ControLyo™ Technology and TDLAS in Commercial Manufacturing as a QBD tool supporting scale up

Application of scalable tools to aid process development in scale up, and batch recovery by scale down

PDA Europe
Event
City/Country, Day Month Year

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CMO
SP Scientific

ICH Q11 - Development and Manufacture of Drug Substances

Summary Statement of ICH Q11 guidance:

- Identifying potential CQAs associated with the drug substance so that those characteristics having an impact on drug product quality can be studied and controlled
- Defining an appropriate manufacturing process
- Defining a control strategy to ensure process performance and drug substance quality

Importance of PAT

- Enhance understanding of critical product attributes which can impact over final quality
- Characterize product temperature profile and product resistance during development and scale up
- Rationalize information in product life cycle management and quality decision
- Regulatory expectation - *PAT – A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance (FDA Guidance for Industry)*

ControLyo is Quality by Design

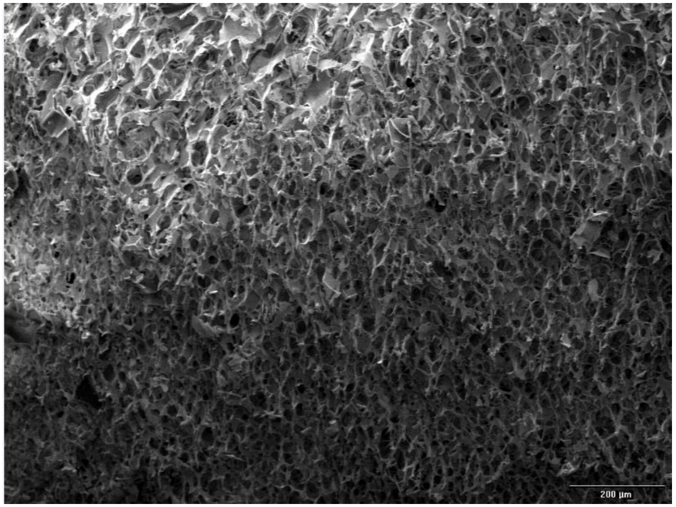
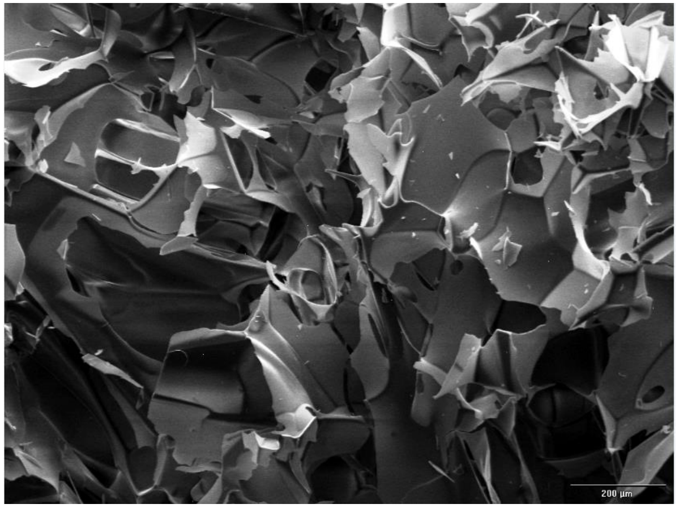
ControLyo™ Technology Manufacturing Adoption

- 40 SP LyoStar3 R&D freeze dryers with ControLyo™ technology in use world wide

Commercial Units:

- Evaluation of production batch for stability study in human injectable products
- Use in commercial manufacturing for animal health products

Scanning Electron Microscope (SEM) Image of Uncontrolled and Controlled Freezing

Uncontrolled Freezing	ControLyo™ Freezing -3°C
	
Using 1°C/min shelf cooling rate	Using ControLyo™ at -3°C Shelf SP

SEM images of sucrose, 75 mg/mL

SEM Image

GILYOS® GmbH

ControLyo™ in a Manufacturing Environment

- Scalability in freeze dryers of any size
- Increases product consistency and uniformity
- Less vial damage
- Reduces cycle times and improves product yield
- Technology Differentiator – added capabilities
- Robust, non-invasive, and easily implemented/maintained
- Conforms to regulatory expectation

Recent Work Using *ControLyo*™

- “Application of **controlled nucleation** during lyophilization to improve cake appearance and product quality” – SP Webinar by Dr. Stuart Wang, (formerly of Biogen IDEC)

- “Impact of **controlled ice nucleation** on process performance and quality attributes of a lyophilized monoclonal antibody”, FDA, Awotwe-Otoo, D., Agarabi, C., Read, E., Lute, S., & Borson, K. (2013), *International Journal of Pharmaceutics, 450*(1-2), 70–78.

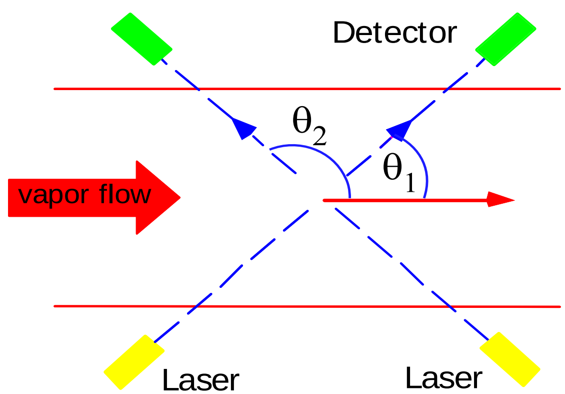
PAT: TDLAS Mass Flow Measurements

Near-IR (~1.4 µm) water vapor absorption measurements to determine:

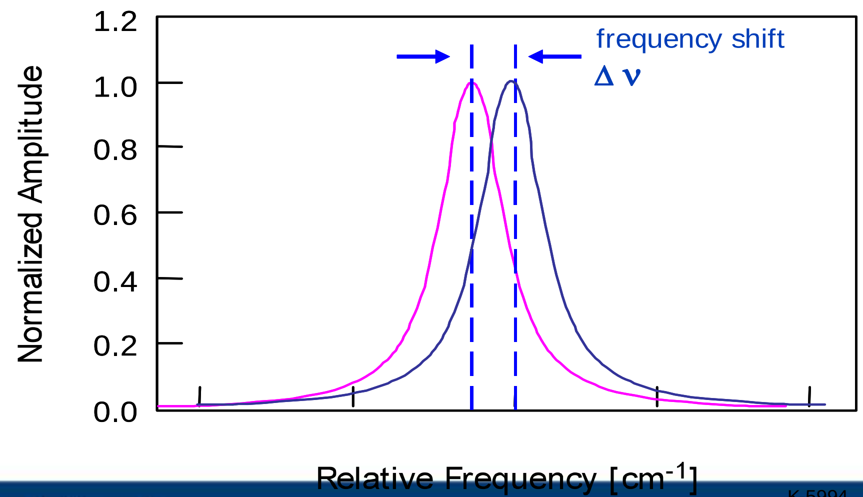
1) Gas temperature (K)
2) Water vapor concentration [molecules/cm^3]
3) Gas flow velocity [m/s]

→ *Calculate the water vapor flow rate, dm/dt [grams/s]*

→ *Integrate the water removal rate to predict the mass balance*



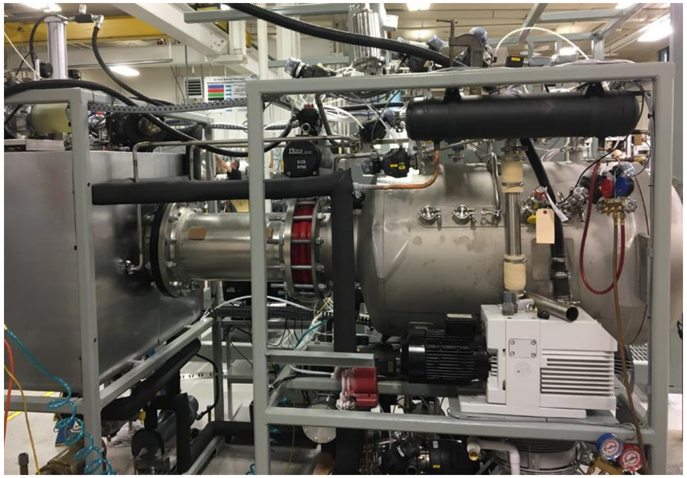
Absorption lineshapes from two line-of-sight measurements across the spool connecting the lyophilizer chamber and condenser



Information Courtesy of Physical Sciences Inc.

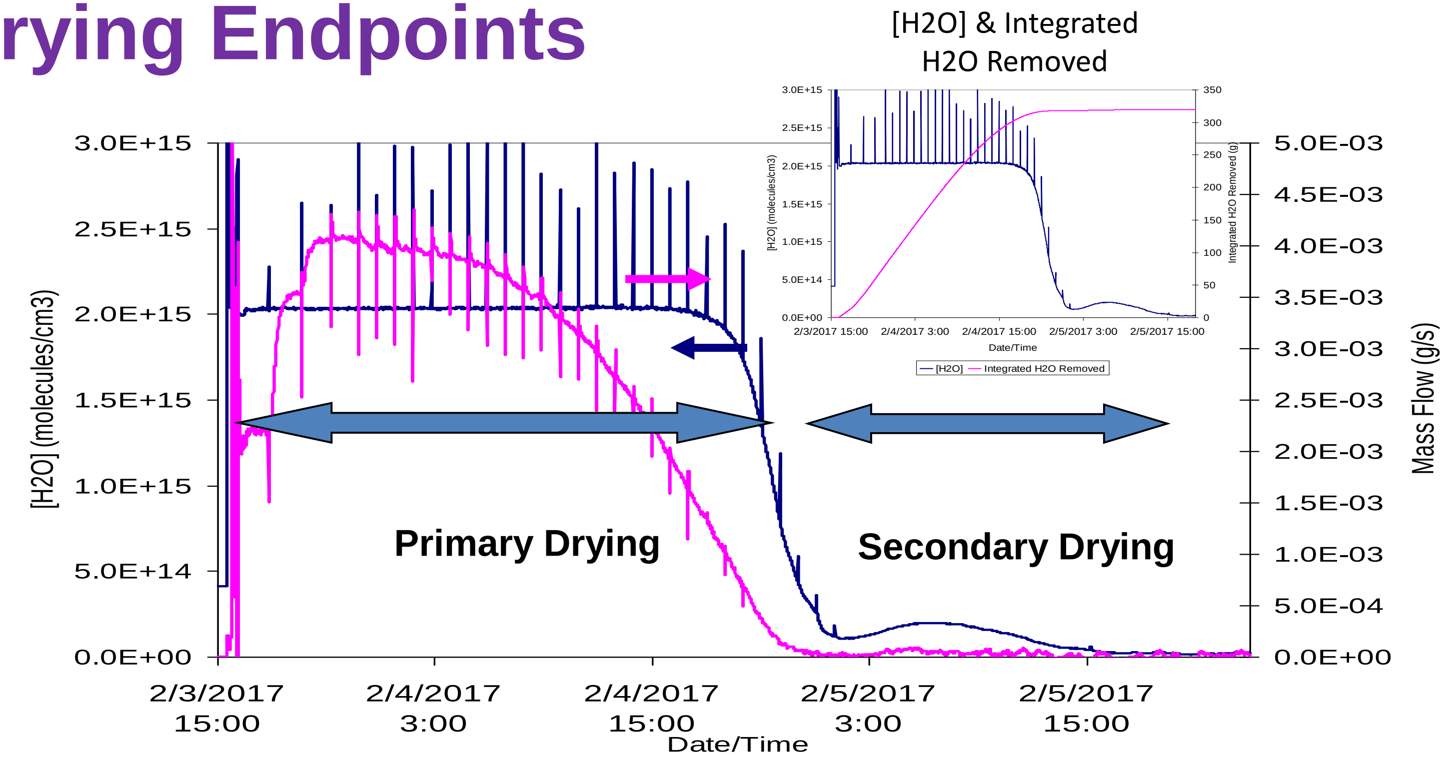
TDLAS Measurement Applications

- Determination of primary and secondary drying endpoints
- Continuous determination of batch average product temperature (T_b and T_p)
- Continuous determination of:
  - R_p: product resistance to drying
  - ℓ: product dry layer thickness



Information Courtesy of PSI Physical Sciences Inc.

Determination of Primary and Secondary Drying Endpoints

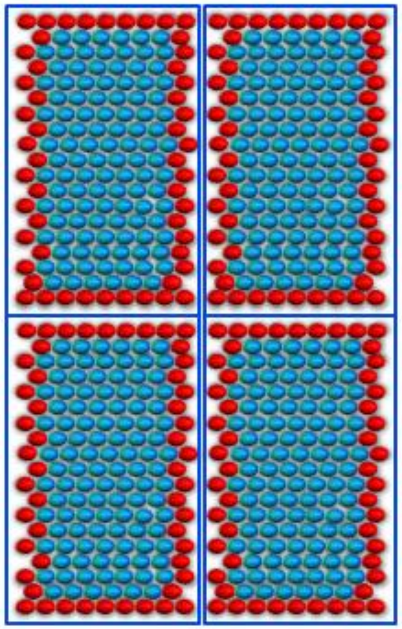


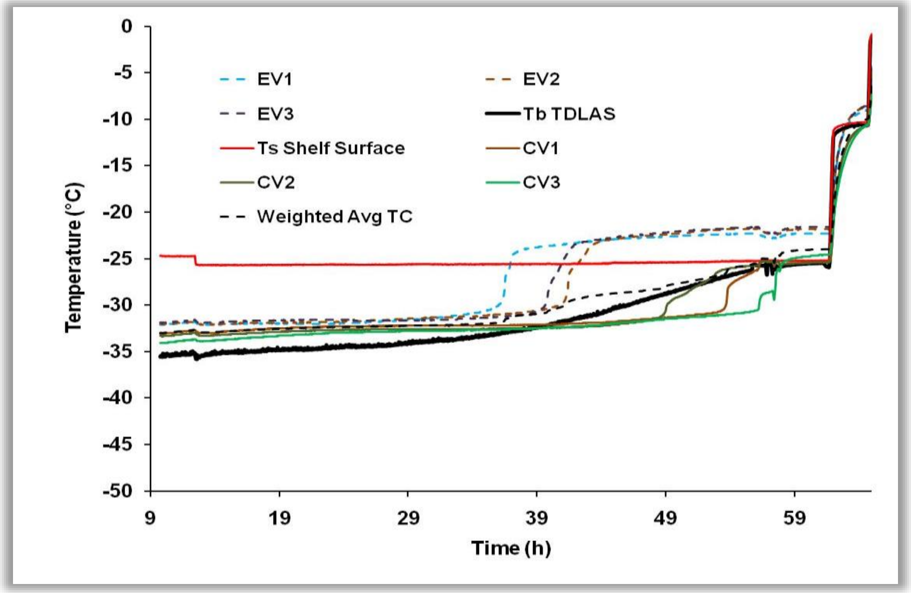
Data spikes: TDLAS data recorded during MTM-based SMART experiment

SMART FD Cycle
5% sucrose formulation
3 mL fill
20 mL vials
112 vials

Information Courtesy of Physical Sciences Inc.

Pilot Scale FD Batch Product Temperature Average



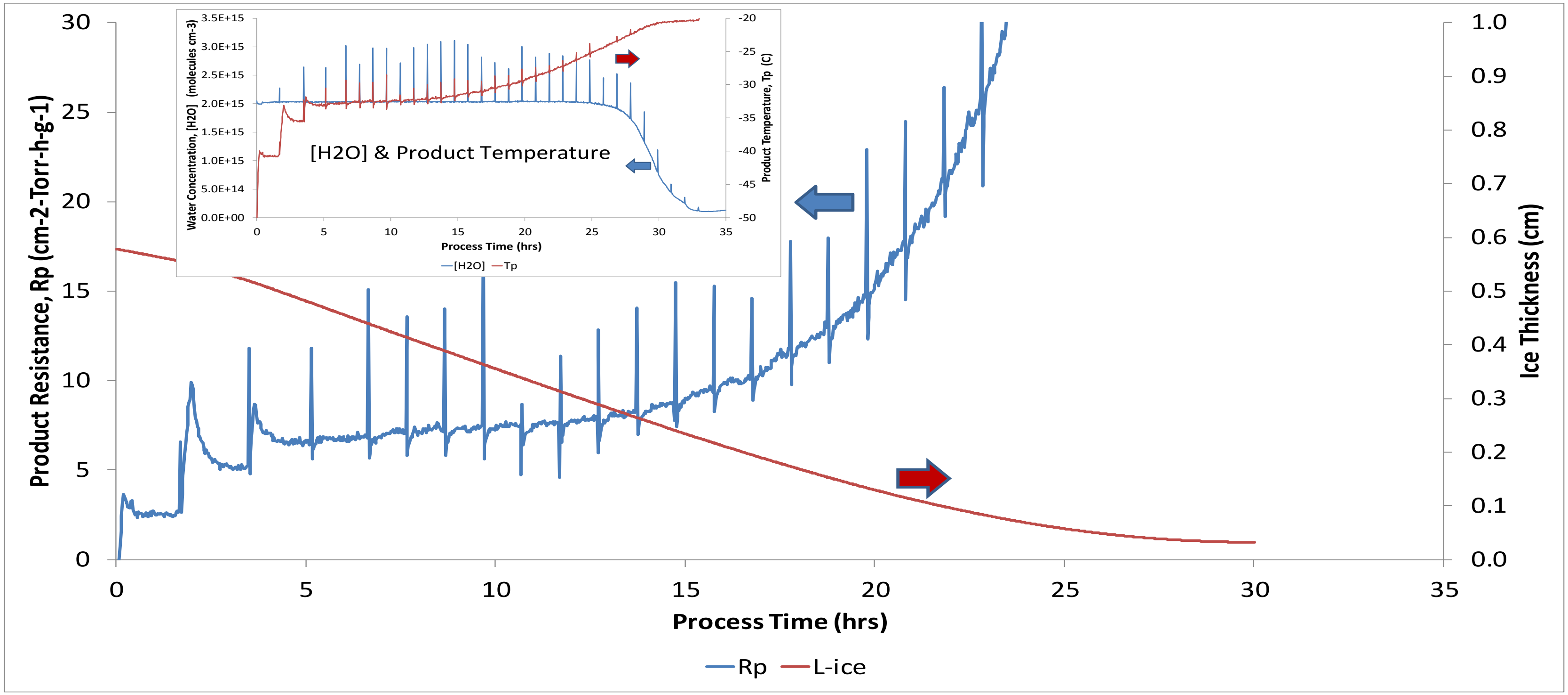


Weighted average thermocouple temperature (for edge and center vials) was calculated for comparison with TDLAS T_b. EV: Edge vials; CV: Center vials; TC: Thermocouple. K_v 2.90 x 10^{-4} cal/sec.cm^2.K, N= 1620, A_v: 7.17 cm^2, ΔH_s: 660 cal/sec.

K_v scaled from lab FD measurements: emissivity & edge vial ratio

Information Courtesy of Physical Sciences Inc.

Continuous Determination of Product Resistance and Ice Thickness



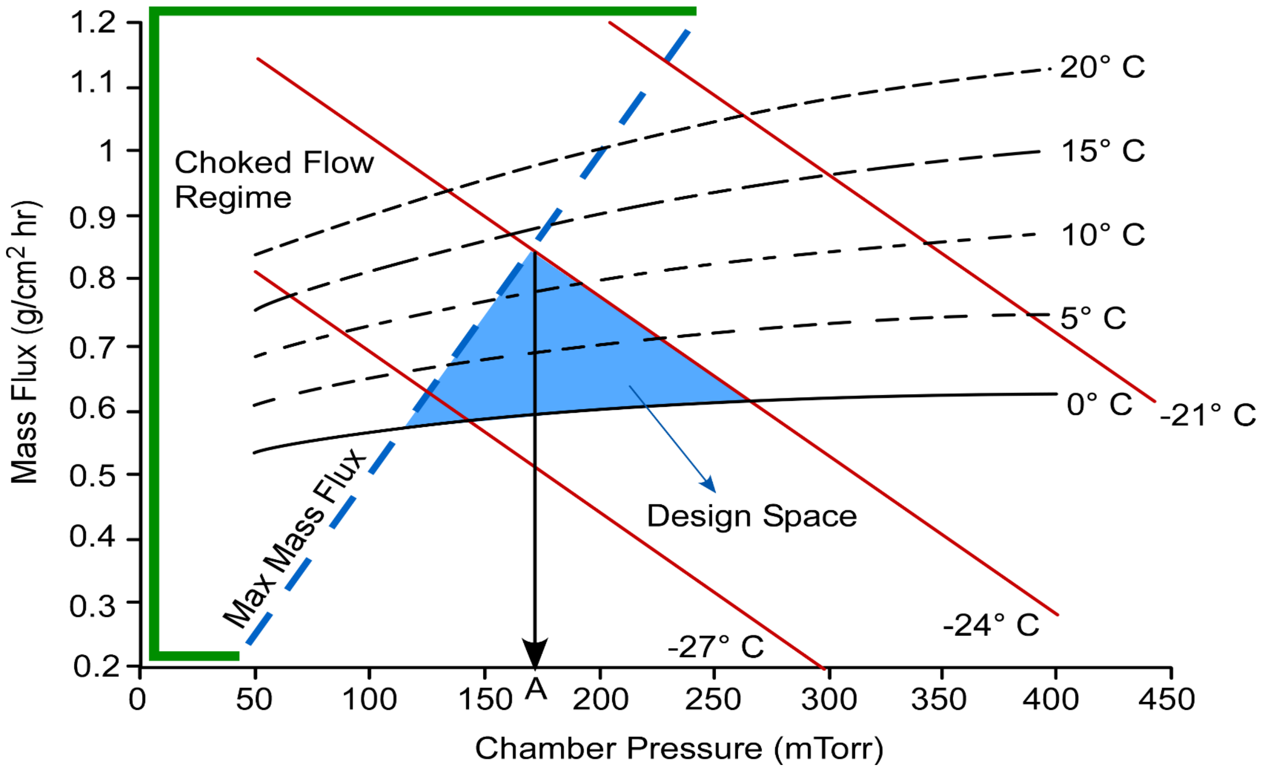
Information Courtesy of Physical Sciences Inc.

TDLAS Application in QbD

- PAT tool providing key data for QbD based drying cycle development by determination:
  - Vial heat transfer coefficient (K_v)
  - Product dry layer resistance (R_p)
  - FD capability limits: Onset of choked flow
- Assessment of drying heterogeneity: prediction of # of vials completing 1^o drying
- Applicable to all freeze dryer sizes enabling scale up experiments and technology transfer

Information Courtesy of PSI Physical Sciences Inc.

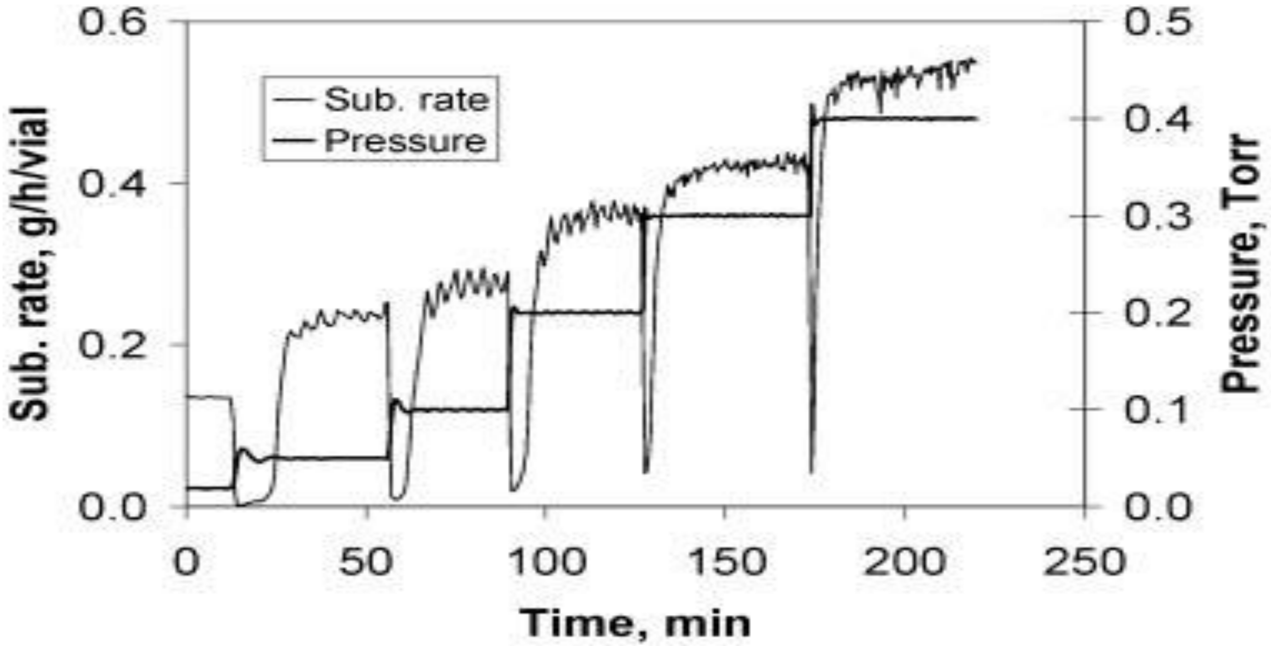
Construction of Design Space



TDLAS Determination of:
- Kv: vial heat transfer coefficient
- Rp: product resistance to drying
- FD equipment limit: choked flow

Information Courtesy of Physical Sciences Inc.

Kv Determination With Changing Chamber Pressure



Kuu,W.Y., Nail, S.L., Sacha, G., Rapid Determination of Vial Heat Transfer Parameters Using Tunable Diode Lase Absorption Spectroscopy (TDLAS) in Response to Step-Changes in Pressure Set-Point During Freeze –Drying, J Pharm Sci, 98(3) 2009.

Information Courtesy of Physical Sciences Inc.

Sample Kv Data Using TDLAS Measurement

- Use of TDLAS enables generation of this table in one experiment
- Gravimetric approach requires one experiment per pressure level (12 experiments)

Pressure (mT)	K_v (j/hr-cm^2- ^{o}K)
25	3.58
50	5.25
75	6.11
100	7.24
125	8.20
150	9.01
175	9.75
200	10.31
250	11.21
300	12.07
350	12.92
400	13.77

Adapted from Nail & Kessler:
Experiences with TDLAS at Laboratory & Production Scales, Garmisch 2010

Information Courtesy of PSI Physical Sciences Inc.

Scale up to Production Freeze Dyer Opportunity for use of TDLAS

- Lab scale QbD-based cycle development: knowledge & design space
  - Determination of vial heat transfer coefficient, K_v
  - Determination of product resistance to drying, R_p
  - Establishment of FD equipment limitation: choked flow measurements

Production Scale QbD Based Cycle Modifications

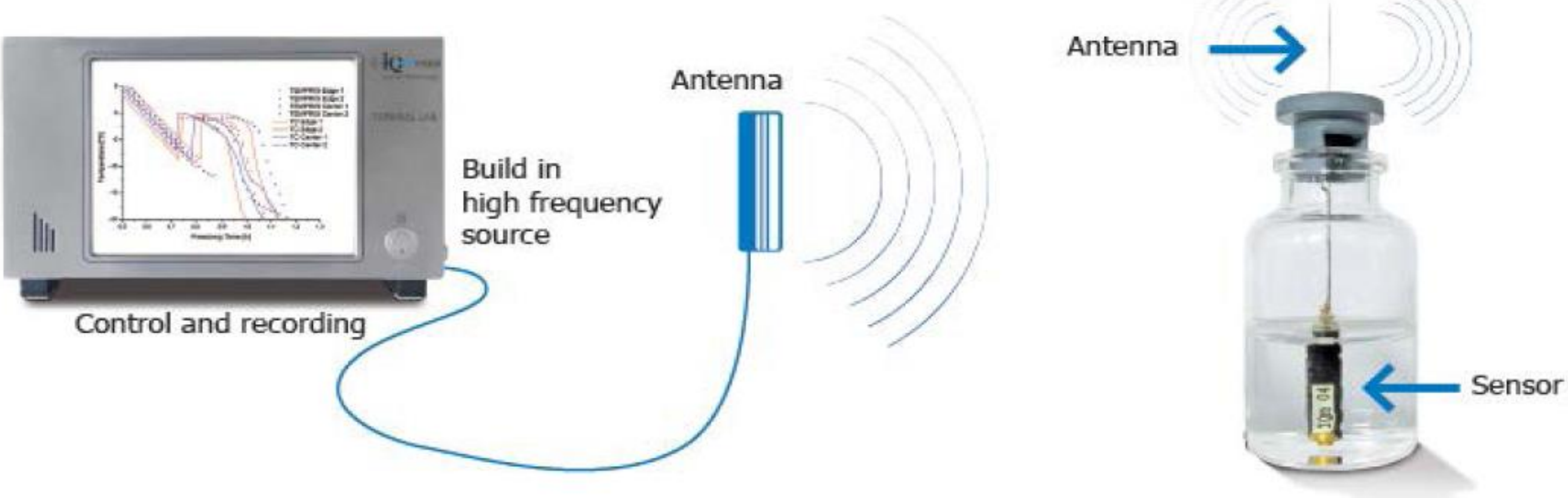
- Commercial scale QbD-based cycle development: knowledge & design space
  - Evaluate freeze dryer limitation: choked flow measurements
  - Adjust lab scale dryer K_v for production dryer

    Scale by differences in ratio of center/edge vials and shelf & wall emissivities
  - Re-evaluate design space using adjusted K_v and lab scale R_p
  - Freeze dry demonstration batch using modified cycle design with data from batch (R_p)

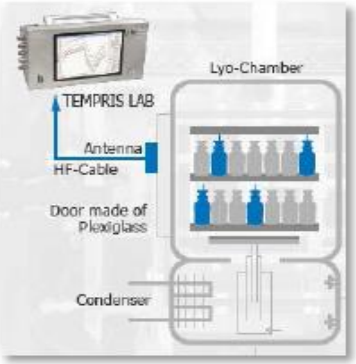
    Verify design space with measured values: dm/dt & T_p

    Confirm new cycle design with second demonstration batch

PC with build in high frequency source

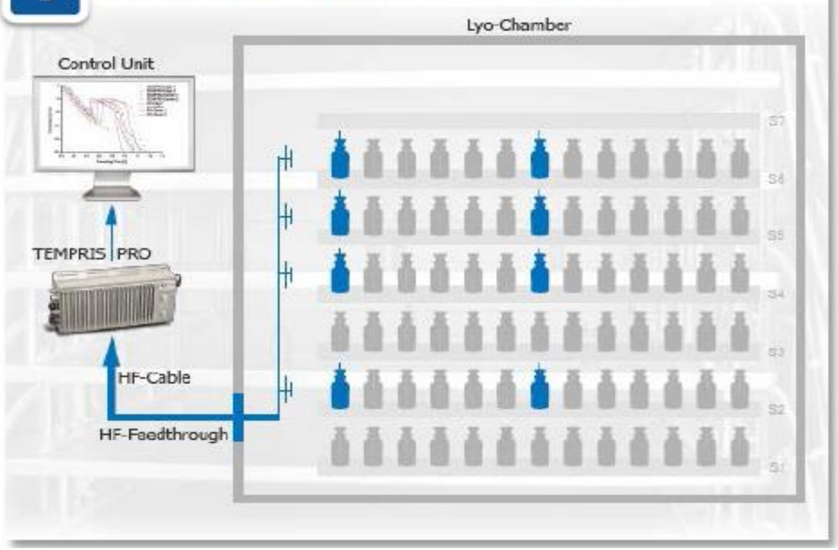


Quartz based sensor, operating on the principle of temperature dependent resonance: after excitation by a modulated microwave signal (2.4 GHz) the sensor keeps on oscillating in a temperature dependent frequency. Overlaying the sensor response with the carrier signal leads to a frequency shift from which the product temperature Tb can be derived.

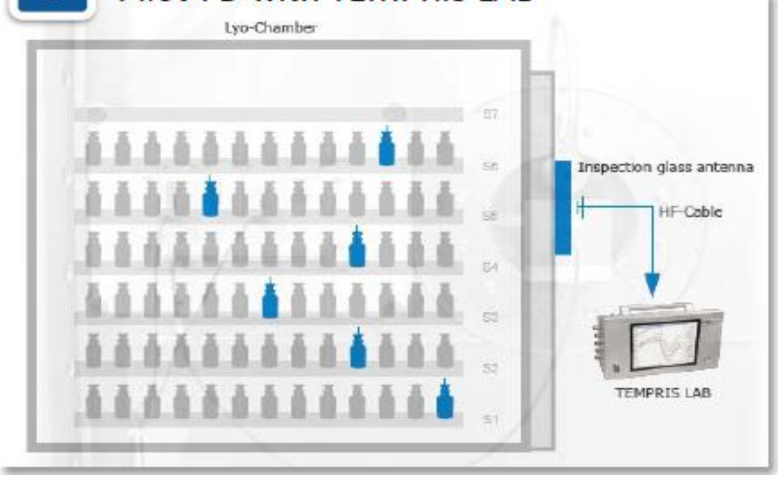


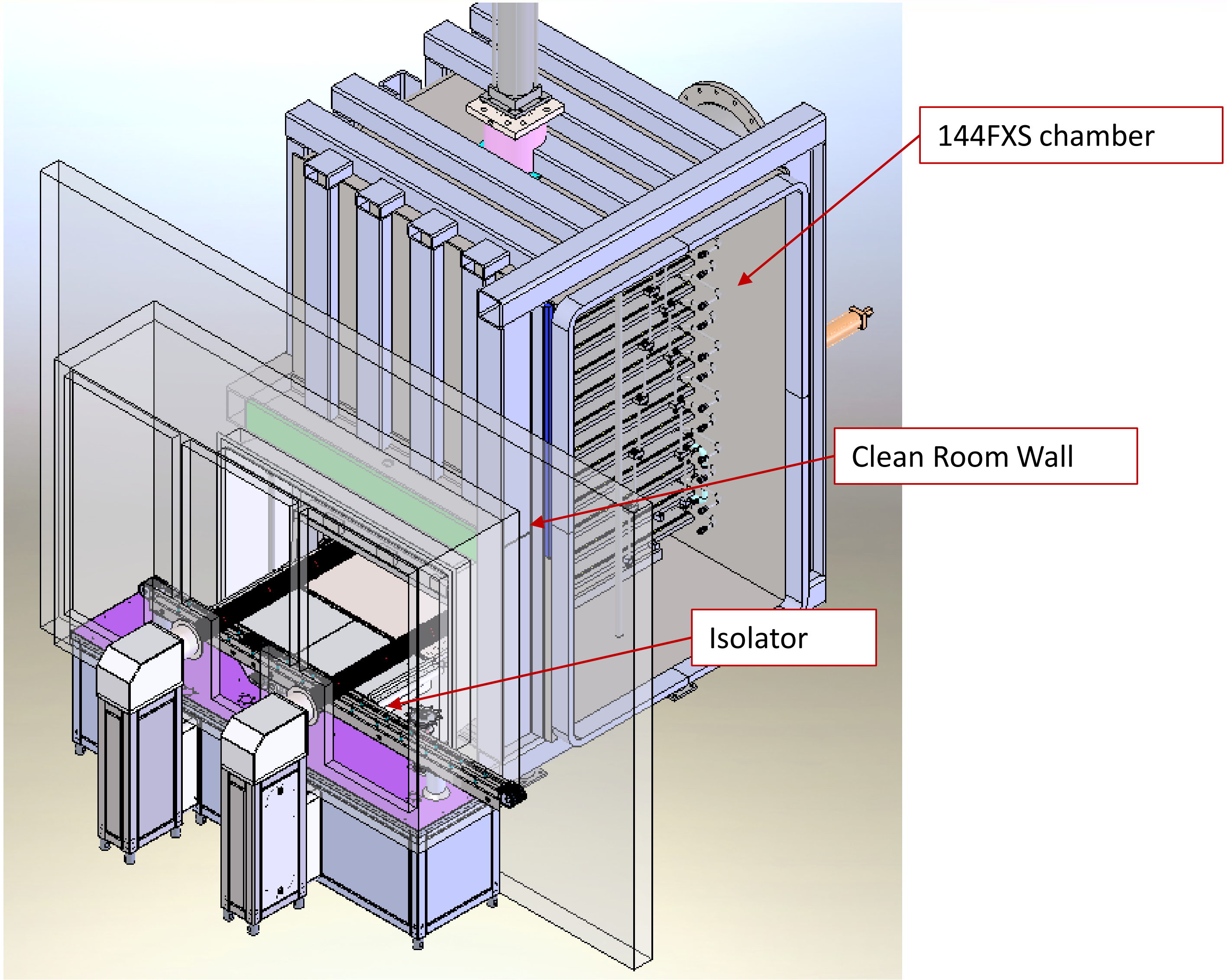
1 Lab FD with TEMPRIS LAB

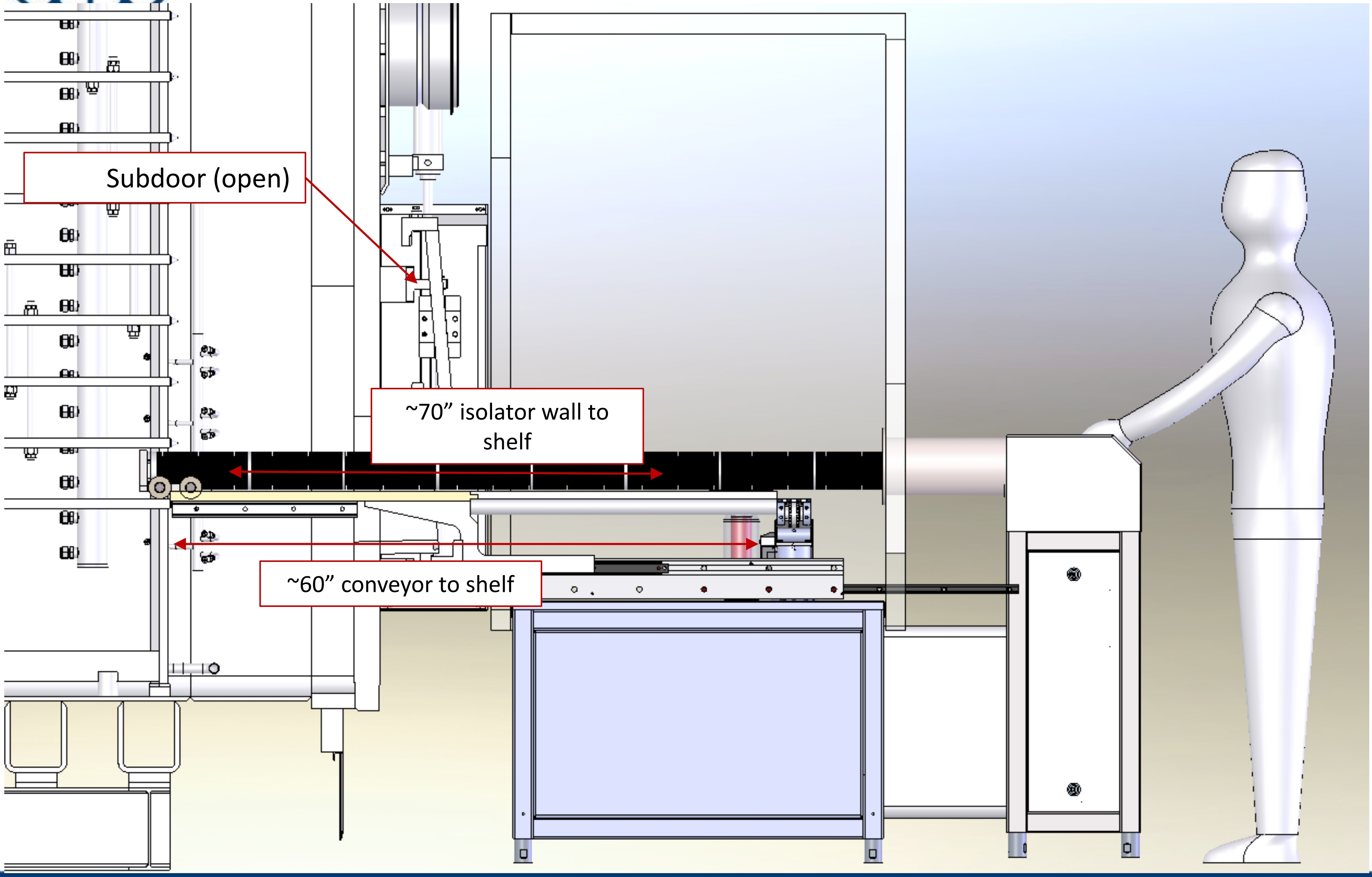
3 Production-FD with TEMPRIS PRO



2 Pilot-FD with TEMPRIS LAB



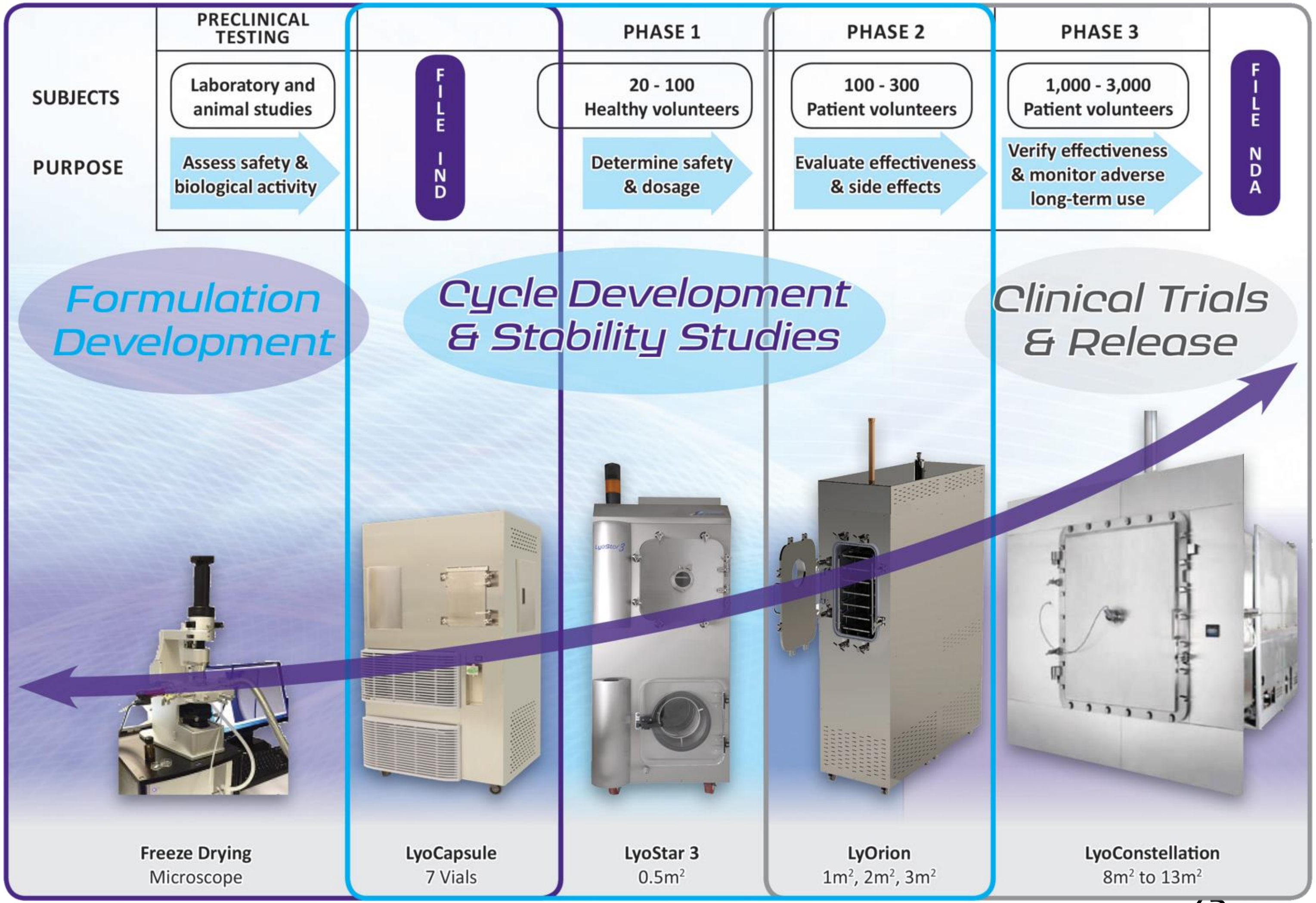

144FXS chamber
Clean Room Wall
Isolator


Subdoor (open)
~70” isolator wall to shelf
~60” conveyor to shelf

In Summary

- Process control and PAT tools facilitate the QbD approach and conforms to regulatory expectations
- ControLyo™ technology is gaining more commercial manufacturing adoption in the industry
- Controlled nucleation minimizes variabilities in product quality
- Use of TDLAS can provide product information which can impact quality attributes

Line of Sight across the SP Range



References

- ICH Q8 (R2)Guidance for Industry – Pharmaceutical Development
- ICH Q11 - Development and Manufacture of Drug Substance (Chemical Entities and Biotechnological/Biological Entities)
- FDA Draft Guidance - Advancement of Emerging Technology Applications to Modernize the Pharmaceutical Manufacturing Base Guidance for Industry
- FDA Guidance - PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance
- FDA – Guide to Inspection of Lyophilization of Parenterals

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