Real-Time Temperature and Heat Flux Measurements for Lyophilization Process Design and Monitoring

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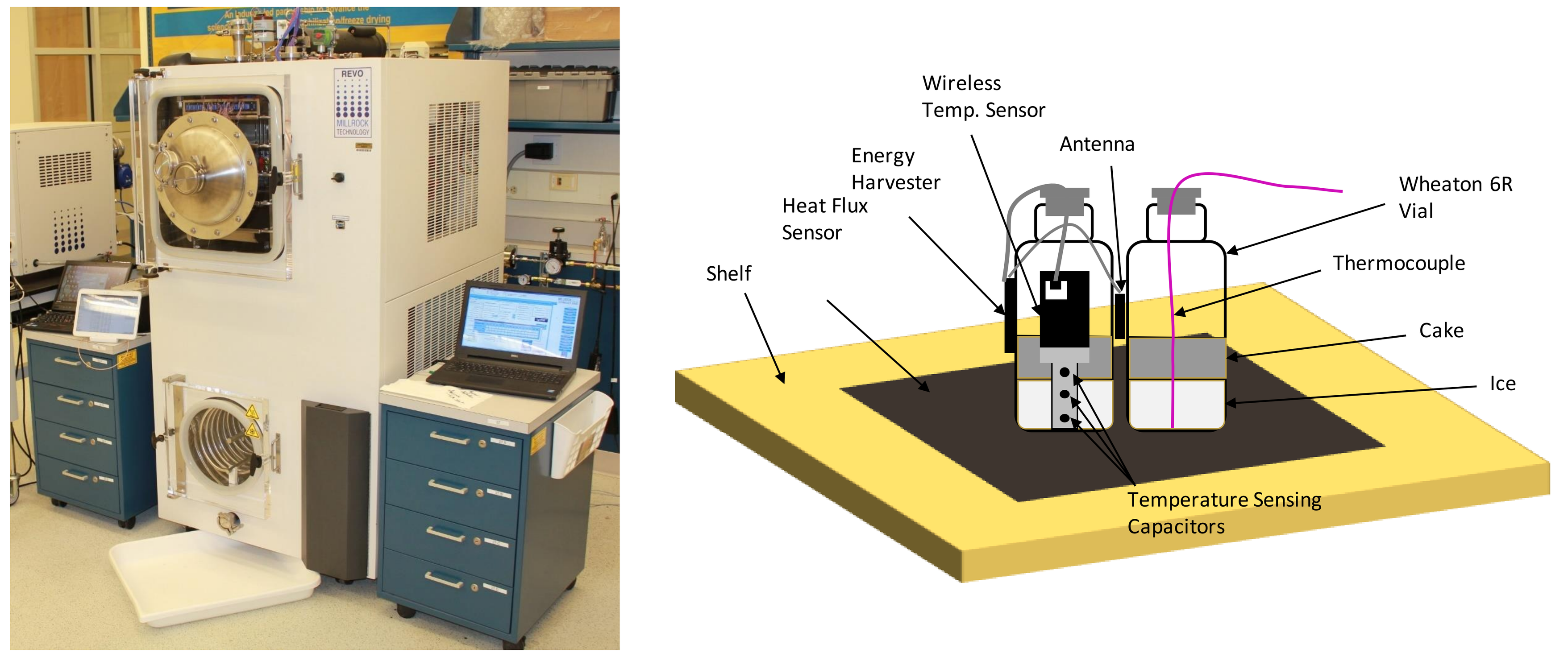
Introduction and Objectives

Accurately measuring temperature during the three stages of lyophilization, freezing, primary drying and secondary drying, is important to ensure product quality and to reduce operating costs. This study focuses on testing a new method of measuring the temperature in the product through the use of new wireless temperature sensors. Our goal is to assess the limitations and benefits of using wireless temperature sensors compared to commonly used thermocouples as well as to determine methods to further improve and use the wireless temperature sensors.



Figures 1-2. (left) REVO lyophilizer used during experimentation, (right) model of vial pair on a LyoPAT® heat flux sensor.

Lyophilization Process

- **Freezing**: Temperature reduced well below 0˚C and held for several hours to complete crystallization.[3,9]
- **Primary Drying**: Pressure in the lyophilization chamber pressure is reduced to vacuum in order to remove mobile water from the product by sublimation.[3]
- **Secondary Drying**: Temperature is increased to remove residual water by the process of desorption. The secondary drying stage has the largest impact on the structure of the cake.[9]

Sample Preparation → Annealing/ Freezing → Primary Drying → Secondary Drying → Final Product

Chart 1. Lyophilization Process Steps

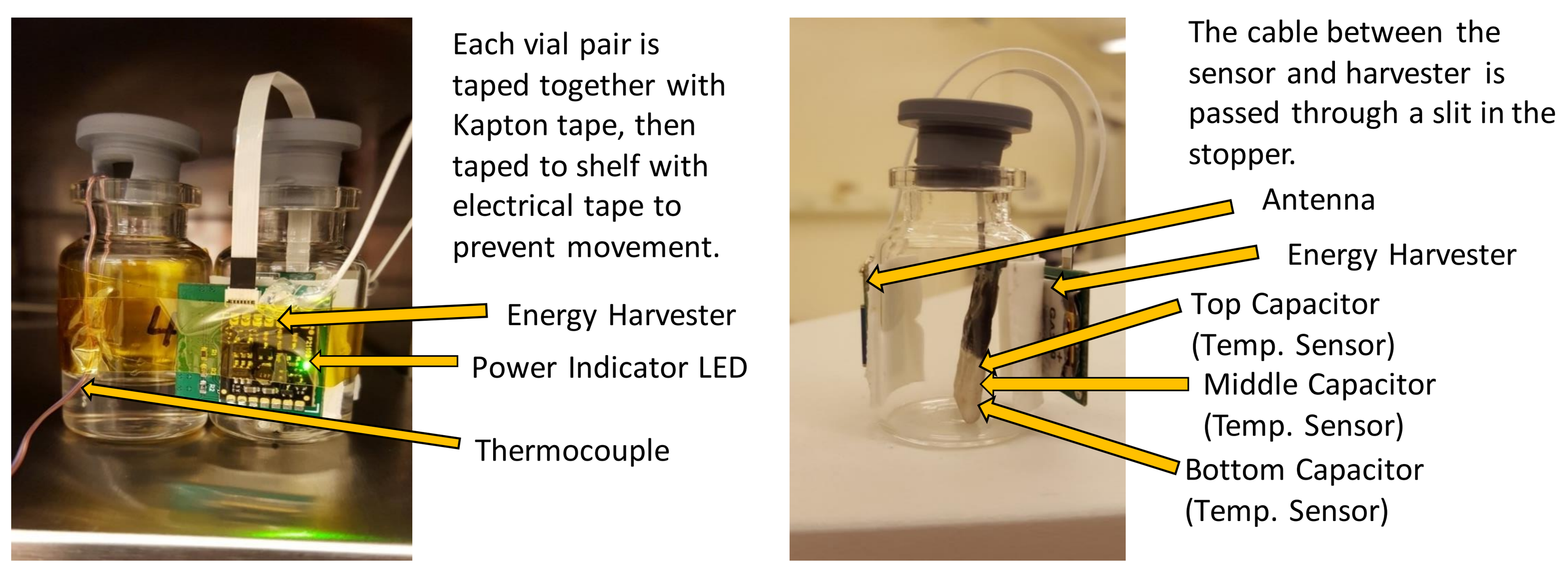
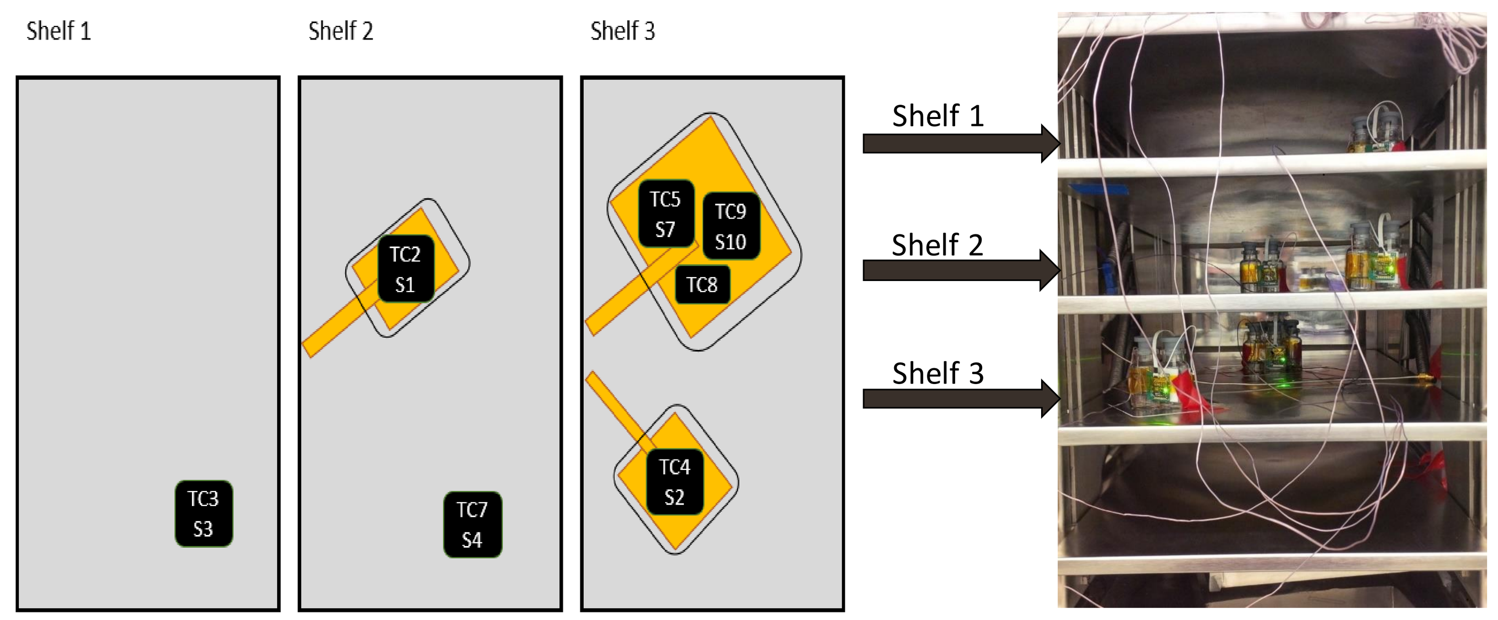


Figure 3-4. (Left) pair of vials, one with thermocouple, other with wireless temp. sensor, (right) side view of vial with wireless temp sensor.

Methods and Materials

- For the water run, 3 mL of ultra-pure water was pipetted into Wheaton 6R vials and placed into the lyophilization chamber.
- For the sucrose runs, sucrose was dissolved in Ultra-Pure Water at a concentration of 5% w/v and 3 mL was pipetted into Wheaton 6R vials.
- The vials were placed in pairs, one with a thermocouple, the other with a wireless temperature sensor and placed in the same location for each run (the placements can be seen in the map and figure below).



Figures 6-7. (left) Sensor location map, a top view of the shelves, (right) actual vial placement in the chamber.

Thermocouple	Percent Sublimated	Thermocouple Sublimation Rate [g/hour]	Wireless Temp. Sensor	Percent Sublimated	Wireless Temp. Sensor Sublimation Rate [g/hour]
2	82.6%	0.777	1	79.4%	0.770
3	79.2%	0.737	3	83.2%	0.777
4	70.9%	0.707	2	82.2%	0.770
5	83.4%	0.853	7	85.2%	0.863
6	72.0%	0.693	10	81.9%	0.843
7	78.8%	0.793	4	83.6%	0.833
8	73.2%	0.730			
Average	**77.2%**	**0.756**	**Average**	**82.6%**	**0.809**
Average Heat Flux		**1670 W/m²**	**Average Heat Flux**		**1789 W/m²**

Thermocouple	Percent Sublimated	Thermocouple Sublimation Rate [g/hour]	Wireless Temp. Sensor	Percent Sublimated	Wireless Temp. Sensor Sublimation Rate [g/hour]
2	53.9%	0.53	1	56.3%	0.56
3	58.4%	0.57	3	63.4%	0.62
4	60.9%	0.603	2	58.7%	0.573
5	54.1%	0.53	7	55.3%	0.55
7	55.3%	0.553	4	61.7%	0.613
8	54.9%	0.543			
9	51.7%	0.516	10	60.8%	0.6
Average	**55.6%**	**0.549**	**Average**	**59.4%**	**.586**
Average Heat Flux		**1214 W/m²**	**Average Heat Flux**		**1295 W/m²**

Table 1-2. Sublimation rates and percent sublimated for the ice sublimation (1) and sucrose freeze drying run (2).

Results

The Millrock REVO interface takes a recipe for the lyophilization process. Included in the recipe are the temperatures, pressures and times for which each step is run, the recipe specifications are shown on the graphs. The radiative contribution to heat flux is ~145 W/m².

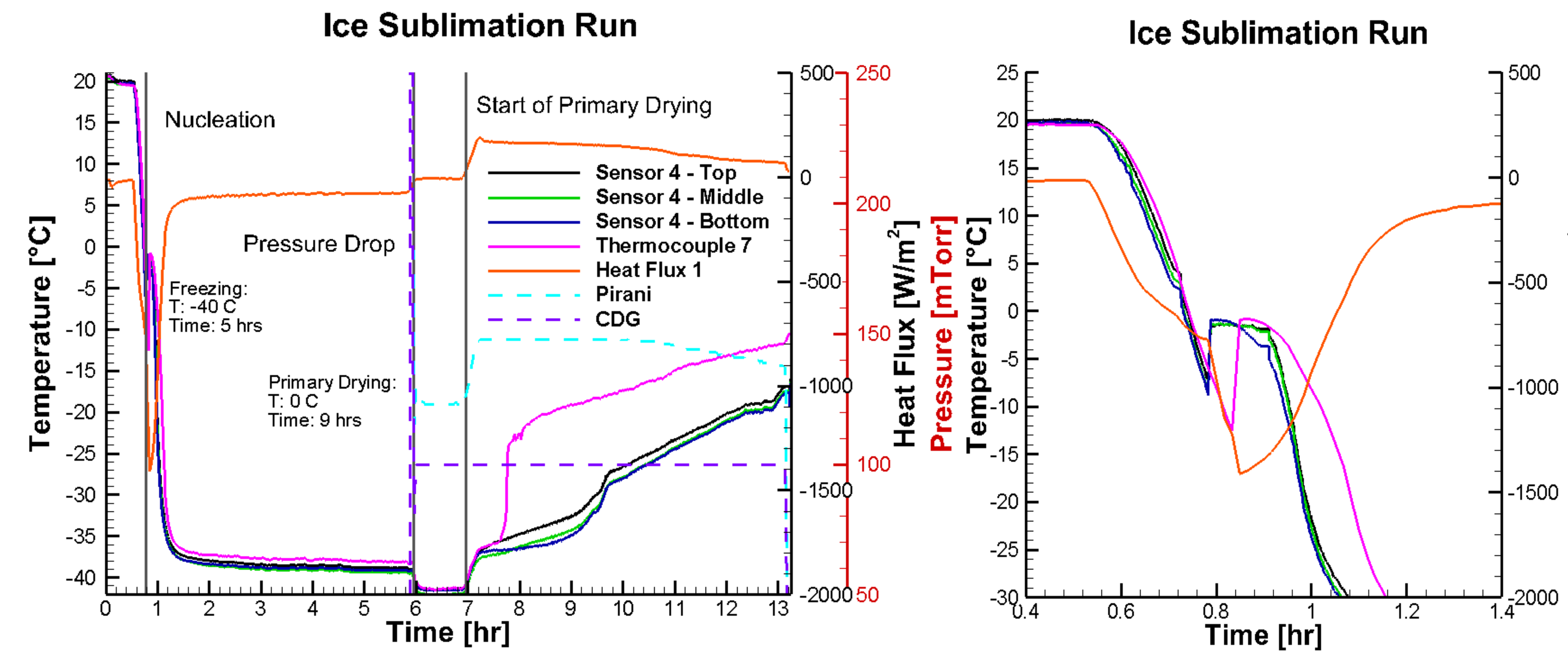
Heat Flux:

- $q = \frac{\dot{m}\Delta H_{sub}}{A}$
- q is heat flux, $\dot{m}$ is sublimation rate, ΔH_{sub} is heat of sublimation, A is area.

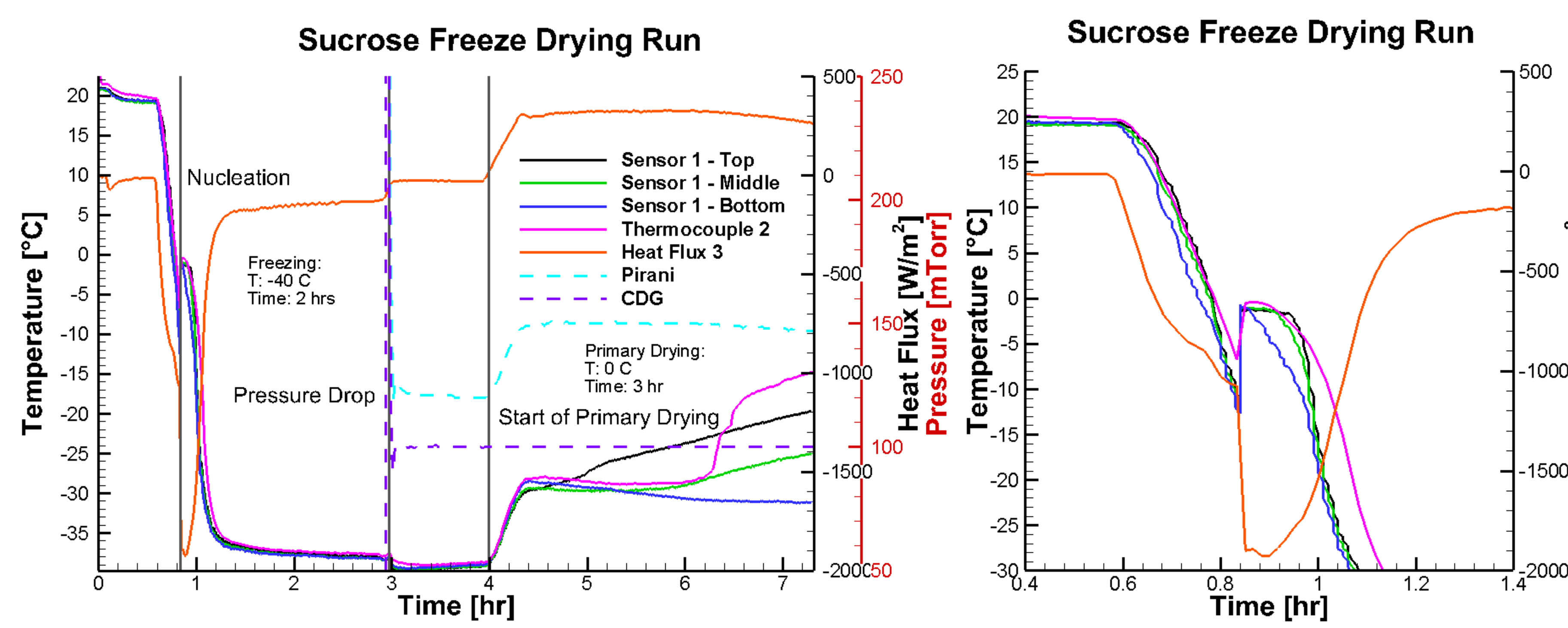
Percent Sublimated:

- $\%Sub = \left(\frac{M_{cake}}{M_{initial}}\right)$,
- %Sub is the percent sublimated, M_{cake} is the mass of the cake, $M_{initial}$ is the initial mass of the product[5].

Discussion and Conclusions



- The maximum freezing rate occurs at nucleation, during which the heat flux was measured to be approximately -1500 W/m².
- The average heat flux during the primary drying stage of the ice sublimation run was ~110 W/m², with a maximum of ~200 W/m² and decreasing almost linearly, as compared to the calculated 1670 W/m² average total heat flux.



- LyoPAT® sensor was demonstrated to capture the heat flux dynamics, showing that energy consumption is maximum during nucleation (-2 kW/m²) which is about 7 times larger than that during primary drying in this cycle.
- The maximum heat flux during primary drying stage of the sucrose freeze drying run was ~350 W/m², with at average of ~325 W/m², showing steady state behavior.
- The wireless temperature sensor data does not exactly correspond to the thermocouple data, likely a result of the thermocouples being in contact with the bottom surface of the vial, while the sensors are suspended in the product.

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References

1. Alexeenko, Alina A., Arnab Ganguly, and Steven L. Nail. "Computational Analysis of Fluid Dynamics in Pharmaceutical Freeze-Drying." Journal of Pharmaceutical Sciences 98, no. 9 (September 2009): 3483–94. doi:10.1002/jps.21862.
2. Beaty, N. "Lyophilization: heat and mass transfer." Am Pharm Rev, 9, 2009: 81–83.
3. Fetterolf, David M. "Lyophilization." Journal of GXP Compliance, 14, no. 4, August 2010: 52-60.
4. Ganguly, Arnab, Alina A. Alexeenko, Steven G. Schultz, and Sherry G. Kim. "Freeze-Drying Simulation Framework Coupling Product Attributes and Equipment Capability: Toward Accelerating Process by Equipment Modifications." European Journal of Pharmaceutics and Biopharmaceutics 85, no. 2 (October 2013): 223–35. doi:10.1016/j.ejpb.2013.05.013.
5. Karpuk, Stanislav. "LyoCalculator: User Manual." Purdue University, 2015.
6. Patel, Sajal M., Takayuki Doen, and Michael J. Pikal. "Determination of End Point of Primary Drying in Freeze-Drying Process Control." AAPS PharmSciTech 11, no. 1 (March 2010): 73–84. doi:10.1208/s12249-009-9362-7.
7. Pikal, M. J. "Freeze Dryer Operational Qualification to Allow Science Based Scale-Up and Quality by Design: OQ data you can actually use!." University of Connecticut, 2016.
8. Schneid, Stefan, and Henning Gieseler. "Evaluation of a New Wireless Temperature Remote Interrogation System (TEMPRIS) to Measure Product Temperature During Freeze Drying." AAPS PharmSciTech 9, no. 3 (September 2008): 729–39. doi:10.1208/s12249-008-9099-8.
9. Sundaran, Jagannathan, Shay, Yun-Hua M., Hsu, Chung C., and Sane, Samir U. "Design Space Development for Lyophilization Using DOE and Process Modeling." Biopharm International. (Sept. 2010): 26-36.
10. Velardi, Salvatore A., and Antonello A. Barresi. "Development of Simplified Models for the Freeze-Drying Process and Investigation of the Optimal Operating Conditions." Chemical Engineering Research and Design 86, no. 1 (January 2008): 9–22. doi:10.1016/j.cherd.2007.10.007.
11. Wang, Qiming. "LyoPAT® Training Course." Millrock Technologies. (Accessed May 25, 2016).
12. Ben Adams. (May 2011). "Remicade." Pharmafile. Retrieved from http://www.pharmafile.com/news/154461/jj-and-merck-reach-compromise-arthritis-drug-rights.
13. MIMS. (2016). "Enbrel inj 25 mg." Retrieved from http://www.mims.com/singapore/image/info/enbrel%20inj%2025%20mg/25%20mg.
14. AARDA. (2016). "Questions and Answers." Retrieved from http://www.aarda.org/autoimmune-information/questions-and-answers.