Practical Design Requirements For New Lyophilization Equipment

PDA Israeli Chapter
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- FDA comment: **Shelf temp. Mapping**: :

"Inadequate empty chamber shelf temperature and product temperature mapping…..

"TCs are typically placed in 4 corners and in center of each shelf."

"Identify cold and hot spots, variability of 1-2°C between shelves might be expected".

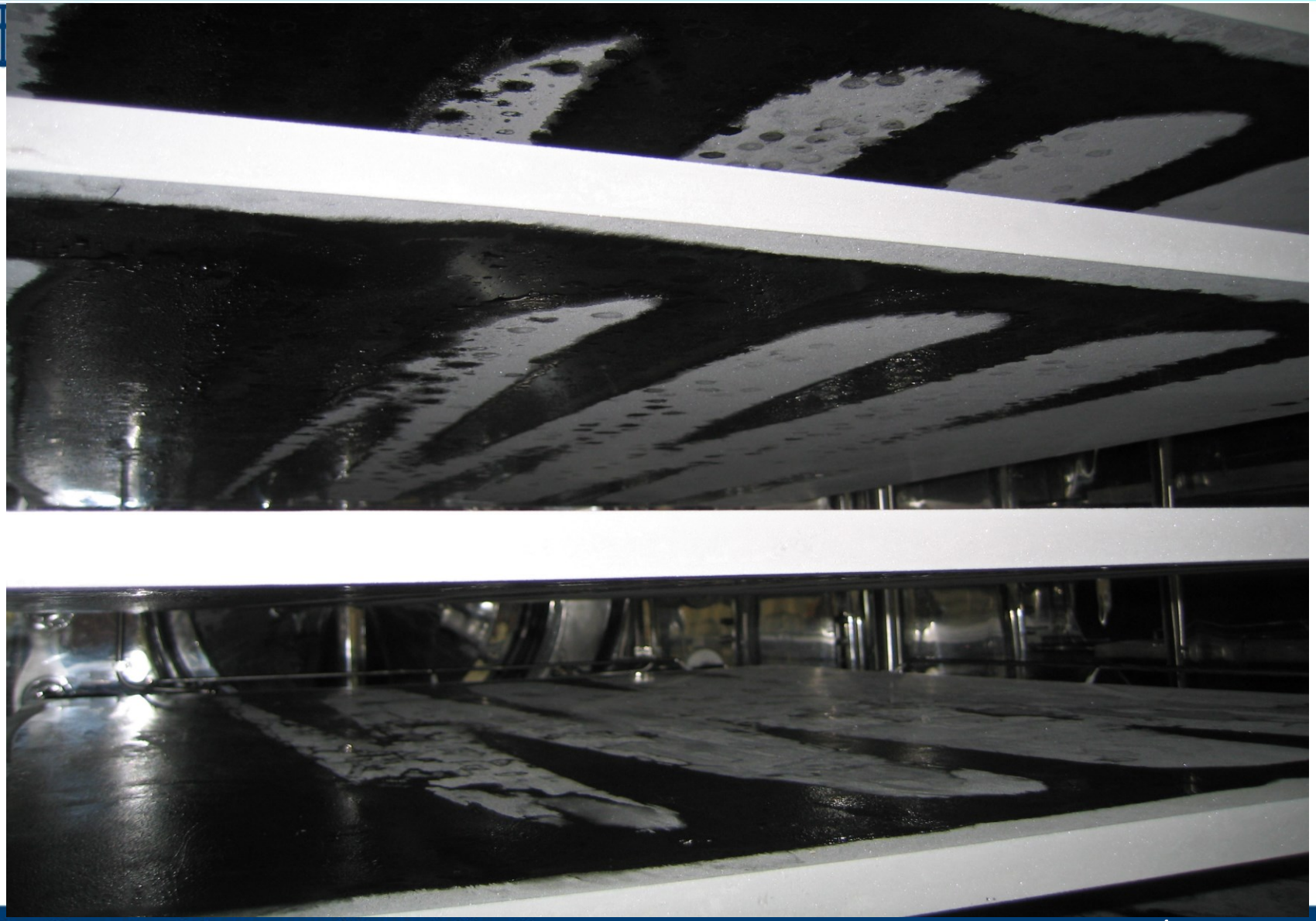
Test is done in static condition. In dynamic conditions 3-5 degrees difference can be observed between inlet and outlet of diathermic fluid

Not acceptable!!!

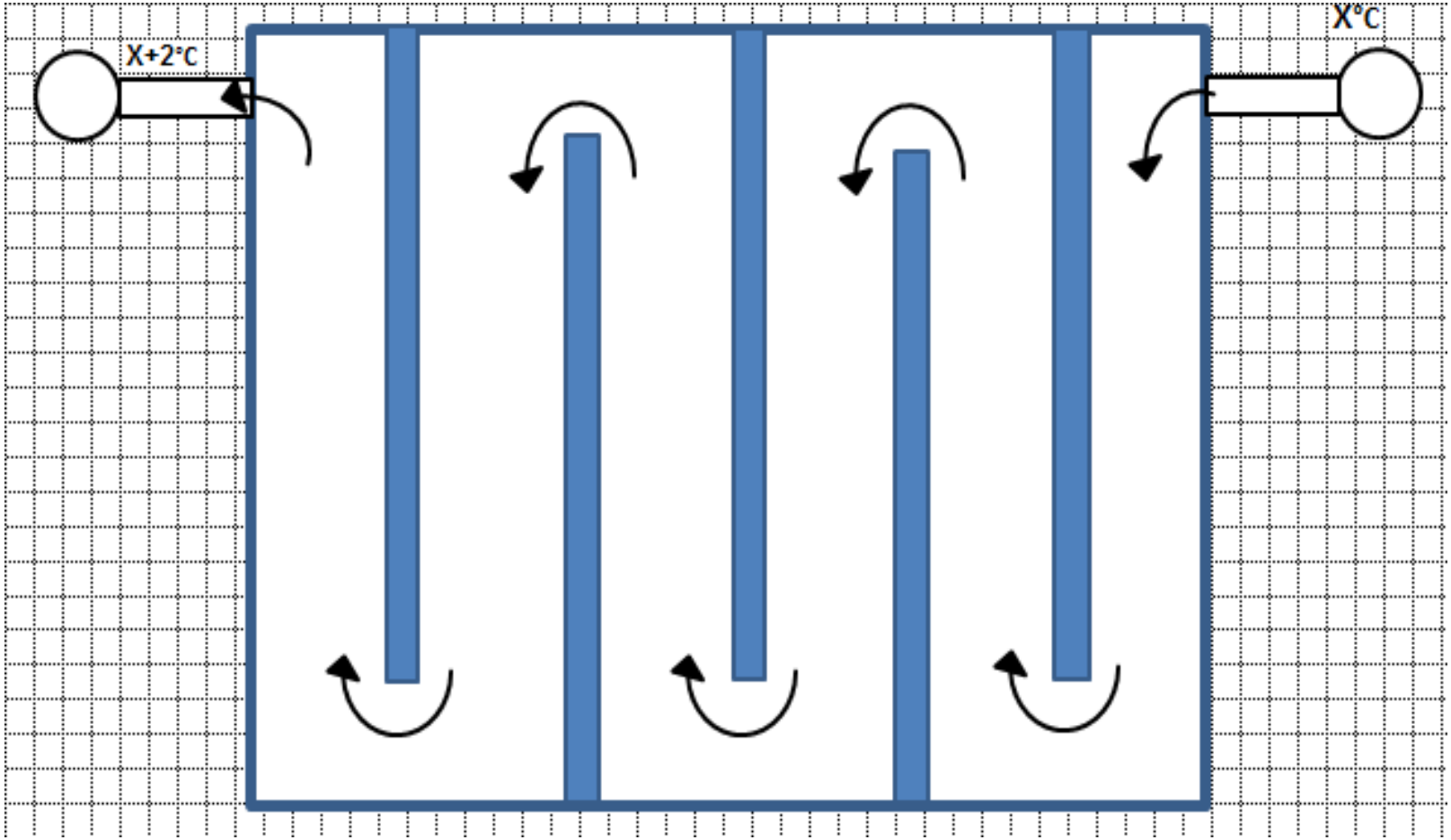
When lyophilizer is already constructed what can we do with exceeding points? **The 4 corners and center point do not represent anything!!!**.

- **Vendor will increase circulation pump output? Change labyrinth form? Turbulent flow rather than "laminar"?**
- **Vendor will Change FAT SAT shelves mapping procedures!**

Shelves Temperature Uniformity



Shelves Temperature Uniformity



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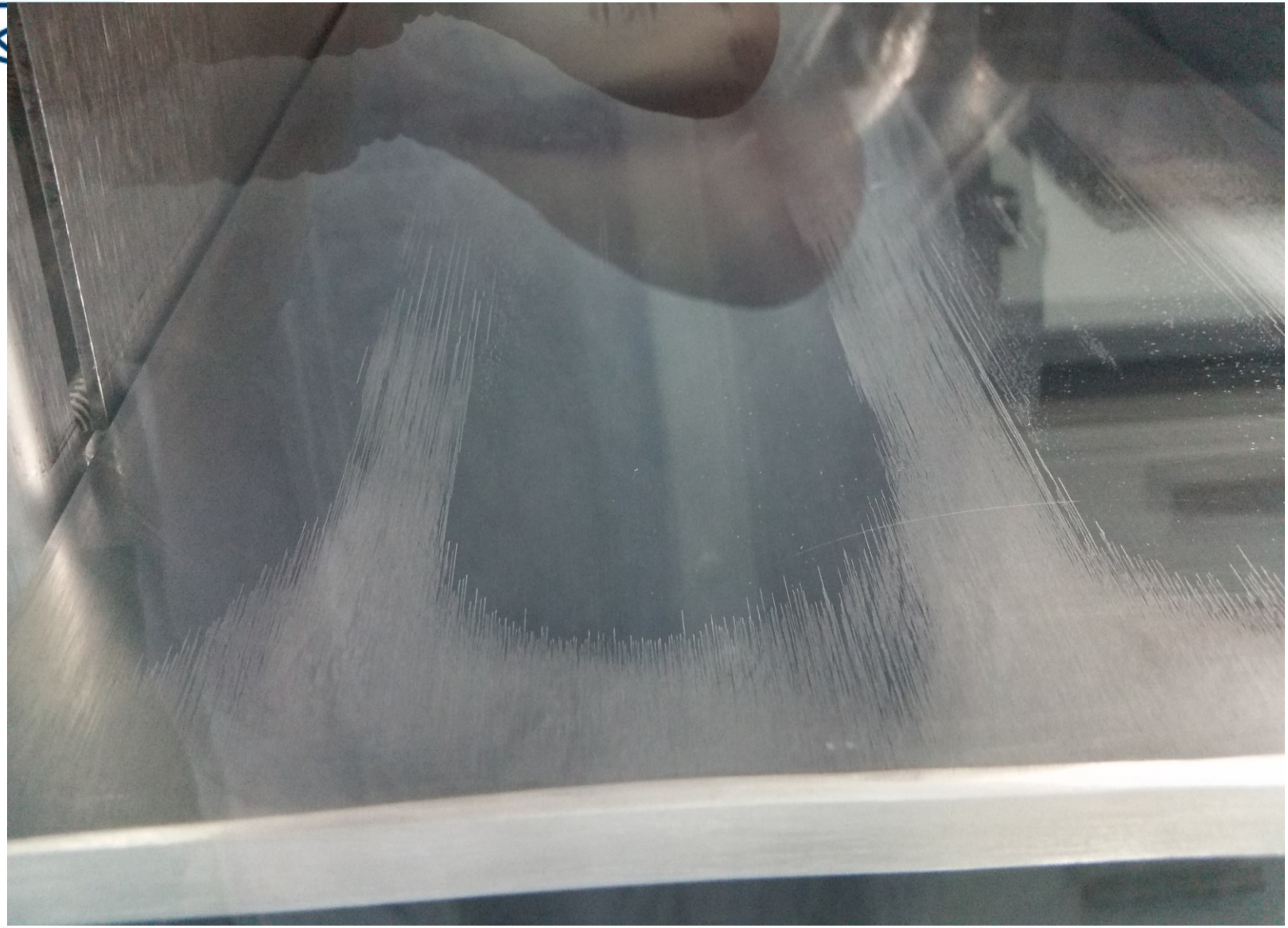
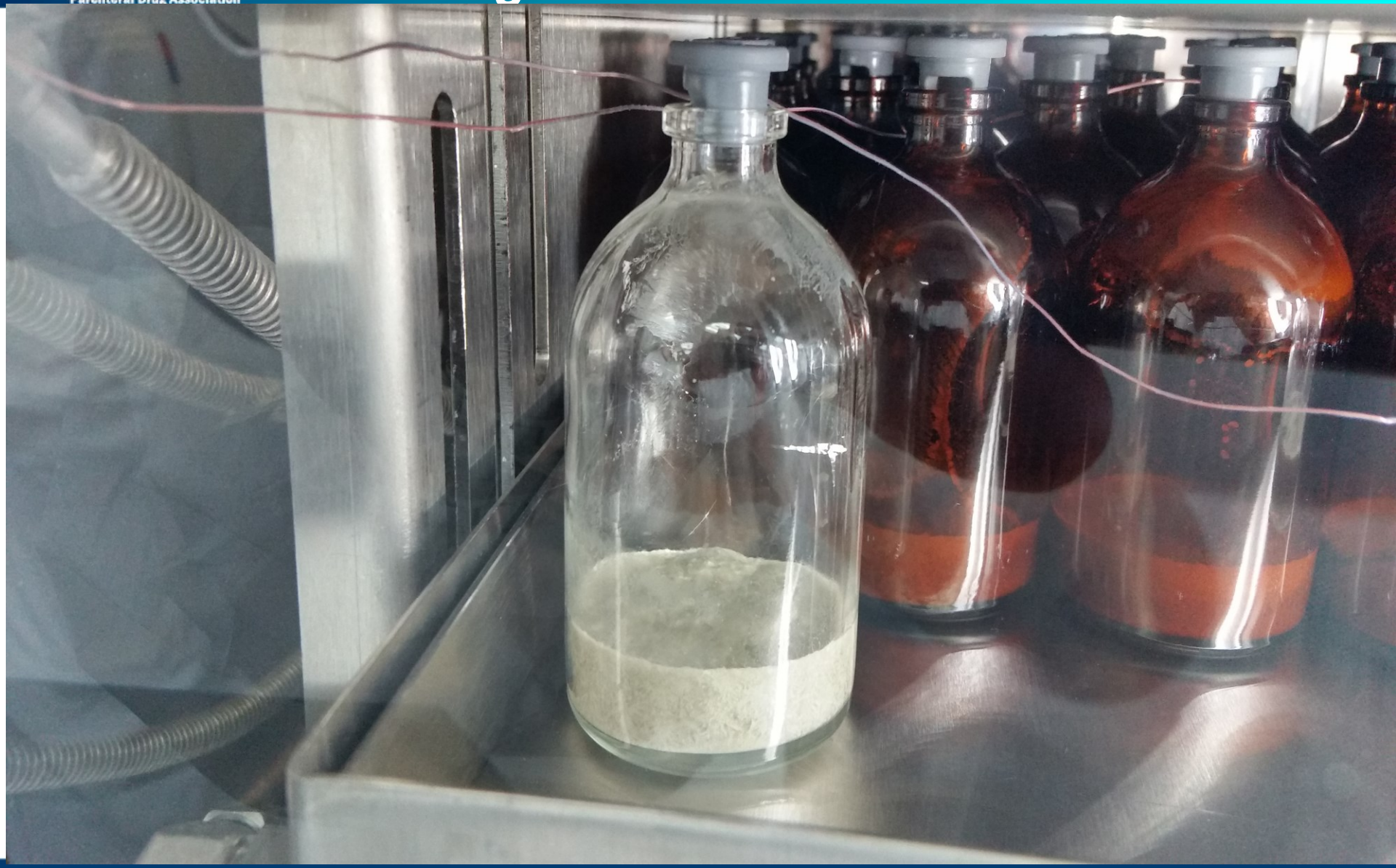
Shelves Temperature Uniformity….



Shelves Temperature Uniformity - Freezing



Shelves Temperature Uniformity - Freezing

Shelves Temperature Uniformity - Drying

- FDA Comment: **product mapping**

"To demonstrate product uniformity and ability to repeat and consistently manufacture product. Product uniformity is demonstrated through product temperature mapping and extended sampling/testing of reconstituted product…. (experiments/runs) are usually performed as engineering runs since using TC throughout the load is not aseptic"

- **Vendors should provide wireless sterilizable vials temperature mapping sensors, including appropriate SCADA to accumulate the data. Particularly where ALS (Automatic Loading System) is used.**

Pressure Rise Test

Determining drying end point- PRT

Pressure Rise Test (PRT) is an accurate residual moisture test.

It is measuring chamber's pressure rise within certain duration (seconds).

PR Test results are influenced by:

1. **Product's residual moisture**
2. **Amount of product/ vials/trays in the lyophilizer's chamber**
3. **Temperature of the shelf**
4. **Chamber's pressure**
5. **Chamber's volume**
6. **Test duration**

Pressure Rise Test

$$PR_1 = \frac{P2-P1}{t\ (secs)}$$

$$PR_{(1+30min)} = \frac{P2-P1}{t\ (secs)} = PR_2$$

$$PR_{(1+60mi)n} = \frac{P2-P1}{t\ (secs)} = PR_3$$

Drying end point is obtained when:

$$PR_1 - PR_2 = PR_2 - PR_3 = \sim const. = \sim 0$$

- **Vendors should upgrade PRT algorithm program.**

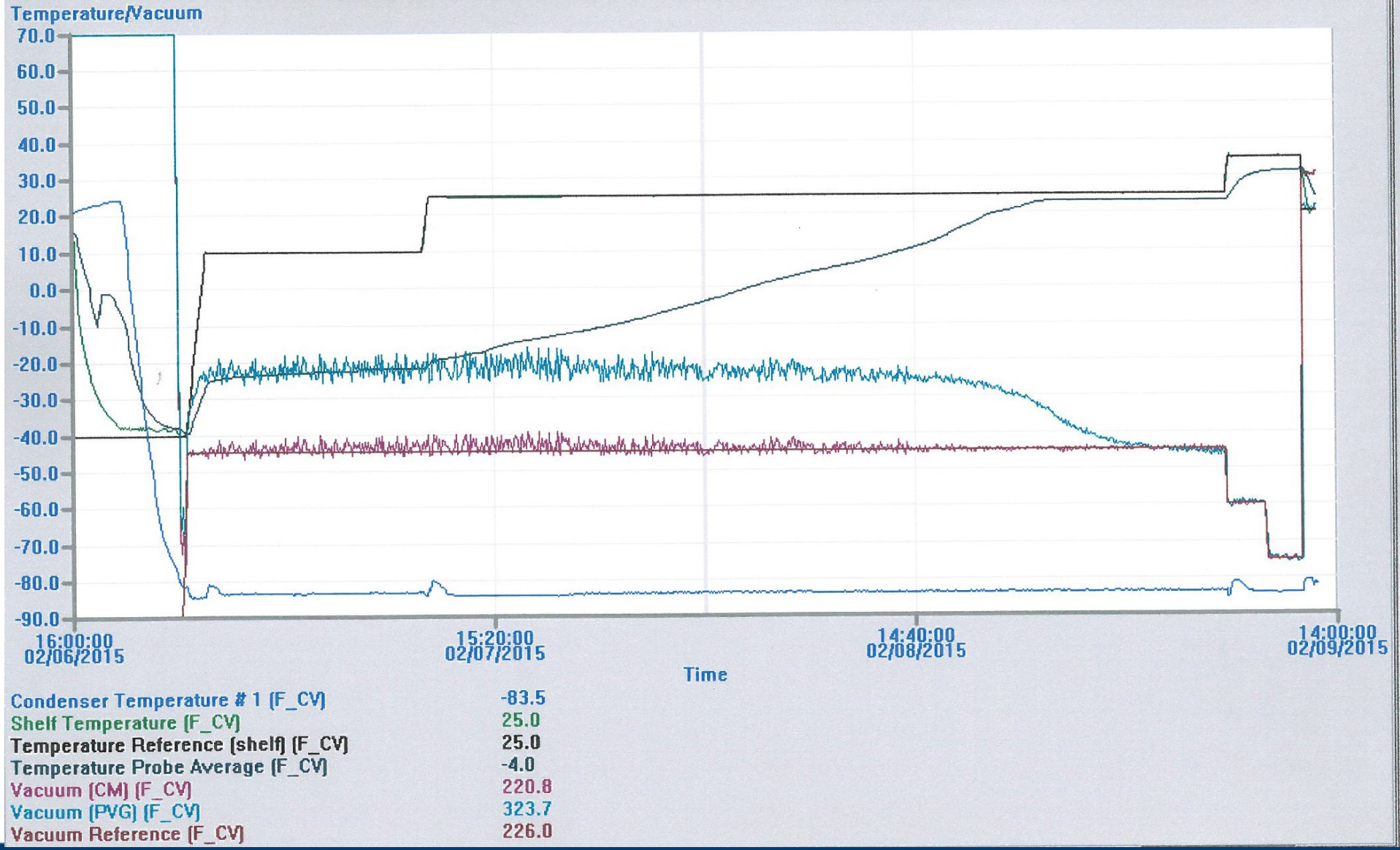
Primary drying end point is not concluded by PRT.

- **FDA comment**:

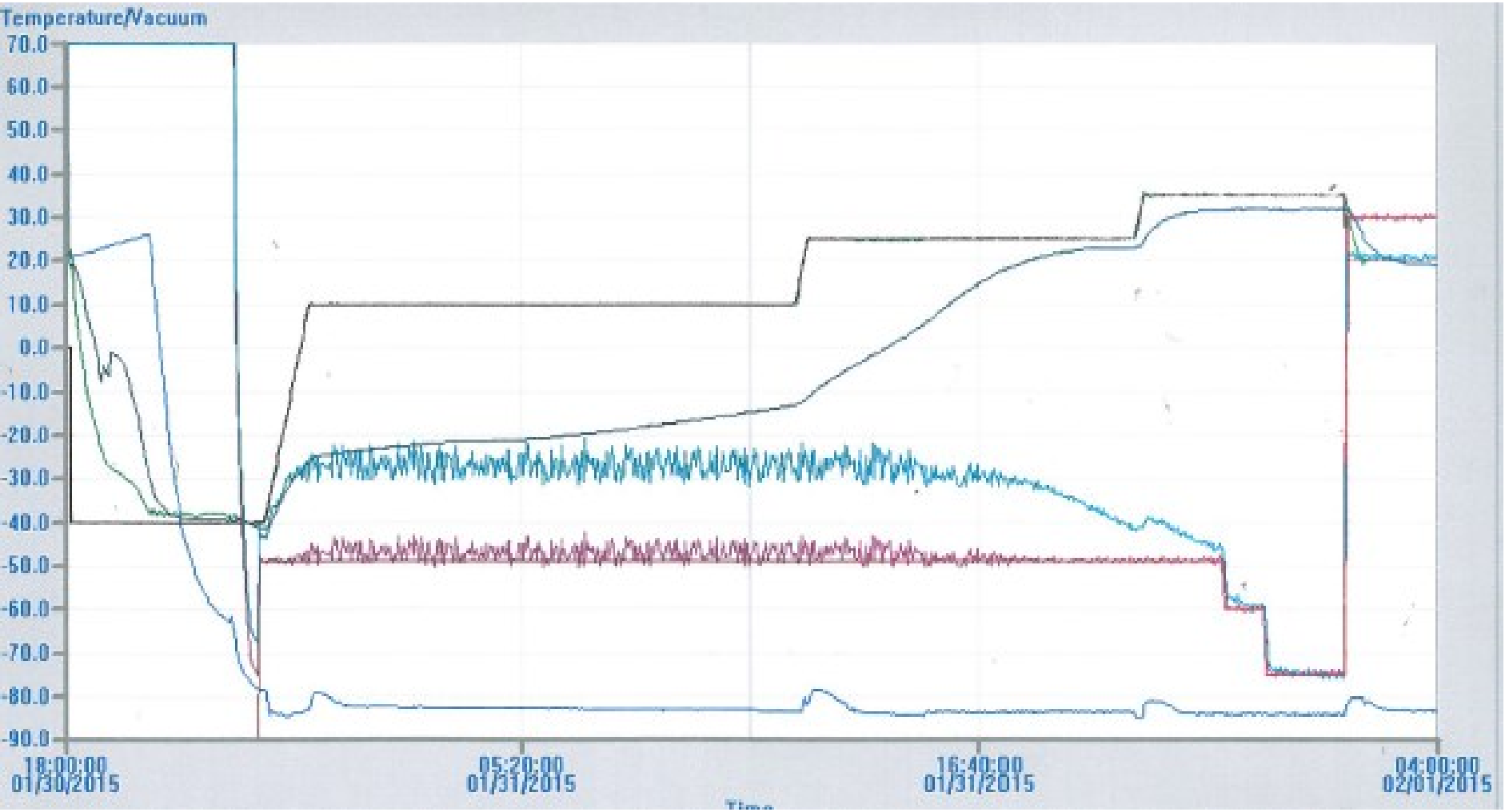
"Temperature profile diagrams are useful in determining when primary and secondary drying have completed."

"Usually performed as engineering runs since TC using in the load is not aseptic".

Primary Drying end point determination



Determining primary drying end point determination



Primary Drying end point determination

Primary drying complete should be determined by the Pirani to capacitance pressure sensors reading difference.

- **Vendor should install Pirani and Capacitance pressure sensors at list lyophilizer‘s chamber**
- **Vendor will develop an optionally use algoritm for monitoring the difference between the pirany and capacitance sensor. While difference is reduced, automatically move to secondary drying parameters**

FDA comment:

"**in equipment qualifications FDA would like to see qualification of condenser capacity.**"

Vendors are quoting average ice thickness on condenser coils: 11- 18mm.

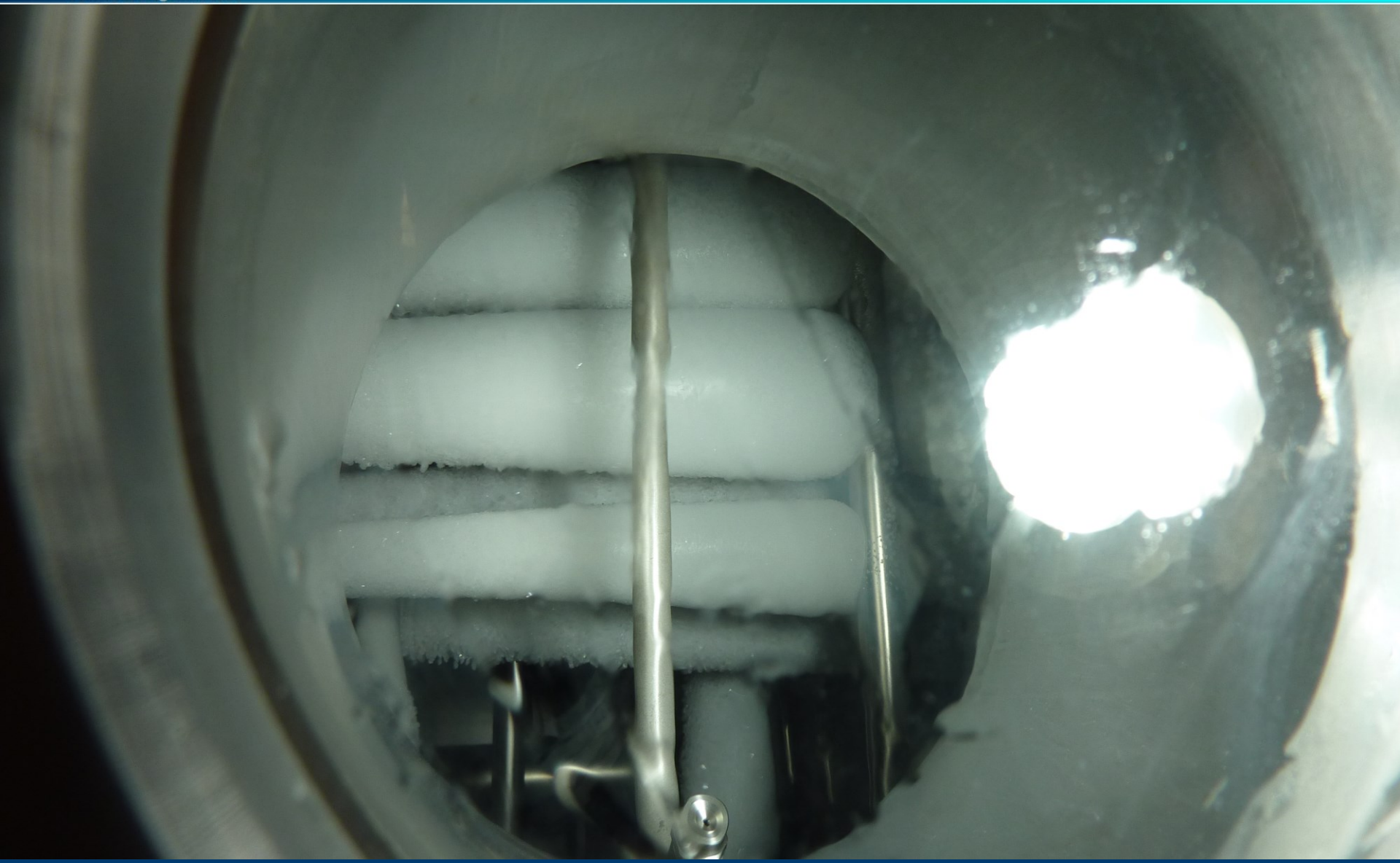
This ice quantity can be accumulated within 5 days/ 24 hours. As can be seen ice thickness is less important but condensation rate is the important factor.

Vendor should add lyophilization rate!

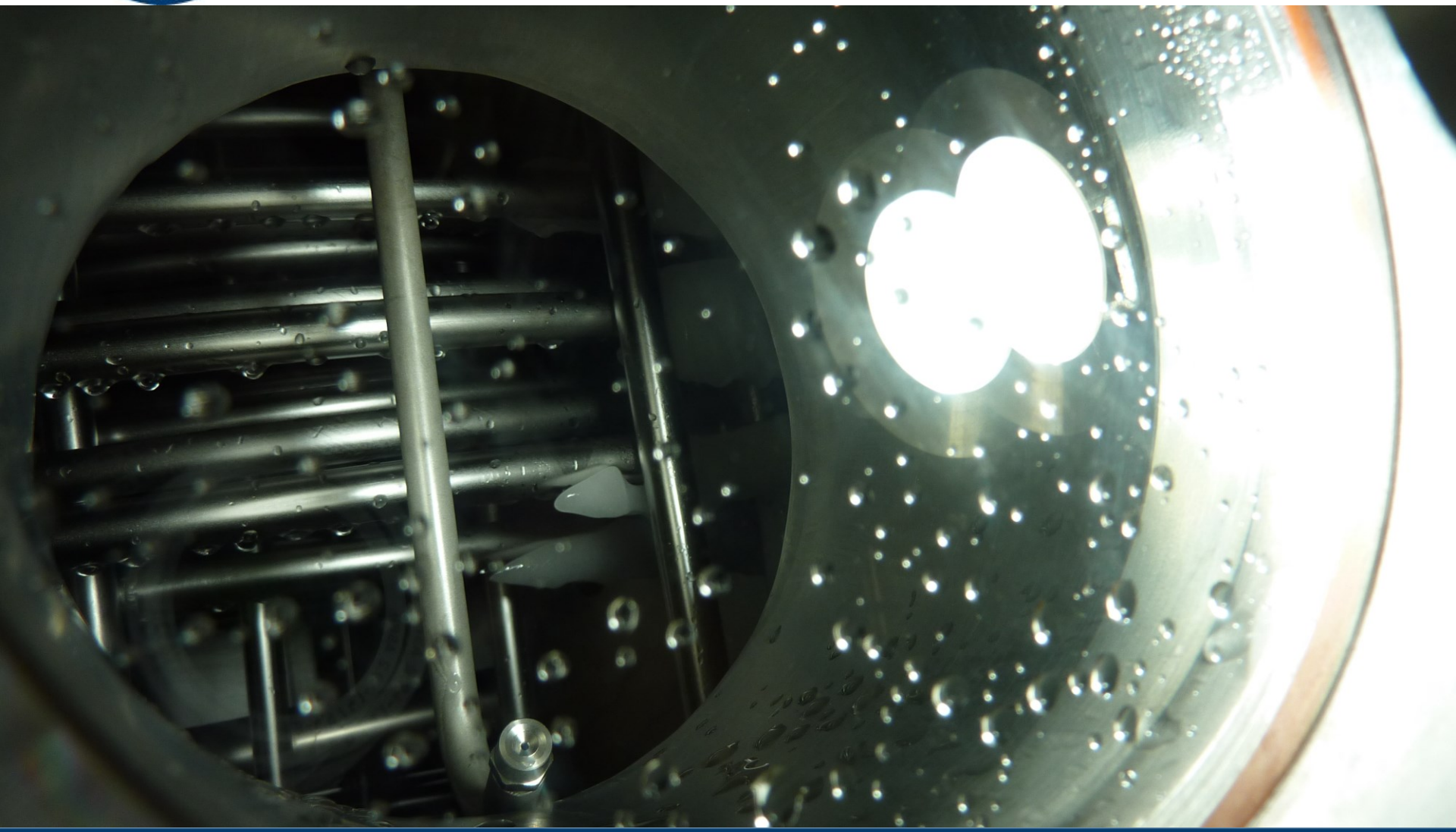
Condensation rate is influenced by:

1. **Heaters strength in Kw,**
2. **Condenser coil temperaure while sublimation take place.**
3. **Condenser / chamber passage diameter.**

Determining condenser capacity



Determining condenser capacity



THANK YOU

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