FTS Systems
SP SCIENTIFIC
Making Time for Science

LyoStar™ 3

Research & Development Freeze Dryer

Developed with SMART™ and
Praxair *ControLyo™*
Nucleation On-Demand Technology

Engineered with the Scientist in Mind

The Choice for Cycle Development, Optimization and Scale-Up

Configured with the latest innovations in freeze-drying technology, the *Lyostar™3* delivers pinpoint process control and robust reliability to protect valuable product. Its exclusive combination of instrumentation and flexible software meets the demands of the most discriminating lyophilization scientists.

Performance

First and foremost, the LyoStar™3 is a reliable, robust Lyophilizer. Its benefits and features have been designed and manufactured with the needs of the research and cycle development scientist in mind. It offers design characteristics similar to large production freeze dryers to facilitate scale-up and down.

"Our LyoStars are in use nearly 24/7. They have proven to be vital instruments in the development of formulations and drying cycles."

Development Versatility

Standard LyoS™ software includes total process control of temperature and pressure, full historical trending and detection of the endpoint of primary drying utilizing Pirani-Capacitance Manometer differential and/or pressure rise testing. With optional optimization tools such as **SMART**™ and ***ControLyo***™ Technology, the LyoStar offers more capability in a development freeze-dryer than any system available. Additional equipment options include a clean-room configuration, sample thief, shelf latching kits and 21 CFR Part 11 compliant software.

Control System Features in the LyoStar™ 3

Standard

Vacuum Integrity Testing with Vacuum Preseal

Product Driven or Shelf Driven Mode

Vacuum Ramping During Primary Drying

Batch reports

Automatic Leak Rate & Function Testing

Automatic Stoppering and Backfill with Adjustable Stoppering Pressure

Primary Drying endpoint detection provided by:

- Pirani / Capacitance Manometer Differential

- Barometric Endpoint/Pressure Rise testing

TDLAS Compatible

Optional

SMART™ Freeze Dryer Technology & Auto-MTM Technology

Praxair ***ControLyo™*** Nucleation On-Demand Technology

Sample Thief

21 CFR Part 11 Compliant Software

IQ/OQ Documentation Packages

Programmable Logic Controller (PLC)

Allen-Bradley

Scale-up...

The LyoStar™3 has greater than a 1:1 ratio between the cold surface area in the condenser and the area of the shelves. This enables aggressive drying cycles and is consistent with the principles of proper production freeze-dryer design. A four inch port between the chamber and condenser maximizes vapor flow. Researchers find scale-up of cycles developed in the LyoStar to be greatly simplified.

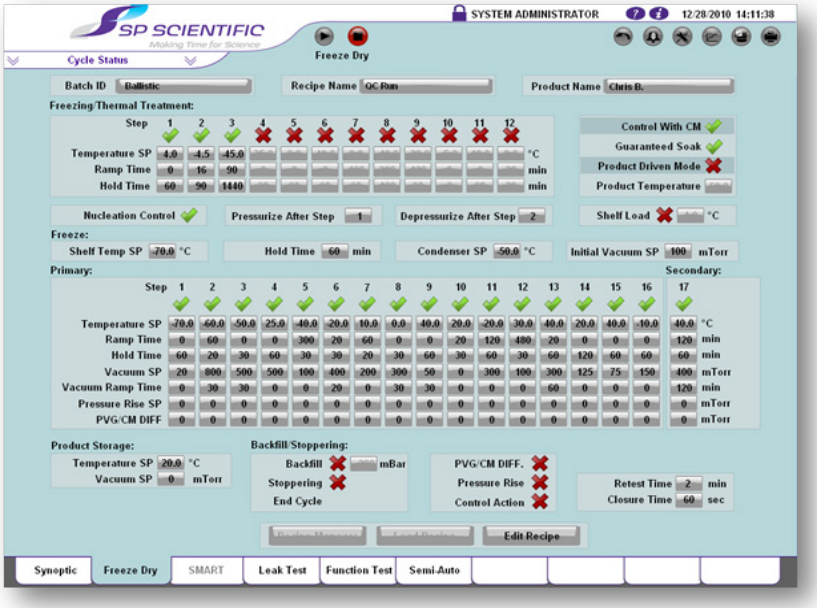
Documentation and Support

The LyoStar™3 is fully configurable and validatable for regulated pharmaceutical applications. SP Scientific offers onsite SAT and IQ/OQ validation support. Additionally, a more comprehensive factory initiated System Integration Test (SIT) program is available. The LyoStar™3 comes standard with the versatile LyoS™ software control system. Back-up copies of the software are provided and PLC source code is auditable.

The LyoS™ Software Control System

Back-up copies of the software are provided and PLC and source code is available.

The new LyoStar™3 enhances the proven technology and capability of the LyoStar™II, offering even more development tools as well as the significant advantages of ***ControLyo***™ Technology to control nucleation during the freezing step.



SMART™ TECHNOLOGY

Significantly reduces **freeze drying cycle development time and optimization.**

smart
FREEZE-DRYER TECHNOLOGY

Worldwide, the choice of experts.

The first to offer product resistance information...

What is SMART™?

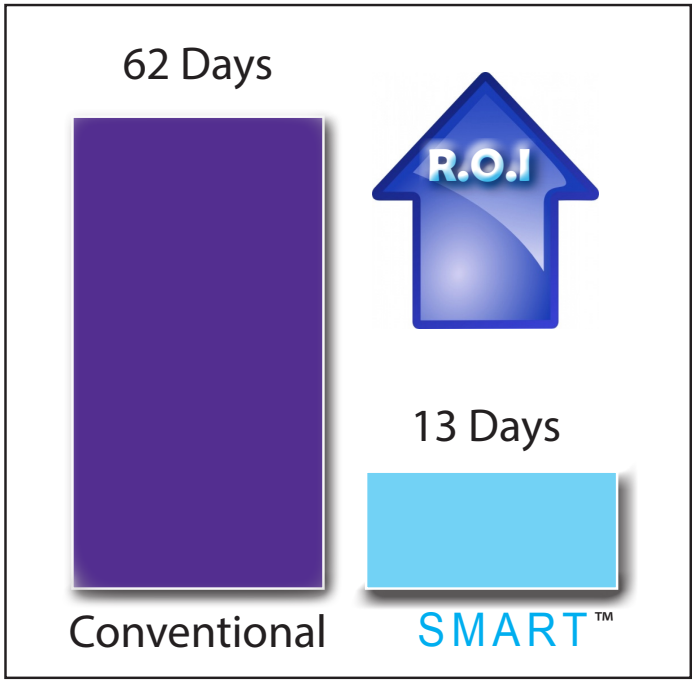
SMART™ is an "expert system" for freeze drying that allows optimization of primary drying from the first laboratory experiment. SMART™ optimizes the cycle as follows:

a. Based on operator inputs, SMART™ suggests a default freezing program, utilizes ***Controlyo***™ Technology or can accept a custom freezing recipe designed by the scientist.

b. Monitors product temperature at regular intervals, calculating how much heat to add via the shelf to quickly bring the product to its target temperature.

c. Selects the optimum chamber pressure & shelf temperature.

d. Identifies the end of Primary Drying and automatically steps into Secondary Drying

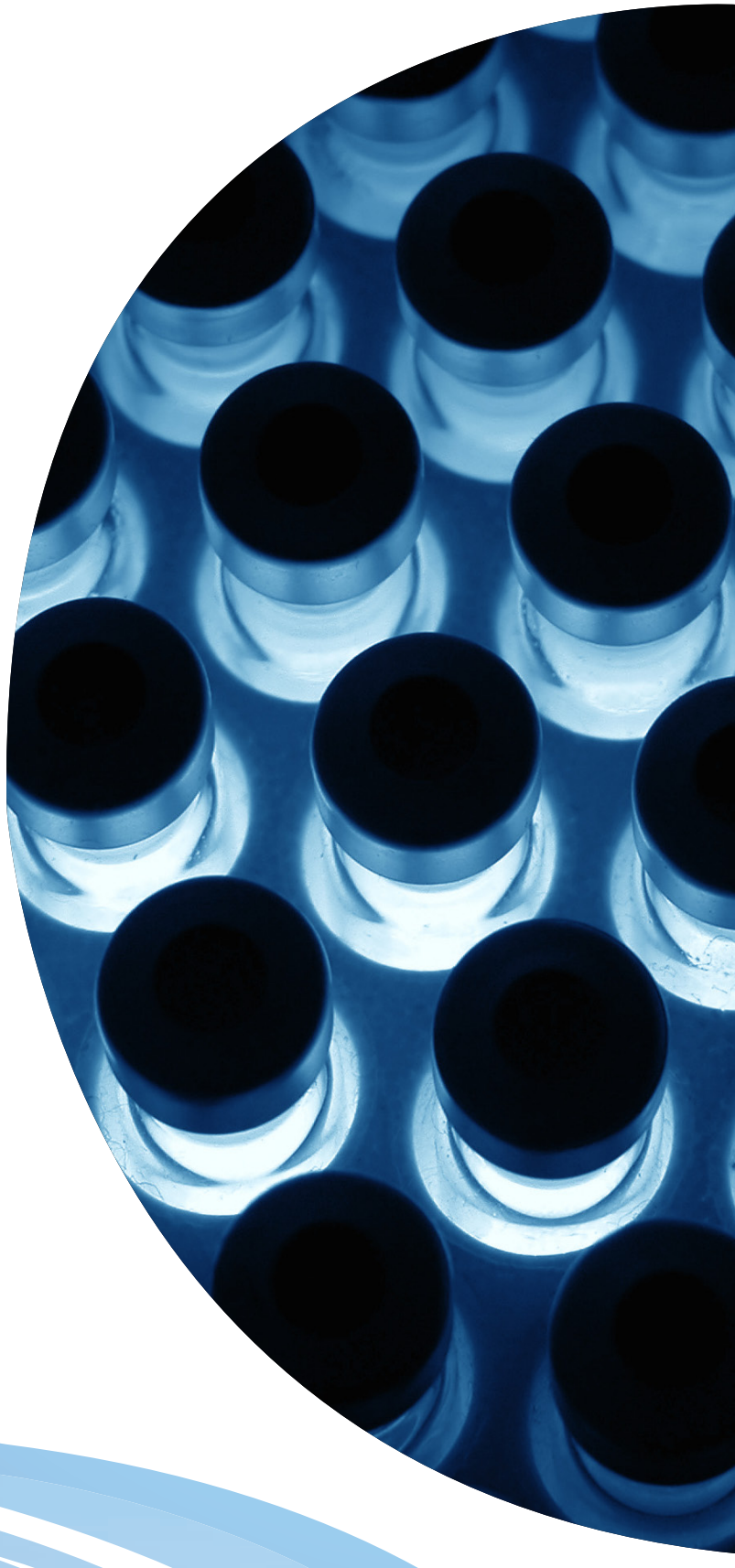


Increase return on investment with shortened cycle development times and decreased dwell time in production dryers.

SMART™ enables development scientists to significantly reduce the time and cost of cycle development, eliminating the iterative trial and error approach traditionally used. Case studies have shown cycle development times reduced by as much as 79% and annual cycle development costs reduced by 60%. Researchers find scale-up of cycles developed in the LyoStar with SMART™ to be greatly simplified.

See more on this topic in LyoLearn Webinar: "*SMART™ Freeze Drying*"
Presented by: Dr. Henning Geiseler on **SPScientific**.com

The History of SMART™



SMART™ was developed by industry experts, *The University of Connecticut and Purdue University*, through the *CPPR* (Center for Pharmaceutical Processing Research.) The goal of the project was to develop a fully automated Freeze Dryer to refine the manometric temperature measurements (MTM) equation and **optimize a cycle in as little as one run.**

How does it work?

The chamber is systematically isolated during primary drying from the condenser for a short period of time (25 sec.) At specified intervals during this time, pressure rise data is collected and fitted to the MTM equation to derive pressure at the sublimation interface (Pice) and Rp + Rs (resistance of the product and stopper.) Since the stopper resistance is minimal, the primary calculation is product resistance (Rp.) Using standard heat and mass transfer equations, a number of critical process and product parameters can be calculated.

What critical information does it provide?

For most freeze drying scientists, controlling the product temperature and freeze drying interface ice temperature for maximum sublimation rates is a matter of tedious trial and error. SMART™ eliminates that trial and error approach, typically with as little as two shelf temperature adjustments.

Optimize a cycle in as little as one run...

Using SMART™

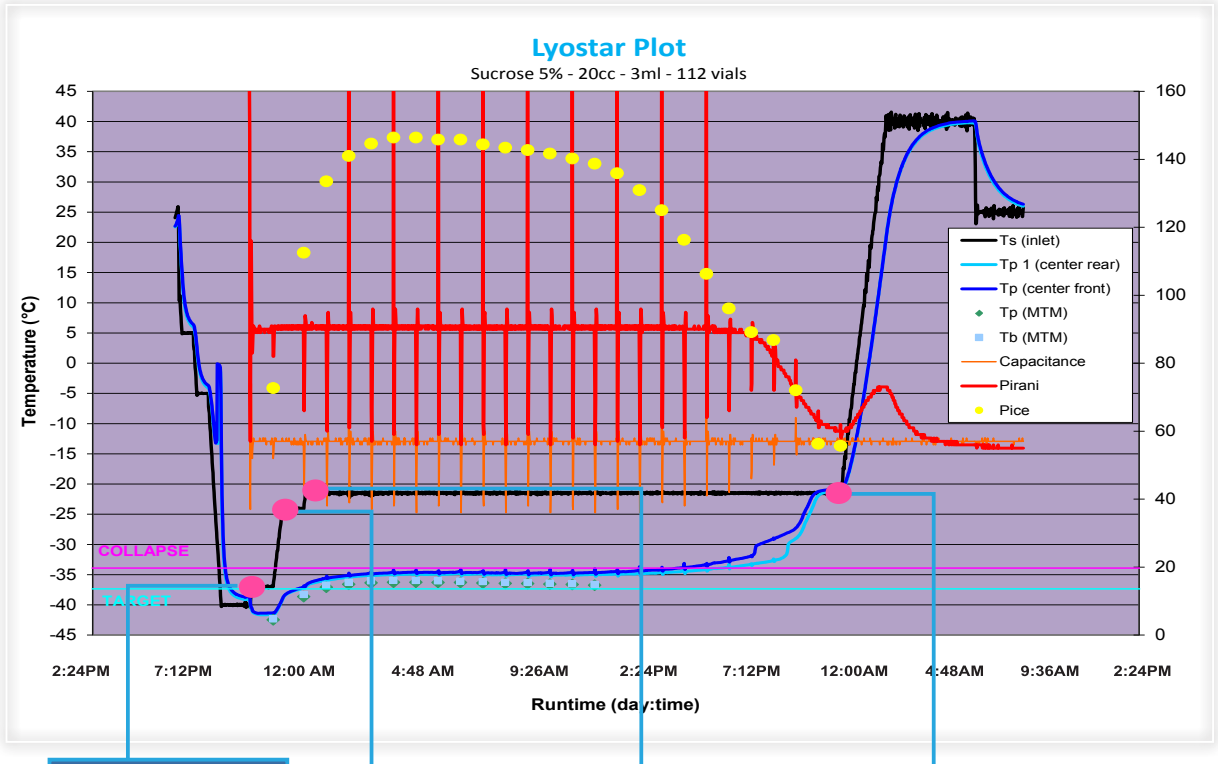
By entering a few key parameters, SMART™ helps optimize a cycle with a touch of a button.

User Input Parameters include *Critical Product Temperatures (Eutectic Temperature, Tg' or Collapse Temperature), Fill depth, Fill volume, Fill weight, Concentration, Nature of Product, Nature of Formulation (amorphous vs. crystalline), number of vials and cross sectional area of vials.*

Critical Product Temperatures must be determined to develop a rational cycle, whether done by trial and error or using SMART™. These are generally determined using Differential Scanning Calorimetry or Freeze-Dry Microscopy.

SMART™ Data Run	
CURRENT RECIPE	10/26/2011
PRODUCT NAME	5% Sucrose
BAT ID	Smart Test
Nature of Drug Product	Small Molecule
Type of Bulking Agent	Amorphous
Type of Vials	Tubing
Density of Solute	1.5
Overload Heat flow	300000
Number of Vials	112
Inner Area of Vials	5.82
Av Factor	1.2
Fill Volume	3
Effective Chamber Volume	113
Collapse Temperature	34
Concentration of Solution	0.05
Predetermined MTM Interval	30
Estimated Primary Drying Time	
Condenser Overflow (Tp overflow)	
Target Temperature (Tp target)	
Chamber Pressure Set Point	
1/3 of Original Ice Thickness	

Your input can lead to your target product temperature being reached in as little as 3 steps.



STEP 1: Initial Shelf Point Selection

STEP 2: Second Adjustment

STEP 3: Third Adjustment

End of Primary Drying, automatically steps into Secondary Drying.

** This also illustrates high correlation of the detection of the end of Primary Drying between the Capacitance Manometer vs. Pirani Gauge differential and SMART™ calculations*

SMART™ adjusts vacuum level & shelf temperature setpoint to reach target temperature in as few as two adjustments.

The Process of SMART™

- Creates an optimized cycle in as little as ***1 run***
- Determines pressure and temperature at the ice surface interface
- Sets shelf temperature to correctly control product temperature close to but below critical temperature
- Shelf adjustment during primary drying is accomplished in two to three steps
- Identifies end of primary drying and automatically steps into Secondary drying

SMART™ Provides Data Not Available Before...

Time Interval (min)	P_{ice} (mTorr)	Rp (cm^2*Torr*hr/g)	Tp (MTM) (°C)	dQ/dt(MTA -1) (cal/hr/Vial)	L_{ice} (cm)	$Ts_{(set)}$ (°C)	P0 (mTorr)	Tb (°C)	Kv X 10^4 (cal/sec*cm^2*K)	W subl (g/vial)	dm/dt g/hr/vial	Ldry (cm)
29.55	67.7	0.8	-43.1	163.42	0.5542	-17.5	57.2	-42.9	3.45	0.04	0.08	0.0073
69.25	102.4	1.1	-39.48	192.76	0.5191	-10.6	57.6	-38.9	2.98	0.22	0.24	0.0424
44.2	127.3	1.34	-37.53	195.73	0.4804	-10.6	57.4	-36.84	3.1	0.42	0.31	0.0812
30.6	135.4	1.48	-36.97	186.53	0.4502	-10.6	57.5	-36.32	3.18	0.58	0.31	0.1113
30.6	141	1.6	-36.6	178.85	0.4201	-10.6	57.3	-36	3.19	0.73	0.3	0.1414
30.6	145	1.7	-36.34	172.67	0.3902	-10.6	56.2	-35.79	3.19	0.89	0.3	0.1713
30.55	147.6	1.77	-39.18	168.95	0.3607	-10.6	57.4	-35.68	3.16	1.04	0.3	0.2008
30.6	149.1	1.82	-36.09	165.31	0.3316	-10.6	56.7	-35.69	3.13	1.19	0.29	0.2299

The Freeze-Dry™ data available for review includes:

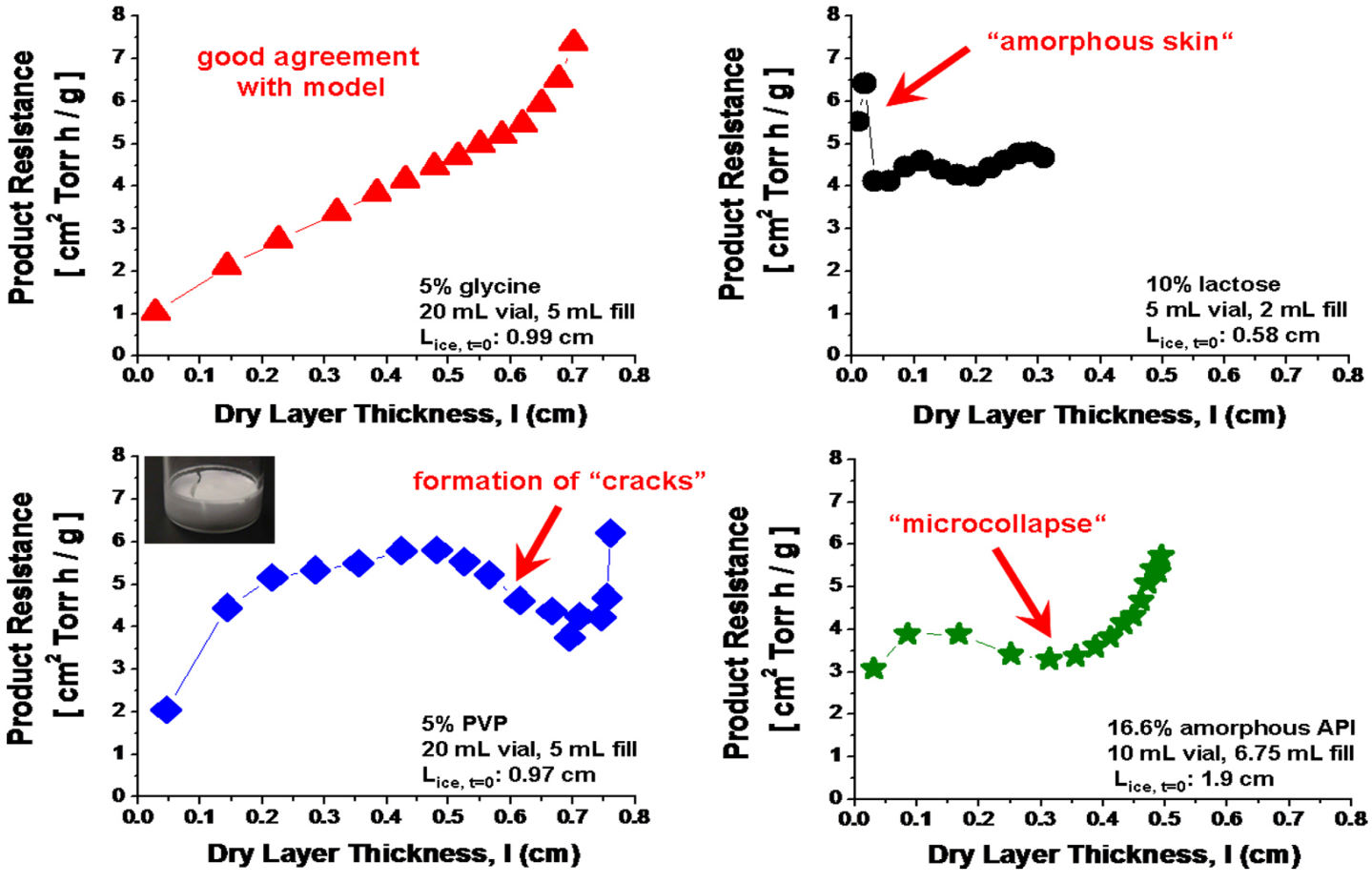
- **Time Pass** - Minutes elapsed in Primary Drying
- **Time Interval** - Minutes since last MTM Measurement
- **P_{ice}** - Vapor pressure at the ice surface in the product at the end of the MTM measurement (mTorr)
- **Rp -** Resistance of the dried layer in the product (cm^2*Torr*hr/g)
- **$Tp_{(MTM)}$ -** Temperature of the product at the ice surface as determined by MTM (°C)
- **dQ/dt -** Rate of heat transfer (cal/hr/vial)
- **L_{ice}** - Thickness of the ice in the product (cm)
- **Ts -** Shelf temperature set point (°C)
- **P0 -** Chamber pressure setpoint (mTorr)
- **Tb -** Product temperature at the bottom of the vial (°C)
- **Kv X 10^4 -** Vial heat transfer coefficient (cal/sec*cm^2*K)
- **W subl -** Accumulated mass loss (g/vial)
- **dm/dt -** Rate of sublimation in (g/hr/vial)
- **Ldry -** Dry Layer Thickness (cm)

What is Auto MTM?

Auto MTM is another mode of operation of the SMART™ technology. Rather than optimizing primary drying, auto MTM allows the researcher to run their own pre-determined cycle and still collect and report the critical process and product parameters calculated by SMART™.

The Importance of Measuring Product Resistance using SMART™?

One of the measurements generated by SMART™ is Product Resistance (Rp). Product resistance is considered to be a critical product parameter (CPtP) because it instantaneously gives a picture of the product cake morphology at the time of measurement. It therefore serves as a good indicator of final product morphology and quality. Structural changes within the product cake, as a function of temperature, can be assessed by Rp data. This includes collapse, micro-collapse, cracking and shrinkage.



Courtesy of Gieseler H, Kramer T, Pikal MJ 2007. Use of Manometric Temperature Measurement (MTM) and SMART™ Freeze Dryer Technology for the Development of an Optimized Freeze-Drying Cycle. J Pharm.Sci 96(12). 3402-3418

ControLyo™
TECHNOLOGY

* "***Control and characterization*** of the degree of super-cooling can provide a solution to what is perhaps the biggest freeze drying problem"

** Pikal MJ, Rambhatla S, Ramot R. 2002. The Impact of the Freezing Stage in Lyophilization. Effects of Ice Nucleation Temperature on Process design and Product Quality. Amer Pharm Rev 5: 48-52.*

PRAXAIR

ControLyo™ **Technology Inside**

Technology at Work for *you...*

"Control and characterization of the degree of super-cooling can provide a solution to what is perhaps the biggest freeze drying scale-up problem."

Now with ***ControLyo***™ Technology, you can have that control.

A primary goal of cycle development and scale-up is to reduce the cycle time (and therefore cost) in freeze drying.

Optimization of the freezing step is rarely a focus. However, to a large extent, the temperature at which freezing takes place and the degree of supercooling that occurs determine what can or cannot be done to reduce the time of primary drying. Part of the reason that the freezing step has been ignored until recently is that the development scientist has not had access to easy tools and technology to impact this step. Other than annealing, the freezing step has been a previously untapped opportunity to improve the process.

What is *ControLyo*™ Technology?

To better understand the benefits of the ***ControLyo***™ Technology in the context of optimizing the freezing step, it is helpful to understand the basics of nucleation and supercooling. This is summarized below:

- **Low degree of supercooling:**

- Larger ice crystals
- Larger pores in the dried matrix
- **Decrease of Rp**

- **High degree of supercooling:**

- Smaller ice crystals
- Smaller pores in the dried matrix
- **Increase of Rp**

Nucleation is the initiation of crystallization of the free (un-bound) water during the freezing step. Nucleation temperature is the temperature at which ice crystal formation begins to take place.

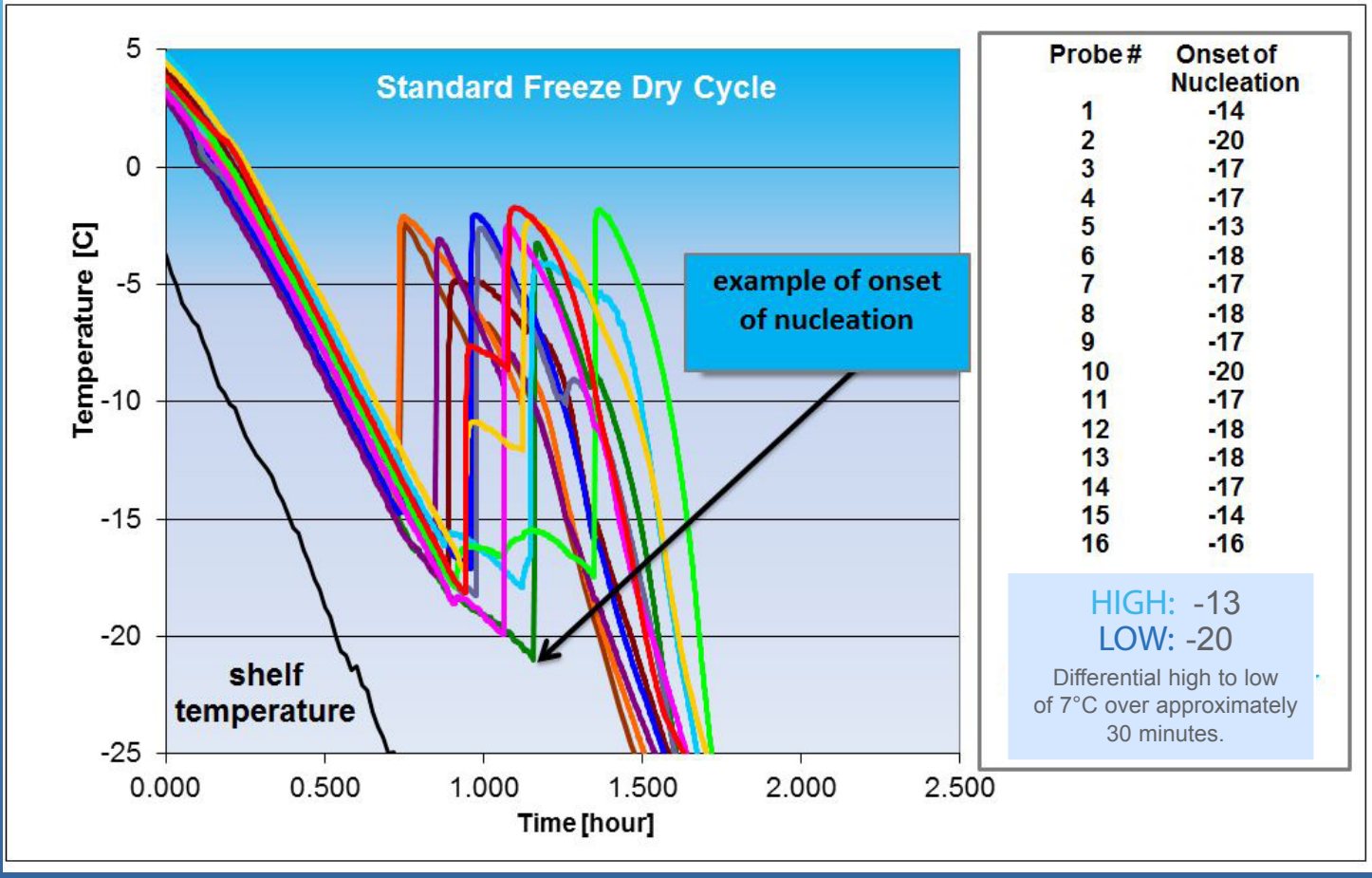
- Nucleation rarely occurs at the thermodynamic freezing point of formulation
- Nucleation is a stochastic process, with nucleation occurring up to 20°C below the thermodynamic freezing point in a class 100 production environment
- The degree of supercooling can have a significant impact on the drying process
- Lower supercooling = larger pores during sublimation. This reduces resistance to mass transfer and reduces primary drying time.
- Higher supercooling equals smaller pores during sublimation. This increases resistant to mass transfer and increases primary drying times.

See more on this topic in LyoLearn Webinar: "The Importance of Controlling Nucleation Temperature During the Freezing Step" Presented by Mark Shon on **SPScientific**.com

Typical Freezing with No Nucleation Control

Freeze dryers ***without*** controlled nucleation will produce product vials with varying degrees of supercooling with nucleation that occurs at random times during the freezing step. The graph below illustrates that the vials in a single batch within the dryer, seeing the same conditions, will actually freeze differently. In clean room environments, the degree of supercooling can be significantly worse because of a lack of nucleation sites. The greater degree of supercooling before nucleation, the smaller the ice crystals, the smaller the pores that form during nucleation and the slower the primary drying time.

No Nucleation Control



Probe #	Onset of Nucleation
1	-14
2	-20
3	-17
4	-17
5	-13
6	-18
7	-17
8	-18
9	-17
10	-20
11	-17
12	-18
13	-18
14	-17
15	-14
16	-16

HIGH: -13
LOW: -20
Differential high to low of 7°C over approximately 30 minutes.

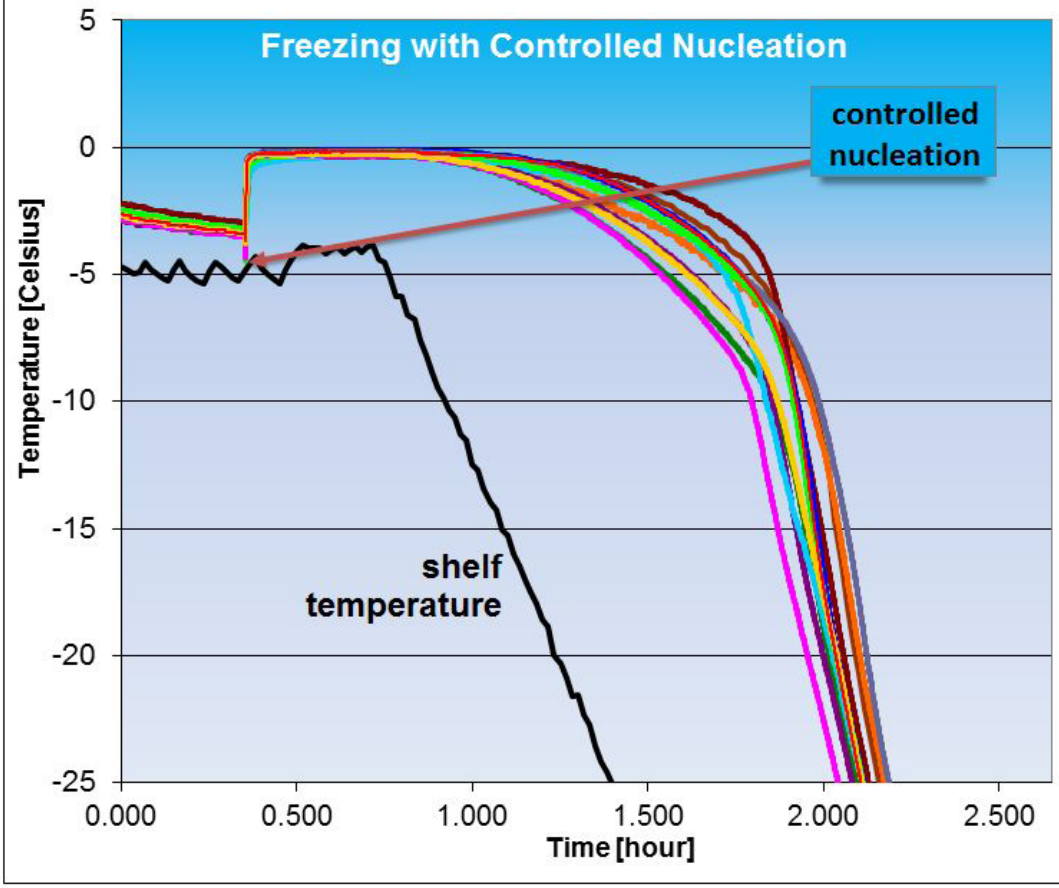
Freeze dryers without controlled nucleation will produce product with varying degrees of supercooling, that consequently are not as homogeneous as would be desired.

See more on this topic in LyoLearn Webinar: "Quality by Design and Scale-up Issues in Freeze Drying: The role of Controlled Ice Nucleation." Presented by Dr. Michael Pikal on SPScientific.com

Freezing with Controlled Nucleation

Significantly less variation in the degree of supercooling results in insignificant variation in ice crystal morphology. Less supercooling produces larger ice crystals therefore less product resistance and faster drying times.

Utilizing Praxair's *ControLyo*™ Nucleation-on-Demand Technology



Probe #	Onset of Nucleation
1	-5
2	-4
3	-3
4	-4
5	-4
6	-4
7	-4
8	-4
9	-4
10	-4
11	-4
12	-4
13	-4
14	-4
15	-4
16	-4

HIGH: -3
LOW: -5

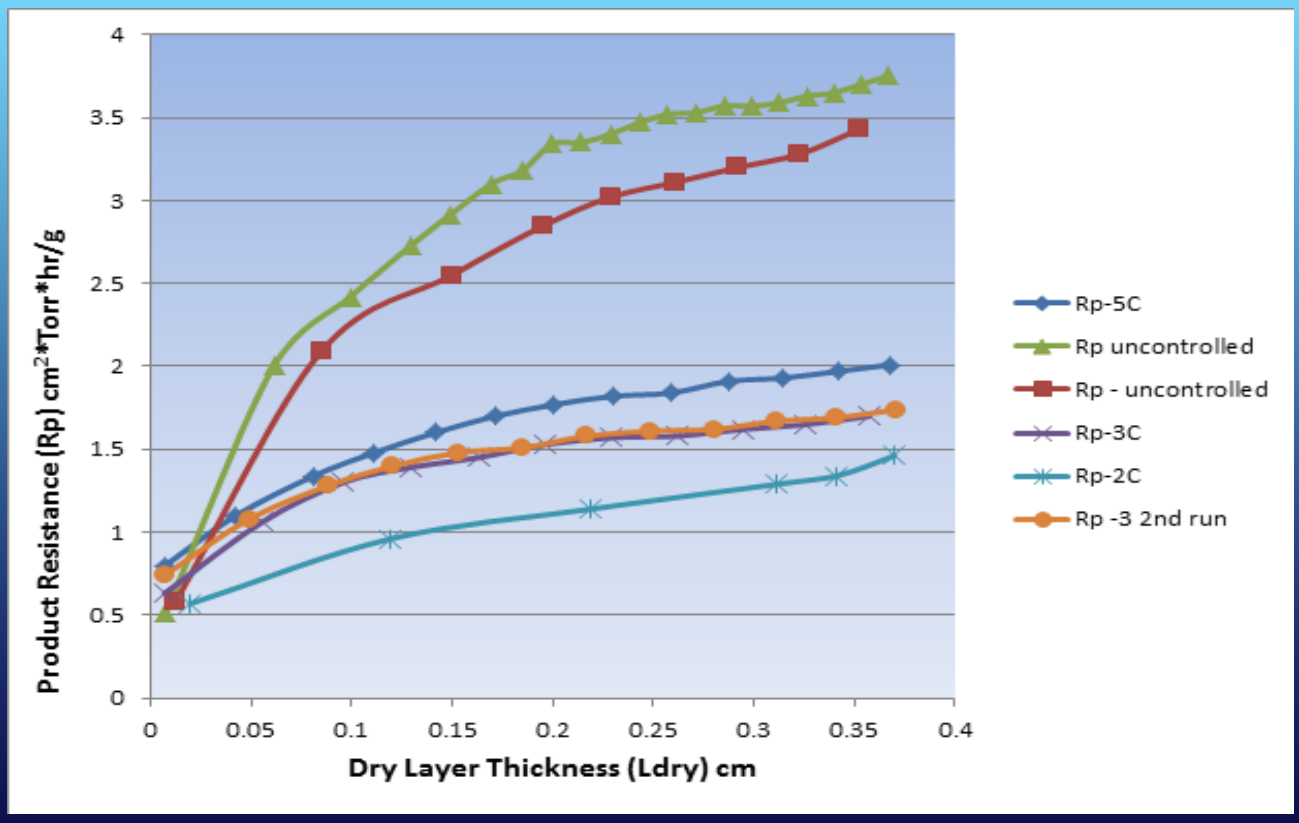
Differential high to low of 2°C over approximately 5 seconds.

Scale-up with Controlled Nucleation:

Existing Production freeze dryers can be retrofitted with ControLyo™ Nucleation On-Demand Technology. Scale-up tests have shown 100% nucleation in fully loaded freeze dryers with as many as 8700 vials.

See more on this topic in LyoLearn Webinar: "***ControLyo***™ Nucleation-On-Demand Technology in Production Freeze Dryers: Retrofit Strategy and Results." Presented by Mark Shon on **SPScientific**.com

Higher Degree of Supercooling = Higher Degree of Resistance



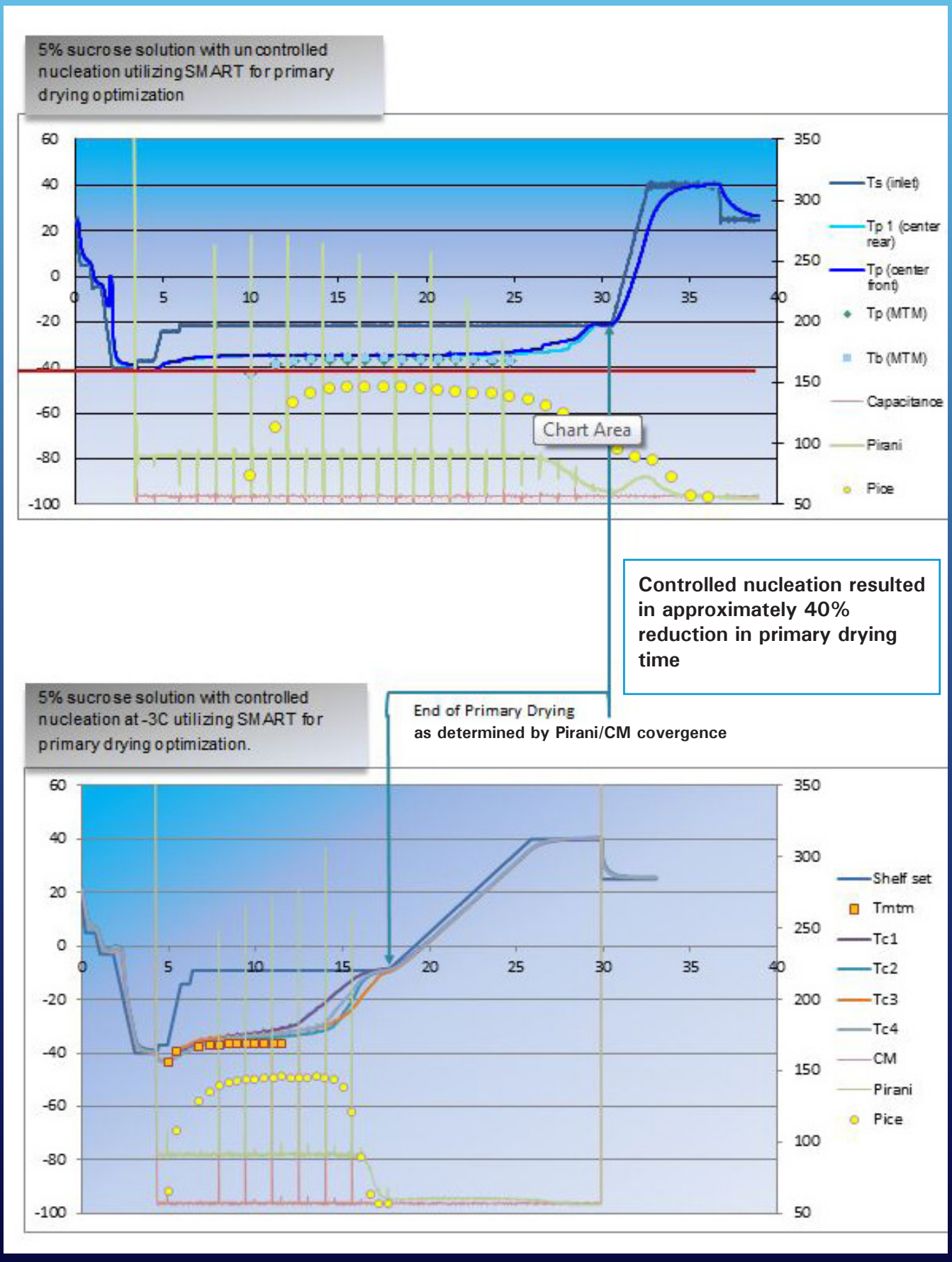
This graph illustrates the relationship between controlling the onset of ice nucleation in the product and the cake resistance. Uncontrolled nucleation produces the product with the greatest amount of resistance to vapor flow. As the onset of nucleation is controlled at ever higher temperatures, the resistance in the product decreases, thus allowing for higher rates of sublimation and shorter cycle times. *(Also note that the two runs done when nucleation was forced at -3°C illustrate repeatability from run to run.)*

The following quote is from a recently accepted publication by the FDA:

"Controlled ice nucleation resulted in a significant reduction in the primary drying time, improved cake appearance, cake morphology, reduced specific surface area, vial-to-vial homogeneity and reduced reconstitution time."

Awotwe-Otoo, D., Agarabi, C., Read, E.K., Lute, S., Brorson, K.A., Khan, M.A., Shah, R.B., Impact of controlled ice nucleation on process performance and quality attributes of a lyophilized monoclonal antibody, International Journal of Pharmaceutics (2013), http://dx.doi.org/10.1016/j.ijpharm.2013.04.041

Control the degree of supercooling to optimize cycle time



See more on this topic in Lyo Tech Brief: "*Optimization of Primary Drying Time Using a Combination of **ControLyo**™ **Nucleation-On-Demand Technology** and **SMART**™ Freeze Dryer Technology* " Written by Mark Shon **SPScientific**.com

Benefits: *What can the LyoStar™3 provide?*

LyoStar™3

- Unmatched process accuracy and reliability
- Sophisticated instrument set
- Advanced cycle development and optimization tools
- Robust 5.5 hp cascade Refrigeration system
- Ultra-reliable scroll compressors
- Optional SMART™ Freeze Dryer Technology
- Optional *ControLyo™* Technology for controlling ice nucleation

SMART™

- Creates an optimized cycle in as little as one run
- Determines pressure and temperature at the freeze-dry ice interface
- Dynamically controls the shelf temperature to keep the product temperature close to but below critical temperature
- Shelf adjustment during primary drying is accomplished in two to three steps
- Identifies end of primary drying and automatically steps into secondary drying

ControLyo™ TECHNOLOGY

- Increase in pore size and reduction in dry layer resistance.
- Freezing uniformity within the dryer and from batch to batch
- Faster primary drying
- Reduced freezing stress on biologicals
- Improved cake appearance
- Reduced protein aggregation
- Easier cycle transfer to production dryers with controlled nucleation

Think SMART™, Take *Control*, be a LyoStar

LYOSTAR™ 3 + SMART™ + *ControLyo™* = Even better cycle optimization

Take two great cycle optimization tools, put them together and have the best tools at your fingertips.

This powerful combination of equipment and software allows the research and development scientists to:

- Control Nucleation (and therefore ice crystal size & resistance) at a pre-determined temperature.
- Utilize SMART™ to optimize the primary drying cycle
- Collect valuable, critical, process and product parameters
- Study pre-existing formulations and determine the impact of controlled nucleation on the product.

FTS Systems

SP SCIENTIFIC

Making Time for Science

SP Scientific Supports You in Ways Unrivaled in the Industry:

LyoLearn Webinars: Free online seminar series featuring topics of interest to lyophilization scientists and presented by industry experts. Live sessions allow participants to interact with reowned freeze-drying specialists, such as Dr. John Carpenter, Dr. Steve Nail, Dr. Michael Pikal, and other who's who of the freeze drying community. Each online LyoLearn Session is recorded and archived for future viewing.

Hands-On Training: SP Scientific's hands-on training courses offer attendees the chance to optimize their learning experiences by using tangible applications in a controlled setting. Led by "go-to" leaders in the lyophilization industry, these courses are a must for anyone getting started in freeze drying or scientists looking for collaborative environment to share best practices, ideas and theories.

Technical Briefs: SP Scientific's technical briefs are relevant papers covering in-demand topics. Available in a variety of languages, titles include: *The Relevance of Product Resistance in Primary Drying, The Importance of Controlling Nucleation Temperature During the Freeze Step, Case Studies in Diagnosing and Correcting Problematic Lyophilization Cycles and/or Formulations, Basic Principles of Freeze Drying and Basic Lyophilizer Maintenance Helps to Assure Good Results.*

All of this is available on our website SPScientific.com
Logon to learn more!

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