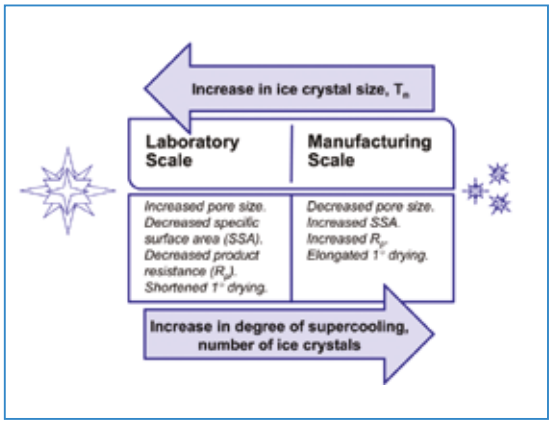
Tempris® is a registered trademark of iQ-mobil solutions GmbH, Holzkirchen, Germany and used by permission.

ControLyo® Nucleation Technology

Precise Control of Nucleation Point Eliminates Supercooling

- Controls nucleation point of every vial in a batch simultaneously
- Delivers a fully homogeneous batch with less quality rejects and higher cake visual quality
- Enables nucleation at higher temperatures leading to:
  - Larger ice crystals
  - Shorter primary drying time
  - Reduced vial breakage
- Enables freezing of high protein concentration formulations

A considerable body of published work reports that vials in a batch nucleate randomly during the freezing step and each of the vials supercool to different degrees. Supercooling is a term describing the state where a product remains in liquid state well below its thermodynamic freezing point which is usually around 0°C. Supercooling is especially prevalent where the particulate level in the environment is well controlled such as in classified aseptic areas, Grade A or ISO 5 rooms. The lower the temperature when the product nucleates, the higher the degree of supercooling. As a result, smaller ice crystals are formed which in turn leads to a small pore when the ice sublimes, and a difficult path for the water vapor from the frozen part to escape through the dry cake layer. Therefore yielding higher dry layer resistance to vapor flow. This can impact sublimation rate and product temperature profile, resulting in performance differences between a laboratory generated cycle and commercial manufacturing generated cycle.



Depiction of the effect of ice crystal size on the freeze-drying process performance

Differences in freezing between vials in a batch means that the freeze-drying cycle has to be developed to accommodate the worst case vial due to the heterogeneity of the batch. Controlled ice nucleation using ControLyo has been widely acknowledged as a vital advance in freeze-drying cycle and control. ControLyo has been proven to enable control of the degree of super-cooling thereby providing a solution to what is perhaps the biggest freeze-drying scale-up challenge. Using ControLyo, all vials in a batch now freeze at the same time and behave similarly. Many new biological drugs are complex formulations with high protein contents and can present a significant challenge when freeze-drying, a challenge that, in many cases, ControLyo has been able to provide the solution for.

Freeze Drying Microscope (FDM)

Reliable Determination of Collapse Temperatures

Every freeze drying formulation has a critical temperature, below which it should be maintained during primary drying in order to prevent processing defects. The freeze drying microscope allows observation of the sample structure during drying and heating so that the exact point of collapse can be determined. Innovative lighting and image capture systems (with articulated head for easy sample loading) provide sharp visualization for easy, accurate identification of structural changes. Once analysis has been carried out formulations and cycles can be developed that are safe, robust, and cost efficient. Every 1°C higher a formulation can be freeze dried at, results in an efficiency saving of 13%.

Visit **www.sp-lineofsight.com** to hear Dr Kevin Ward, Ph.D, Director of Research and Development at Biopharma Process Systems Ltd discuss the benefits of the Freeze Drying Microscope

LyoCapsule™

Accelerate Your Freeze Drying Cycle Development with Just 7 Vials

- Screen formulations for freeze drying feasibility without use of large quantities of API
- Determination of process robustness
- Can process 2 cc to 20 cc vials
- Ensure critical formulation collapse temperature is not exceeded during primary drying
- Define proper shelf temperature and pressure selection for effective sublimation process

The LyoCapsule is a small-scale freeze dryer, able to precisely emulate conditions in larger R&D freeze dryers. This technological advance allows you to jumpstart your freeze-drying cycle development with just 7 vials of your often scarce and costly API. In depth formulation screening and cycle development can now be done in a LyoCapsule freeze dryer using less material, less resources, smaller quantity of vials and less preparation time thereby streamlining your development activities.

LyoCapsule freeze dryers are equipped with the same innovative PAT tools and technology - SMART/AutoMTM, TDLAS, and ControLyo - enabling the identical level of development effort as you would in a larger R&D freeze dryer such as the SP Scientific LyoStar 3. The LyoCapsule freeze dryer operates with SP Scientific's LyoS™ control software which delivers the highest level of process-control and flexibility. This software package is also easy to use, multi-functional and provides a seamless transition between systems at all scales.

LyoStar™ 3
Process Development in a R&D Freeze Dryer

- Substantially decreases cycle development time and conserves valuable API
- Delivers increased process information
- Easier transfer of cycles to larger systems
- Maximizes process control and repeatability
- Meets even the most stringent QA requirements

The LyoStar 3 is the ultimate cycle development, optimization and scale-up tool for R&D professionals. This advanced freeze drying system is proven to deliver pin point process control and robust reliability to protect your valuable product. A "go-to work-horse" for cycle development and cycle optimization activities, the LyoStar 3 can be equipped with scalable technology and PAT tools such as ControLyo, SMART, AutoMTM and TDLAS.

Using SMART and AutoMTM PAT tools on a LyoStar 3 substantially decreases cycle development time and conserves valuable API. In addition, these tools generate data to increase your product and process understanding enabling you to further scale the process to commercial batches. Furthermore, these tools deliver increased process and product understanding, such as how different freezing protocols impact cake resistance and generates data such as product temperature profile, so the information can serve as a target going into larger freeze dryer equipment. The LyoStar 3 also operates using LyoS control software.

LyoConstellation™
Process Development in an R&D Freeze Dryer

- Enables ***Line of Sight*** approach to cycle development and scale-up assuring product safety and quality
- 2 shelf sizes cover cycle development, stability, pilot and clinical batch production, through full aseptic production
- Accommodates vials up to 30ml
- Isolator ready with auto locking doors
- Integrates with PennTech filling line and semi-automatic loading system

LyoConstellation represents a brand new range of development and pilot freeze dryers, configured to order for faster delivery and specifically designed for aseptic operation. Covering cycle development, stability, pilot and clinical batch production to fully aseptic production, all systems are powerfully equipped as standard to provide very high capacity, broaden equipment capability and expand design space. When handling high value API, and with a need to bring product to market as quickly and safely as possble, LyoConstellation addresses early stage development under aseptic and low particle controlled conditions. This means product behaves in the same manner once the product is ready for scale up and eventually ready for commercialization. Using a LyoConstellation freeze drying system will enable you to achieve faster product progression from development to clinical phases with less scale up issues to deal with.

LyoConstellation S10, S20, and S30 are all equipped with the same advanced suite of technologies as other SP Scientific R&D freeze dryers providing data for full process and product life cycle management, including the LyoS software and scalable technology and PAT tools such as ControLyo, SMART, LyoFlux-TDLAS and Tempris.

LINE OF SIGHT ENABLED

Conclusion

Each element of the ***Line of Sight*** suite taken separately provides a valuable tool to help lyophilization scientists better understand different facets of the freeze-drying process. Taken together, these tools uniquely enable development scientists to create new freeze-drying cycles and scale them quickly and confidently from the laboratory, through development stages and into production.

In addition, should a production cycle deviate into uncharted territory, and therefore put at risk a batch worth potentially many millions of dollars, ***Line of Sight*** technology may be used to research that process deviation in miniature to provide insight as to whether the batch can be safely released, saving the at risk value. ***Line of Sight*** is a data rich set of tools, technology and equipment provided by SP Scientific with these latest freeze-drying solutions.

For more information, please visit www.sp-lineofsight.com or for an in-depth discussion on both the technical and financial significance of SP Scientific's *Line of Sight* concept, and how this will enable lyophilization scale-up for pharmaceutical manufacturers, please contact:

Ian Whitehall, Chief Marketing Officer, SP Scientific on:
Tel: M-US: +1 267 966 5034 or M-UK: +44 7748 638703
Email: ian.whitehall@spscientific.com

For further press enquiries, please contact Dr Bill Bradbury, Primetek Solutions:
tel: +44-208-546-0869
SKYPE: William Bradbury
email: info@primetek-solutions.com

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Mission: Freeze Drying Control

SP SCIENTIFIC

SP INDUSTRIES/SP SCIENTIFIC
935 Mearns Road, Warminster, PA18974

Toll Free: (800) 523-2327
Local: (215) 672-7800
Fax: (215) 672-7807

www.spscientific.com

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