Introduction to Line-of-Sight & New Fill Finish Tools

Ian Whitehall
What is Line of Sight?

Suite of equipment & technologies that increase understanding & control over the fill finish process

- Scalable technologies that create a data-rich environment across all sizes of freeze drying systems; laboratory, development & production.
- Enables an expanded design space and the understanding of your freeze drying process within this space
- Control the process of freezing – no longer a stochastic process
- Recreate failure state in small scale when process excursions happen in manufacturing scale
Line-of-sight

- Partnering with iDositechno SP Provides full lines tailored to suit your capacity requirements
- Technologies embedded in our freeze driers allow accurate comparison between all scales of manufacturing from seven vials to thousands...
- 4 principal freeze drying technologies:
  - LyoFlux® TDLAS gives accurate measurement of vapor mass flow
  - TEMPRIS® wireless thermocouples
  - ControLyo® gives precise control of the freezing point
  - LyoCapsule™ miniaturized freeze dryer

LyoFlux® is a registered trademark of Physical Sciences Inc, Andover, MA, USA
Tempris® is a registered trademark of iQ-mobil Solutions GmbH, Holzkirchen, Germany
Line of Sight Across the SP Range

- **Preclinical Testing**
  - Freeze Drying Microscope

- **File IND**
  - LyoCapsule
    - 7 vials

- **Phase 1**
  - LyoStar 3
    - 0.5m²

- **Phase 2**
  - LyoConstellation
    - 1m², 2m², 3m²

- **Phase 3**
  - LyoConstellation
    - 8m² to 13m²

**CLINICAL TRIALS AND RELEASE**

**Cycle Development and Stability Studies**
ControLyo®

- ControLyo gives precise control of the point of freezing in all vials simultaneously by means of sudden depressurization
- Requires a pressure rated chamber but it adds nothing to the vial
- Higher nucleation temperature, less super-cooling, saving time and money
  - Same nucleation temperature and time stamp for all vials, including those with a thermocouple
  - Larger ice crystal size gives reduced cycle time
  - Easy to retrofit to most dryers and requires no change to an existing formulation
  - Results depend on the formulation but typically includes; improved cake appearance, reduced protein aggregation, reduced skin formation, shorter drying times, reduced vial cracking and faster reconstitution times

![Diagram showing low and high Tn degrees of supercooling](image)
Water vapor concentration and gas flow velocity during freeze-drying
  - Expressed as $\delta m/\delta t$

These measurements can be combined to calculate the instantaneous water vapor mass flow rate, the freeze-drying ice sublimation rate.

The determination of the sublimation rate can be combined with a heat and mass transfer model of freeze-drying to determine a Key Process Parameter (KPP) during freeze-drying, the product temperature at the ice sublimation interface. This product temperature is closely linked to product quality, thus the LyoFlux™ sensor enables real-time measurements that will enable process control and the manufacture of high quality product.

Data can be fed into the SMART algorithm to calculate parameters ...
LyoFlux® TDLAS

- $\delta m/\delta t$ measurement is probably the most critical tool when scaling:
  - Internal environment of a larger drier is significantly different to a small one, thus matching shelf temperature, ice temperature and vacuum level will not produce a similar result
- Non-invasive & works at all scales
- Provides true batch average values for all vials
- It continues to grow in popularity as an accurate tool for use in freeze drying technology, applicable to lab, pilot and production dryers to monitor process
- Non-Contact Determination of:
  - Primary & secondary drying endpoints
  - Average product temperature
  - Average product resistance
  - Vial heat transfer coefficients such as $K_v$
  - Freeze dryer performance qualification

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LyoFlux® TDLAS

- Now operational at a range of scales from miniaturized Lyo to Production
- Tested fully on LyoConstellation™ S20 2m² during summer 2017
- 300mm / 12”Ø spool piece between chamber and isolation valve

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TEMPRIS® Wireless Sensors

- Compatible with all sample loading technologies: Manual, Semi-automatic, Fully automatic
- Line of sight across all scales of freeze dryer - proving that you have stayed within the design space
  - Same method of temperature measurement across all scales
  - Monitor sample temperature post filling and during loading
  - Monitored vial has the same stopper as the rest of the batch
- Vials (Sensors) can be autoclaved to sterilize
- Isolator friendly, much easier to load vials, improving safety
- Improved stability, no trailing thermocouple wire reduces risk of fallen vials
- Better positioning within the vial

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Line of Sight Across the SP Range

- **FORMULATION DEVELOPMENT**
  - PRECLINICAL TESTING
  - FILE IND
- **CYCLE DEVELOPMENT AND STABILITY STUDIES**
  - PHASE 1
    - LyoCapsule
      - 7 vials
    - LyoStar 3
      - 0.5m²
- **CLINICAL TRIALS AND RELEASE**
  - PHASE 2
    - LyoConstellation
      - 1m², 2m², 3m²
  - PHASE 3
    - LyoConstellation
      - 8m² to 13m²

- Freeze Drying Microscope
- LyoCapsule
- LyoStar 3
LyoCapsule™- Solution to Scaling?

- LyoCapsule is a small, R&D freeze dryer that delivers results comparable to larger R&D freeze dryers enabling a Quality by Design (QbD) approach to cycle development even when APIs are very expensive or limited in quantity.

- Can be used for scale down studies of excursions to investigate batch integrity – recreating failure mode and allowing multiple scenario reconstructions.

- LyoCapsule is equipped with a full suite of process monitoring tools:

- Only requires 7 vials – ideal for:
  - early stage cycle development
  - troubleshooting a production cycle scaled down to the lab scale
The LyoCapsule

- LyoCapsule chamber has a cylindrical inner chamber ‘the capsule’
  - Temperature controlled to mimic larger freeze dryer conditions
    - All vials can be made to behave as center vials
  - Assures that edge vials dry under the same process conditions as center vials, enabling the utilization of small quantities of materials for more efficient, robust, and less costly cycle development
  - Capsule wall temperature can be directly programmed, or follow center vial TC
- Accommodate up to seven (7) 20cc (15R) – 1 center and 6 edge vials
- Process 2cc to 20cc vials
LyoCapsule™ Freeze Dryer

- LyoCapsule is complete with all critical process monitoring tools:
  - Chamber and condenser capacitance manometers
  - Chamber Pirani gauge
  - 6 product thermocouples
  - Capacitance/Pirani gauge comparison
  - Pressure rise measurement capability
  - TDLAS
LyoConstellation
## Line of Sight Across the SP Range

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LyoConstellation

- A new range of freeze dryers from SP Scientific
  - Designed for aseptic operation
  - Covers cycle development, stability, pilot and clinical batch production, through to full aseptic production
  - Development and Pilot systems powerfully equipped as standard to provide very high capability for mapping expanded design space
  - Production systems configured to order for faster delivery
  - Same software platform and technology options as smaller systems from SP to fit with line of sight strategy
  - Range of shelf areas
    - Development / Pilot – 1m² to 3m²
    - Production – 8m² to 13m²
  - Fully SIP & CIP as standard
- Suitable for cleanroom installation
- Isolator ready
- Integrates with SP’s filling lines
LyoConstellation
Development & Pilot Systems

- Provide largest process space so that highly aggressive cycles may be developed
  - Hold 100mTorr while shelves at +40°C **fully loaded**
  - Ratio of condenser surface area to shelf area is 1:1
  - Shelf Pull-down time < 25 Min @ -40°C
  - Condenser Pull-down time < 35 Min @ -45°C

- Equipped and controlled as a production system
  - Easy to scale up / scale down cycles
  - Can be used for clinical batches and small scale production

- Provides ‘Line of Sight’ approach in cycle development & scale up using same technologies from R&D to production

- Going Green – F Gas Compliant