

Best Practices in Pharmaceutical Freeze-Drying

An Opportunity for Inter-Company Collaboration

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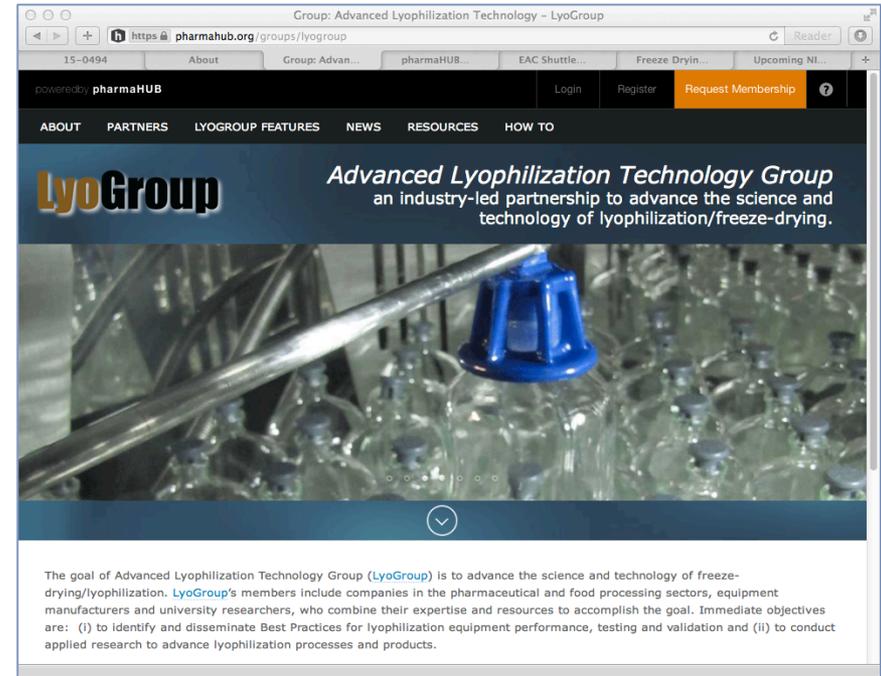
LyoGroup: Advanced Lyophilization Technology Consortium

Mission: Industry-led partnership aimed at advancing science and technology of freeze-drying / lyophilization.

Goals of LyoGroup consortium are

- engage the full value chain
- set research priorities
- conduct pre-competitive research
- disseminate best practices and inform regulatory policy

Do all of the above far more quickly and effectively than can end-users and equipment manufacturers acting alone.



pharmahub.org/groups/lyogroup

LyoGroup: Advanced Lyophilization Technology Consortium

Best Practices Working Group

IMA  **LIFE**

Pfizer

Janssen 

MILLROCK
TECHNOLOGY 

 **INFICON**

PURDUE
UNIVERSITY

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Purpose

- **To establish, and maintain, a collaborative effort among industrial and academic thought leaders that will result in a set of “best practice” documents focused on non-proprietary areas of freeze drying operations.**
- **To identify areas where more research is needed, and to stimulate collaboration between industrial scientists and academic faculty.**

Why?

- **Uncertainty over best practices in many areas of freeze drying operations can lead to delays resulting from lengthy internal debate over what constitutes “best practice.”**
- **Too many industry people fail to think deeply enough about scientific rationale for these kinds of practices. We hope that this effort will promote deeper understanding of the freeze dry process. This is the intent of the Quality by Design paradigm.**
- **When asked a technical question by a regulatory agency, the last thing anyone wants is to be taken by surprise, and have no thoughtful response to offer.**

- These “best practice” documents are intended to bring out points to consider and to stimulate reflective thought about best practices. There is no intent to “lay down the law” about what must be done.
- Since controlled nucleation involves proprietary technology, this subject area is out of scope of the “best practice” collaboration.

Potential Subject Areas

- **Scientific justification of acceptance criteria for freeze dryer leak rate testing.**
- **Instrumentation for process monitoring and capability testing.**
- **Acceptance criteria for cake appearance.**
- **Sampling plans for final product testing, particularly for residual moisture.**
- **Equipment qualification**
- **Cleaning validation**
- **Process validation**
- **Batch acceptance criteria**

Example: Establishing Acceptance Criteria for Leak Rate Testing of Freeze Dryers

- With the chamber and condenser clean and dry, the system is evacuated to a representative pressure, say 100 mT, then the valve between the vacuum pump and the condenser is closed. Pressure is monitored for a fixed period of time – commonly 30 minutes to one hour, and ΔP is recorded.
 - **Question: What is the maximum acceptable value of ΔP , and why?**
- Approaches:
 - Equipment capability
 - Parenteral Society recommendation:
 - 2×10^{-2} mbar-L/sec
 - Question: Where did this number come from?
 - Answer the following question: “How much can the freeze dryer leak without violating Class A microbial specifications in the freeze dryer?”

Assumptions

- **All leakage comes from the “dirty” side of the freeze dryer; that is, the mechanical room, which is usually an uncontrolled environment.**
- **Product sterility is most at risk from the time primary drying is over until the stoppers are seated at the end of the process.**
 - **During primary drying, the vial headspace is under positive pressure, with a robust flow of water vapor out of the vial.**
- **The leak rate is approximately constant over the time course of freeze drying.**
- **Any microorganisms that enter the chamber stay there; that is, they are not swept immediately out of the system by the vacuum pump.**

Procedure

- **Active air sampling was done at different times of the year in the mechanical room, at three points adjacent to the freeze dryers.**
 - **We multiplied the “worst case” data by a factor of two to establish a wide safety margin.**
- **Measure the “void” volume of the freeze dryer chamber and condenser (the volume not occupied by shelves, condenser hardware, tubing, and so forth):**
 - **Attach a cannister of known internal volume to a spare port on the freeze dryer**
 - **Evacuate the system to a known pressure, say 100 mT. With the valve between the chamber and condenser open, close the valve between the condenser and the vacuum pump. Record initial pressure.**
 - **Open the valve between the cannister and the chamber. Record the new pressure.**

Procedure (continued)

- Calculate the void volume using the Ideal Gas Law:

$$V = \Delta n RT/\Delta P$$

Note that Δn must be corrected for non-standard temperature and pressure

- Determine the product-specific freeze dry cycle with the longest secondary drying time. Consider including a safety factor.

An Example Calculation

- **Void volume of the freeze dryer: 8636L, or 8.64m³**
- **Bioburden in the mechanical room: 300 cfu/m³**
- **Maximum volume of leak: 28.8 L**
- **Maximum secondary drying time: 36 hr (includes a safety factor)**
- **Maximum allowable leak over 30 minutes:**

$$\Delta P = \Delta n RT/V$$

$$\Delta P = 0.017 \text{ mole (62.36 L mmHg/K-mole) } 298\text{K}/8636\text{L}$$

$$= 0.036 \text{ mm Hg} = 36 \text{ mT}$$

Leak Rate Testing (continued)

- **This approach has already been published (Hardwick et al., Int. J. Pharm., 85, 236-9 (2013)).**
 - **Is it best practice?**
 - **If not, why not?**
 - **Are there other approaches that are better?**

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Some Thoughts on Best Practice for Process Monitoring Instrumentation

- **Concerning product temperature measurement:**
 - Use thin-gauge thermocouple wire
 - Use some type of device to secure the thermocouple within the vial
 - Make a best effort to locate the tip of the thermocouple in the center of the vial, touching the bottom
 - If RTD system is used, try to use the smallest sensing element practical.
 - Recognize that all methods of measuring product temperature create a non-representative situation. Monitored vials:
 - Supercool less
 - Freeze slower than the rest of the batch
 - Have a larger average ice crystal size
 - Have a lower product resistance, R_p
 - Sublime faster than the rest of the batch

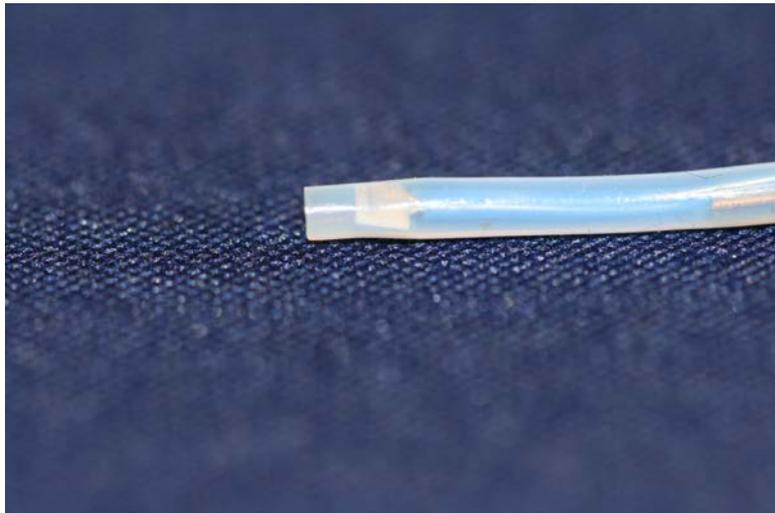
Product Temperature Thermocouples in Production



Product Temperature Measurement in Development Lab



The Ellab System Uses RTDs



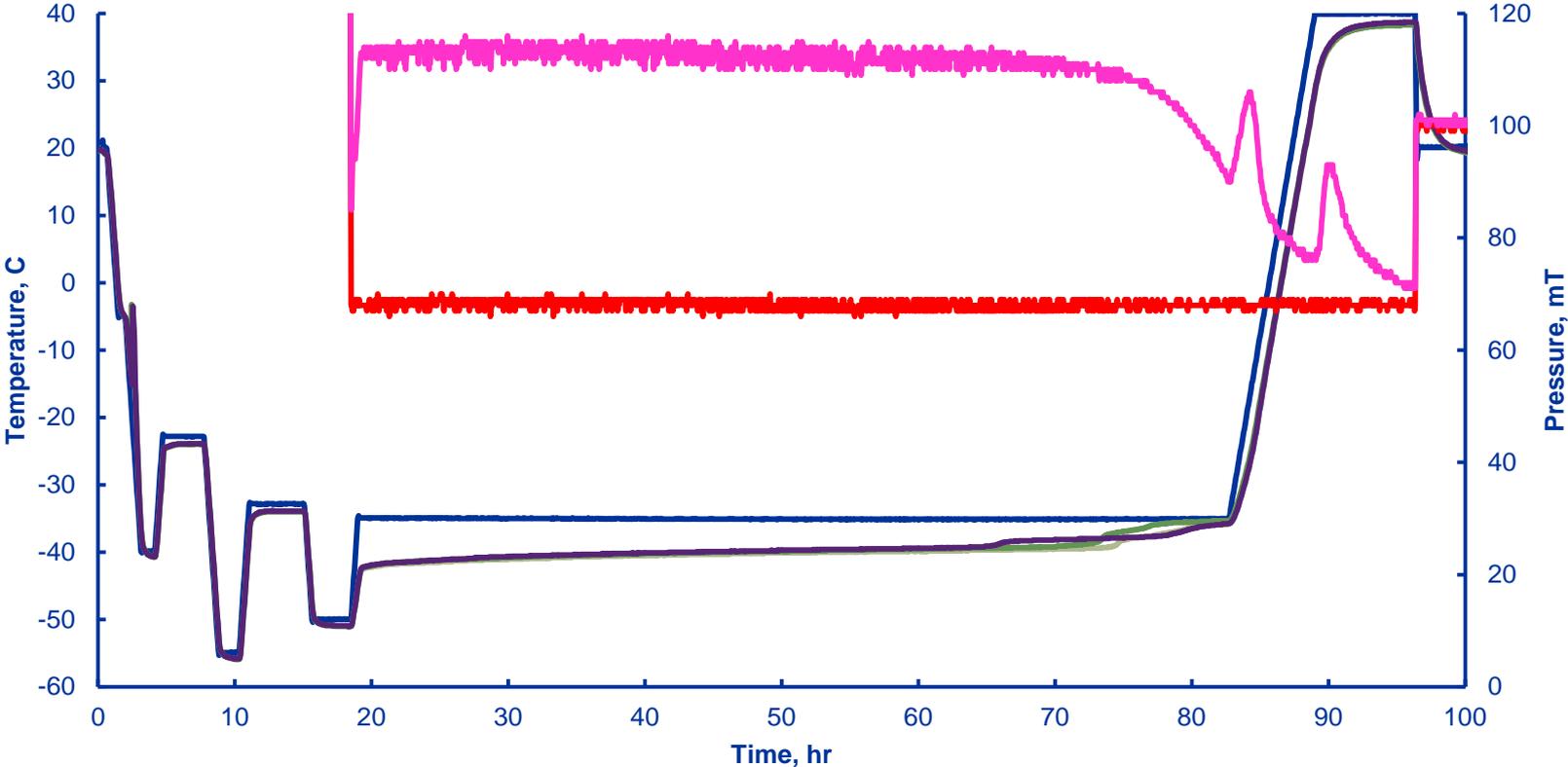
Applied Research Need

- **A review and critical assessment of wireless product temperature measurement technology:**
 - **Tempris system**
 - **Wireless Ellab system**
 - **Others?**

Some Thoughts on Pressure Measurement

- **Put both a capacitance manometer and a Pirani gauge on both the chamber and the condenser.**
 - **Why?**
 - **It enables comparative pressure measurement.**

Representative Process Data



Advantages of Comparative Pressure Measurement

- **Does not depend on monitoring of individual vials**
- **It is:**
 - **Inexpensive**
 - **Sensitive**
 - **Robust**
- **This type of data is useful in:**
 - **Monitoring of routine production batches**
 - **Scale-up**
 - **Handling of process deviations**
 - **Easy to distinguish between primary and secondary drying**

Some Thoughts on Pressure Measurement

- **Have a capacitance manometer on both the chamber and condenser**
 - **Why?**
 - **It facilitates measurement of equipment capability by enabling measurement of the pressure ratio between chamber and condenser.**
 - **This ratio is an indicator of the onset of choked flow:**
 - **For a cylinder, this ratio is 3.0**
 - **For an orifice, it is 1.8**
 - **It may facilitate handling of process deviations**
 - **In the event of a pressure excursion resulting from a leak, it is important to know whether the leak came from the sterile nitrogen used for the controlled bleed, or from the condenser side.**

Research Need

- **Some freeze dryers have a different configuration of chamber and condenser. For some, the condenser is at the bottom of the chamber separated by a hydraulically actuated rectangular plate.**
- **Could we, using CFD, for example, calculate the pressure ratio corresponding to onset of choked flow?**



Some Thoughts on Pressure Measurement

- **Why is it a good idea to have a Pirani gauge on the condenser?**
 - **For troubleshooting vacuum leaks, it is useful to be able to isolate the chamber from the condenser**
 - **The Pirani gauge has a much wider range than a capacitance manometer. Pressure readings that would be off scale of a CM are easily measurable by the Pirani gauge.**

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Acceptance Criteria for Cake Appearance

- Quote from Mike Pikal:

“There seems to be this expectation that all freeze dried drug products should look like mannitol.”

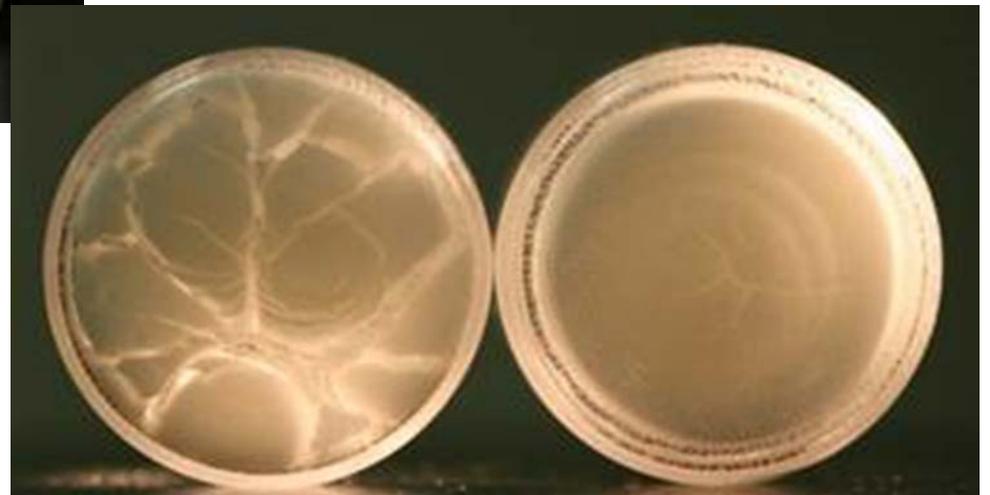
Do we spend too much time trying to fix problems that, in terms of product quality, are not problems?



Cake Shrinkage



Cake Cracking



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