

Recommended Best Practices for Process Instrumentation in Freeze Drying

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Some Area of Common “Best Practice” Interest

- Scientific justification for acceptance criteria for leak rate testing of pharmaceutical freeze dryers.
- Acceptance criteria for visual appearance of freeze dried solids
- Equipment qualification
- Cleaning validation
- Scientific justification of sampling plans, particularly for residual moisture
- Scale-Up
- Process validation

Why?

- Uncertainty over best practice can cause unnecessary delays and overly conservative decision making, particularly when the decision makers only have a superficial understanding of the process.
- There is often not enough reflective thought about the science and engineering behind many operational aspects of freeze drying.
- No one wants to be caught unprepared during technical discussions with regulatory agencies.

Broad Objectives of the Effort

- Highlight points to consider
- Stimulate discussion of best practices
- Encourage reflective thought
- Identify areas where applied research may be needed.

Scope

- Instruments and techniques that are applicable at both laboratory and production scale, or could be applicable to both.
- This represents a “snapshot” of current best practice, but also includes a section on developing technology that could become “best practice” in the future.
 - Wireless temperature measurement
 - TDLAS (production scale)
 - Mass spec for process monitoring
 - Heat flux measurement

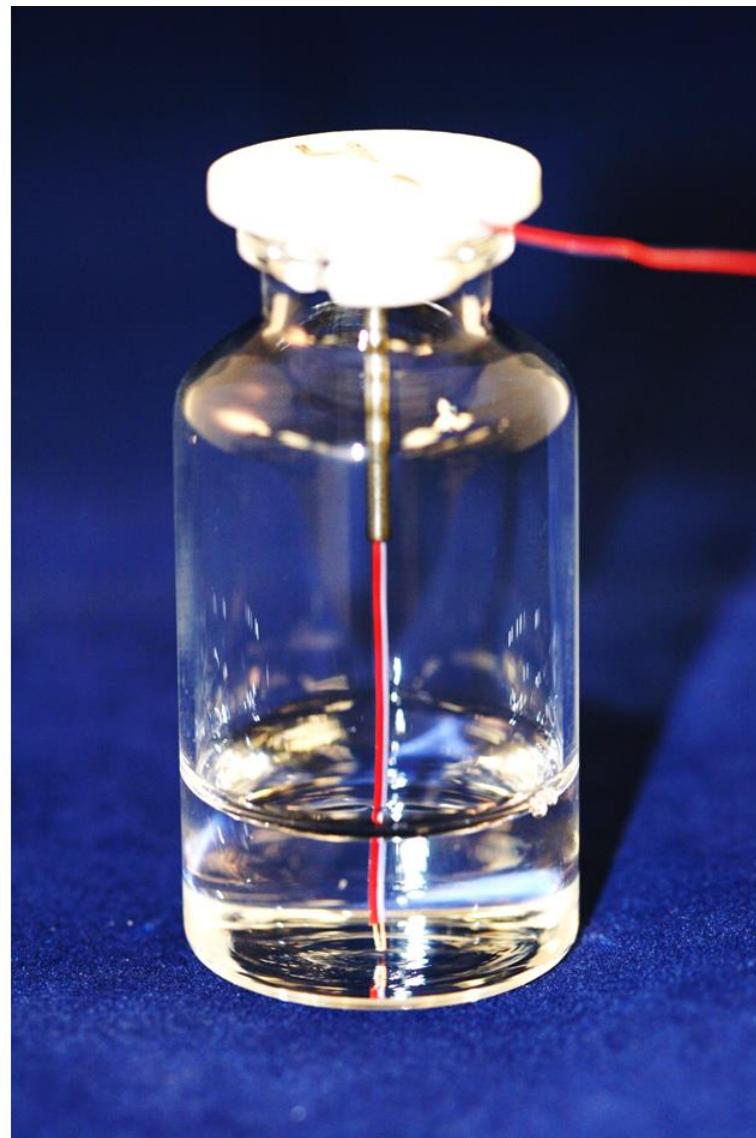
Product Temperature Measurement

- Necessary for cycle development at the laboratory scale
- Practices differ widely across the industry with respect to product temperature measurement at production scale
 - Scale-up
 - Cycle validation
 - Clinical and engineering batches
 - Transfer of cycles between manufacturing sites
 - Monitoring of routine production batches

Product Temperature Measurement



Thermocouple for Product Temperature Measurement



Best Practice for Product Temperature Measurement

- Use fine gauge thermocouple wire along with a device to hold the thermocouple in a fixed position with the tip of the thermocouple in the center of the vial and touching the bottom. The open area of the device should approximately equal the opening of a partially-stoppered vial.
- Be aware of the sources of uncertainty in product temperature measurement in a production environment, and don't over-interpret such data

Product Temperature Measurement: RTDs



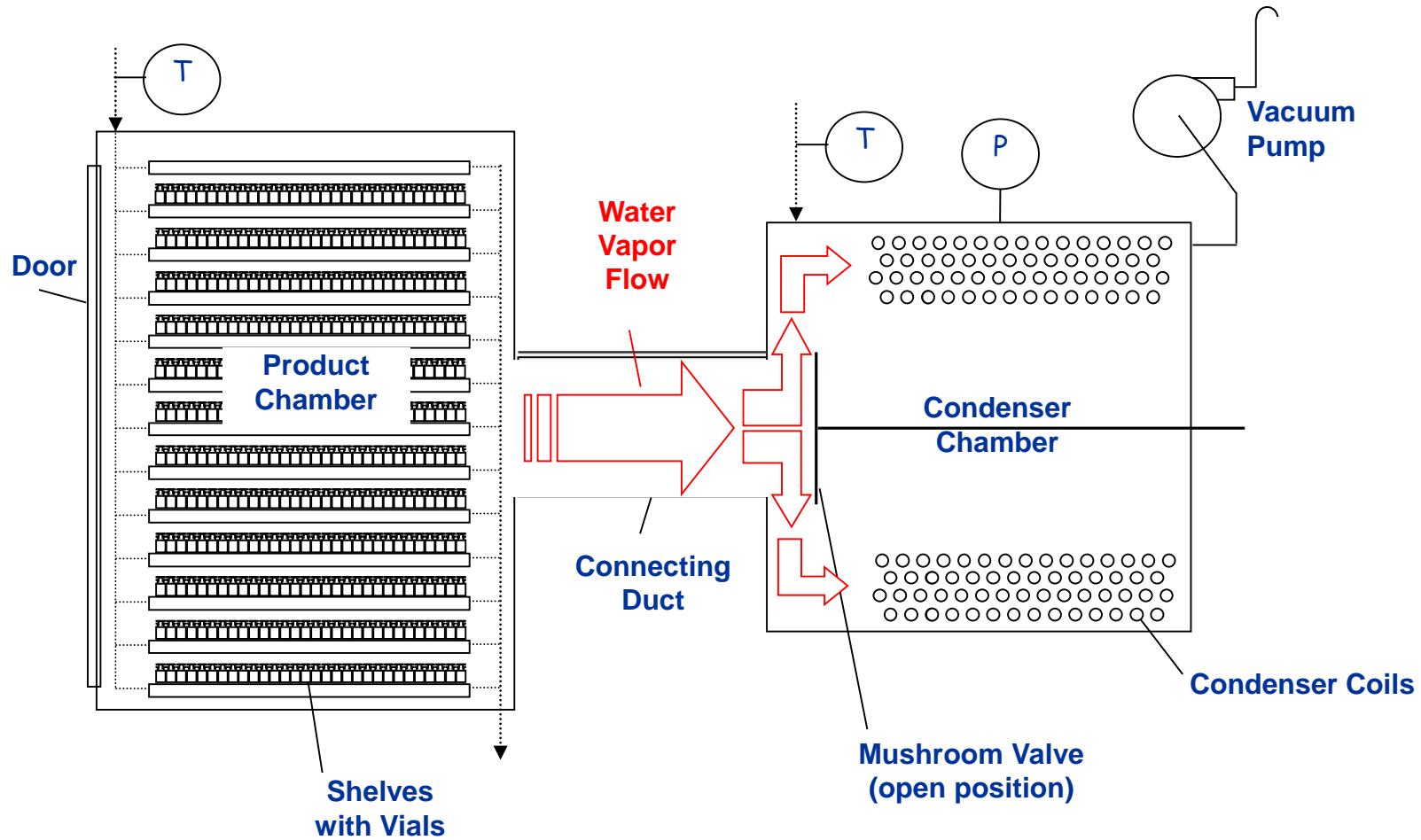
Product Temperature Measurement



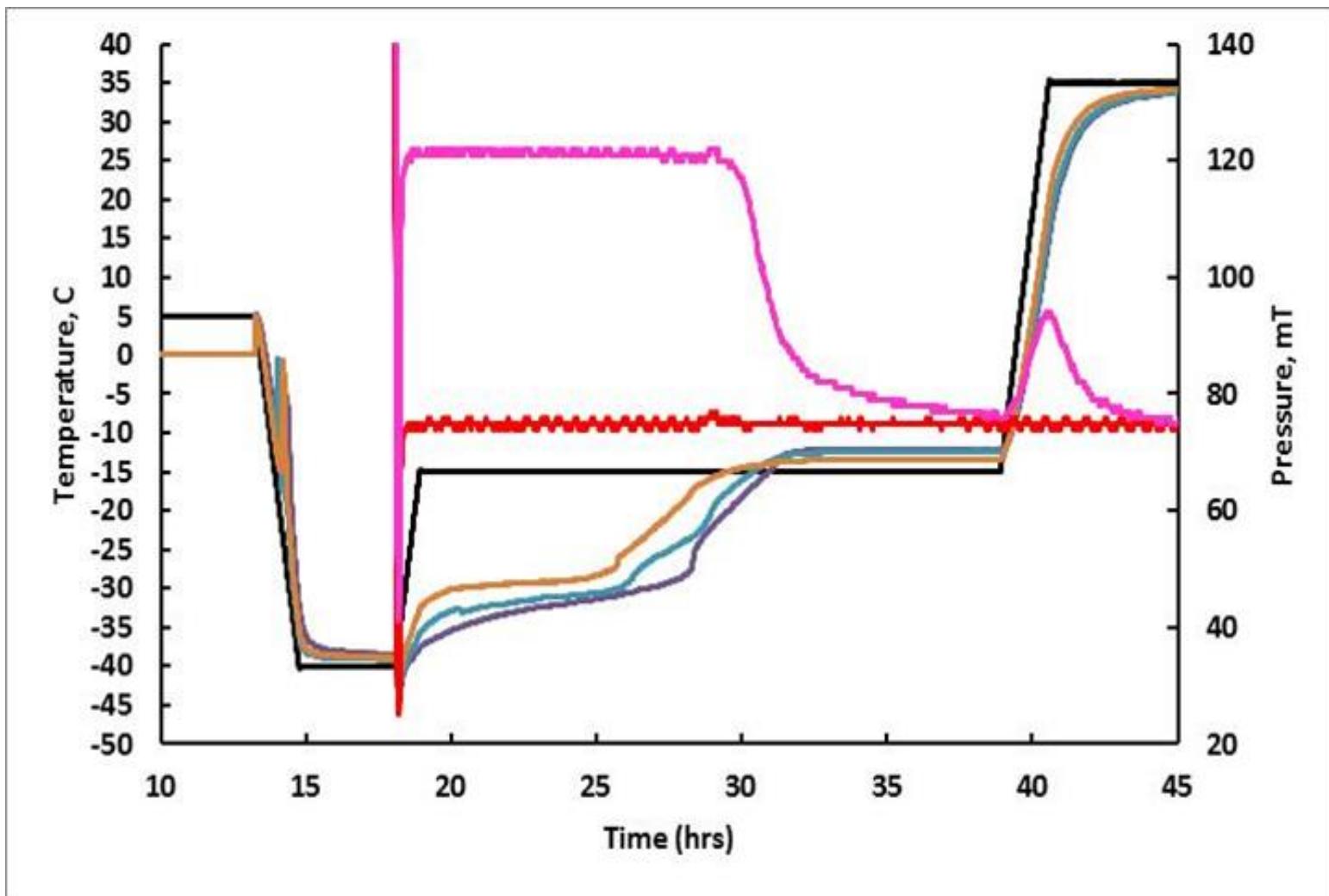
Pressure Measurement

- The capacitance manometer is the instrument of choice for pressure measurement and control in freeze drying.
- Both a capacitance manometer and a Pirani gauge are recommended for both the chamber and the condenser
 - Comparative pressure measurement
 - Always control based on CM – not the other way around
 - Gauge equipment performance
 - Troubleshooting
- Thermocouple gauges not recommended

Flow of Vapor from Chamber to Condenser



Comparative Pressure Measurement



Why Put a Pirani Gauge on the Condenser?

- This is just as an aid in troubleshooting vacuum leaks, since a Pirani gauge has a useful range up to about atmospheric pressure. A capacitance manometer generally doesn't register a pressure above either 1 mm Hg or 10 mm Hg, depending on the sensor chosen.

A Note of Caution About Pirani Gauges

- Remember that the Pirani gauge uses a hot filament. Be careful about formulations containing an organic solvent
 - Turn off the Pirani gauge for such products
 - Flush the system with nitrogen before freezing
- There is a point of view that Pirani gauges cannot be sterilized. For the most part, this isn't true, but certain types of filament may be more robust to steam sterilization than others.

Advantages of Wireless System

- No leads to deal with. Better assurance that the monitored vials are setting flat on the shelf and that the product temperature is as representative as possible of the batch.
- The response appears to be less sensitive to subtle variation in the position of the sensor in the vial.
- A wireless system is more compatible with automatic loading/unloading systems.
- The same instrument can be used at both laboratory and production scale.