BioPharma Solutions

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Support of Scale-Up and Technical Transfer Through Understanding Equipment for Lyophilization

Baxter

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Introduction

Formulation and process development for injectable products are typically conducted at laboratory-scale. Laboratory-scale equipment is useful and necessary during development when there is little technical information available and especially when the active pharmaceutical ingredient (API) is in short supply. There are few challenges when increasing the scale of production for a solution formulation, but the challenges drastically increase when the formulation is intended for lyophilization. There can be differences in design of lyophilizers at laboratory-scale and at full-scale and also between full-scale equipment at different manufacturing sites. In addition, laboratory-scale studies are often conducted using lyophilizers having 0.43 m^2 product chambers and this must increase in scale to lyophilizers equipped with 19.95 m^2 product chambers or larger. The increase in size and equipment design can affect heat transfer within the lyophilizer and can affect the equipment capability. These factors can greatly affect the success of scale-up and technical transfer.

There are three basic steps to a lyophilization cycle. The first is a cooling step to freeze the solution. Next, bulk ice is sublimed during primary drying. The final step is secondary drying which is used to remove unfrozen water associated with the product by increasing the shelf temperature between +30°C and +50°C. Specific controls are needed for each step, and all should be tested (Table I).

Step	Measurement	Control
Cooling	Temperature	Shelf Temperature Cooling Rate
Primary Drying	Temperature	Maintenance of Shelf and Condenser Temperatures
	Pressure	Nitrogen Flow Rate into Chamber
Secondary Drying	Temperature	Shelf Temperature Ramp Rate

Table I. Process Controls for Each Step of the Lyophilization Process.

The capability of controlling temperature and pressure within specified ranges, mapping of temperature across the shelves of a lyophilizer, and many other tests are common for installation and qualification of the equipment and preventative maintenance. The one test that is not often conducted is determining the overall capability of the equipment with regard to the sublimation rate that it can support. There is often little, if any, data on the capability of lyophilizers at full-scale. Obtaining the time to test the equipment at full-scale is often the main challenge. Understanding the equipment design and in-process data available when transferring between sites provides useful information. However, obtaining data on the true capability of the equipment is an integral part of a primary drying design space graph.

Key components of the Quality by Design paradigm include detailed understanding of process equipment capability and the use of design spaces. Both components are important in pharmaceutical freeze drying.

During process development for a freeze dried product, a graphical design space is constructed for primary drying that establishes the relationship between the process variables that are controlled – shelf temperature and chamber pressure – and product temperature, which is not directly controlled, but is critical in terms of its potential impact on product quality. This relationship is determined by the vial heat transfer coefficient and by the resistance of the dry product layer to the flow of water vapor. This resistance term varies considerably between different drug product formulations. In Figure 1, chamber pressure is plotted on the x-axis, and sublimation rate is shown on the y-axis. There are two sets of isotherms – one set representing shelf temperature, and the other representing product temperature. For every drug product, there is an upper product temperature limit, where exceeding this limit would result in product failure, usually collapse. This temperature establishes one boundary of the design space.

The other boundary is the equipment capability, since there is a limit for any freeze dryer on the sublimation rate that it will support. The area under both of these boundaries represents all of the combinations of shelf temperature and chamber pressure that will provide a pharmaceutically acceptable product and are within the capability of the equipment. The highest sublimation rate within this acceptable region of the design space represents the optimal primary drying conditions.

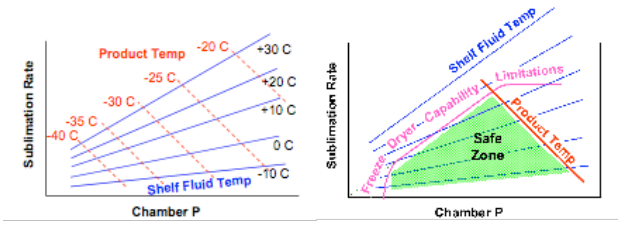

Figure 1. Examples of Primary Drying Design Space Graphs Depicting the Equipment Capability Curve and the Upper Product Temperature Limit

Understanding the performance of full-scale lyophilizers and comparing them to the performance of laboratory-scale lyophilizers can greatly reduce the uncertainty during scale-up.

The purpose of this document is to examine the different designs for lyophilizers, to discuss the in-process data collected during freeze-drying, and examine the equipment available at two manufacturing sites at Baxter. The document will also present a method of determining equipment capability and compare the data between laboratory-scale and full-scale equipment.

Lyophilizer Design and In-Process Data

The design of a lyophilizer must be considered when transferring a process because the design can directly impact the distribution of temperature and the sublimation rates that can be supported during primary drying. Lyophilizers are equipped with a product chamber that contains temperature controlled shelves on which the product is placed and a condenser that is maintained at a substantially colder temperature to capture water vapor as ice. The placement or separation of the chamber and condenser are the main variables in equipment design.

One type of lyophilizer is constructed with an internal condenser (Figure 2). In this design, the condenser is located directly next to the shelves in the product chamber and separated by a stainless steel sheet.

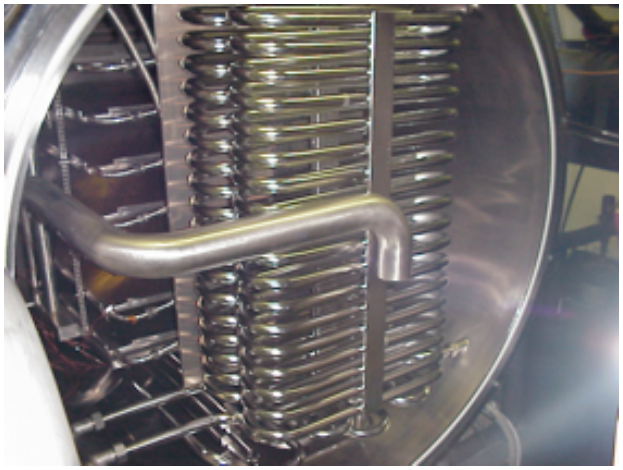

Figure 2. Lyophilizer Equipped with an Internal Condenser

Another type of design is where the product chamber is separated from the condenser using an adjustable platform (Figure 3). The platform is raised during primary and secondary drying and is closed at other times.

Figure 3. Lyophilizer Equipped with an Adjustable Platform Between the Product Chamber and the Condenser.

A third type of lyophilizer is where the condenser is located externally from the product chamber and the two are attached by a connecting duct (Figures 4 and 5).

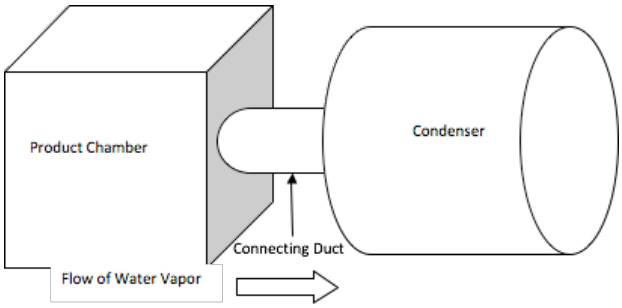

Figure 4. Diagram for a Lyophilizer Designed with a Connecting Duct Between the Product Chamber and the Condenser.

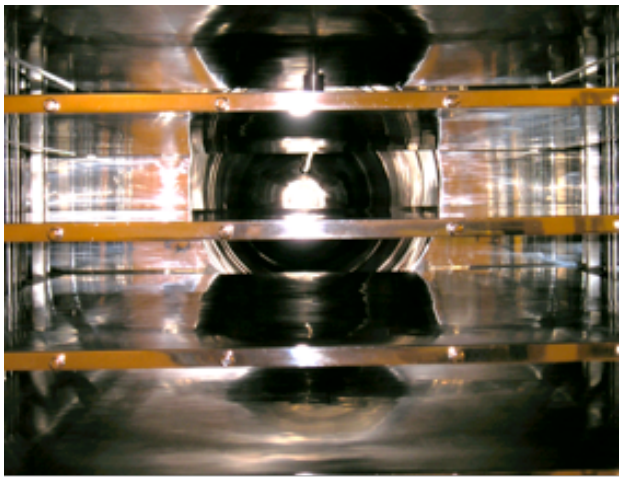

Figure 5. View Inside Product Chamber Showing the Connecting Duct Behind the Shelves.

The different designs can affect the flow of water vapor from the chamber to the condenser and affect how the water vapor is deposited as ice on the condenser coils. Flow of water vapor and deposition of the vapor as ice on the coils can affect the performance of the equipment. Therefore, it is imperative to thoroughly understand the differences in design of equipment when transferring from laboratory-scale to full-scale and when transferring to equipment at different sites. The equipment may not only differ in design. It can also differ in the in-process data collected during a cycle and in the methods of control. Temperature and pressure can be monitored in many areas within a lyophilizer (Table II).

Temperature
Inlet and Outlet Temperature of the Shelf
Inlet and Outlet Temperature of the Condenser Coil
Surface Temperature of the Condenser Coil
Product Temperature (Less Common at Full-Scale)
Pressure
Product Chamber
Condenser
Bellows for the Hydraulic Stoppering Ram

Table II. In-Process Temperature and Pressure Monitoring.

The in-process temperature and pressure measurements are monitored to ensure that the process operates within the desired parameters throughout the cycle. The data are also useful in determining the endpoint of primary drying. The endpoint of primary drying is when all of the bulk has been removed and it is now safe to increase the temperature of the shelf and product to remove the unfrozen water associated with the product. Increasing the shelf temperature too soon or too quickly can lead to product with unacceptable appearance if the glass transition of an amorphous solid is reached or exceeded. Different methods of determining the endpoint of primary drying are used by different companies (Table III).

Method	Description
Time Based	The primary drying step ends based on a predetermined time set point.
Product Temperature	Certain vials are equipped with thermocouples and the cycle is advanced when the temperature of the product is similar to the temperature of the shelf.
Comparative Pressure Measurement	The cycle is advanced when the value of the Pirani gauge is similar to the set point pressure measured by the capacitance manometer.
Pressure Rise Testing	The cycle is advanced when the pressure in the chamber increases no more than a predetermined level when the isolation valve is shut between the chamber and condenser.
Nitrogen Flow Rate into the Chamber	The cycle is advanced when the replacement of water vapor with nitrogen in the product chamber plateaus.

Table III. Methods of Determining the Endpoint of Primary Drying.

The different methods of determining the drying endpoint can lead to substantial differences in cycle time and conditions between different lyophilizers.
For example, endpoints based on product temperature can be misleading. Not all vials can be equipped with thermocouples and those vials equipped with thermocouples can dry sooner than the other vials on the shelf. Therefore, it is necessary to understand how the cycle was initially developed for a certain product and to understand how this will impact transferring the cycle to different equipment.

Equipment Capability and Scale-Up

Equipment Capability

Baxter completed equipment capability studies for laboratory and full-scale lyophilizers by comparing the flow of water vapor from the product chamber to the condenser using Tunable Diode Laser Absorption Spectroscopy (TDLAS). The studies were completed on the full-scale, LyoMax®, lyophilizers and on the laboratory-scale, LyoStar®, Lyophilizers. The full-scale and laboratory-scale lyophilizers have similar designs with the product chamber connected to the condenser via a cylindrical duct or spool piece. The lyophilizers described in this study used spool pieces designed with windows for TDLAS optical hardware (**Error! Reference source not found.**). TDLAS is a near-IR based technology used to calculate the mass flow rate of water vapor from the chamber to the condenser by measuring vapor velocity (m/sec) and density (molecules/cc).

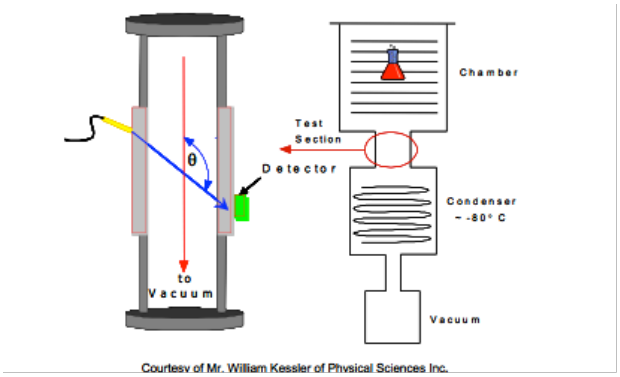

Figure 6. Schematic Diagram of the Spool Piece Equipped with a Laser and Detector for Measurement of the Flow of Water Vapor.

Sublimation rate is determined by the pressure gradient between the vapor pressure of ice at the sublimation front and the partial pressure of water vapor in the chamber, divided by the resistance of the system to the flow of water vapor. Open slabs of pure frozen water were used to generate water vapor and to eliminate the resistance that would be associated with a partially dried solid. The rate of condensation on the condenser is dependent on the rate of sublimation and is also dependent on the temperature of the condenser coil. In the LyoMax® lyophilizers, the temperature of the condenser was controllable and held constant at -60C during these experiments, and the condenser coil temperature was monitored to determine whether the condenser became overloaded during testing. These studies focused on a phenomenon referred to as "choked flow." Choked flow is characterized by the inability to control chamber pressure when the velocity of water vapor flow is so rapid that it becomes restricted through the spool piece. The speed at which water vapor can travel is limited by the speed of sound (about 360 m/sec). Choked flow through the spool piece typically becomes evident at vapor velocities well below this speed. The flow rate calculations were based on the spool piece dimensions for each lyophilizer.

Experiments were conducted by placing frames on each shelf and attaching sheets of plastic to each frame. Water was added to each frame and contained by the plastic sheets. The water was frozen by decreasing the shelf temperature to -40°C and allowing equilibration, followed by evacuating the system and controlling pressure at the low end of the operating pressure range, typically 25 mT. Mass flow and velocity data were collected throughout each study. The shelf temperature was increased step-wise, by approximately 10°C to 25°C increments, allowing the chamber pressure to equilibrate at the set point after each change. When the chamber pressure exceeded the set point, the shelf temperature, chamber pressure, mass flow, and velocity were recorded as the maximum for that pressure set point.

The capabilities of two LyoStar® II lyophilizers (PDE0090 and PDE0122) were compared using ice slab studies to identify the maximum supportable sublimation rate as the temperature of the shelf was increased. Both laboratory-scale lyophilizers are equipped with the same shelf surface area of 0.43 m^2. The equipment capability curves are superimposable, indicating equivalent performance (Figure 7).

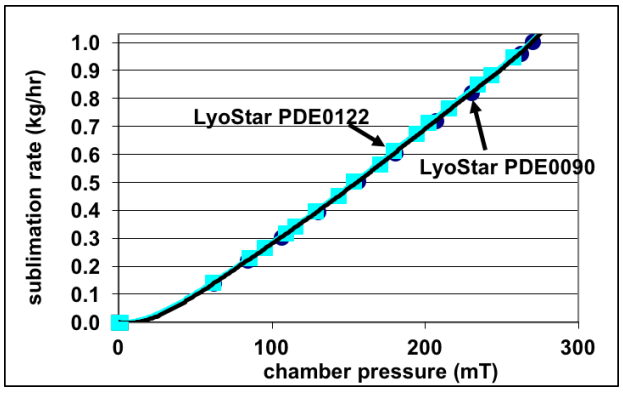

Figure 7. Comparison of the Maximum Supportable Sublimation Rates of Two LyoStar® II Lyophilizers.

Impact of Equipment Capability on Scale-Up

Equipment capability experiments were also conducted with full-scale lyophilizers manufactured by IMA Life and the data were compared with the equipment capability curve for the laboratory-scale, LyoStar II, lyophilizer (Figure 7). The capability studies were conducted using three full-scale, LyoMax®, lyophilizers and a laboratory-scale, LyoStar® II, lyophilizer. Two of the full-scale lyophilizers were LyoMax® 20 models having shelf surface areas of 19.95 m^2 and one was a LyoMax® 9 having a shelf surface area of 9.07 m^2. The laboratory-scale freeze dryer had a shelf surface area of 0.43 m^2.

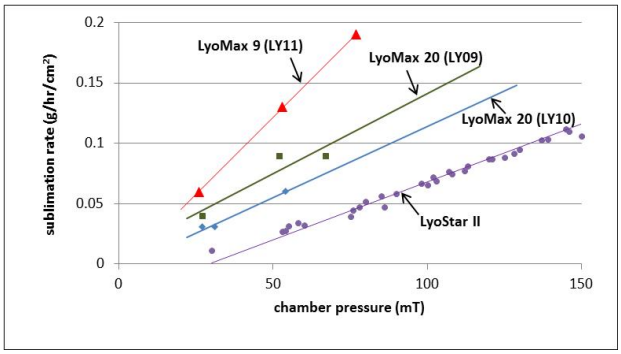

Figure 7. Equipment Capability Curves for Laboratory-Scale vs. Production-Scale Freeze Dryers.

The equipment capability curves for the full-scale freeze dryers are well above that of the laboratory-scale freeze dryer. The data demonstrate that the full-scale lyophilizers are more than capable of running cycles developed at laboratory-scale. Cycles developed at laboratory-scale are actually conservative with respect to the maximum sublimation rates that could be processed using the full-scale freeze dryers.

The differences in the capability curves observed for the full-scale equipment is likely due to differences in the design of the equipment and the accuracy of TDLAS. The quantitative accuracy of TDLAS on production scale equipment is more uncertain than the accuracy at laboratory scale. This is most likely because of the influence of a CIP/SIP water distribution pipe that runs the length of the duct between the chamber and the condenser. In view of this uncertainty and the fact that the larger units did not exhibit choked flow above 75 mT, the capability curves for LY09 and LY10 are likely not to be considered significantly different. The capability curve for the smaller production freeze dryer, LY11, exceeds that of LY09 and LY10.

This is not surprising, given the smaller shelf surface area of LY11 relative to the larger dryers.

Technical Transfer and Full-Scale Equipment

Baxter Research and Development collaborates closely with Baxter manufacturing sites located in Bloomington, IN, and in Halle, Germany. The Baxter Research and Development laboratory located in Bloomington, IN, is well-equipped for formulation and process development of parenteral solutions and lyophilized products. The group specializes in lyophilization and in developing and testing formulations for large molecules. The products and processes to make them have been transferred to full-scale manufacturing in Bloomington and Halle. The manufacturing site in Halle, Germany, specializes in containment of highly potent and chemotherapeutic molecules. The site in Bloomington manufactures most other types of formulations. The likelihood of manufacturing processes being transferred to either site means that comparisons of equipment and processing lines are available for planning technical transfers. An abbreviated comparison of the lyophilizers at each site is provided as an example in Table IV (see page 9). Experts available at each site are included in process development discussions as soon as possible to facilitate planning for technical transfer, to ensure clients are familiar with representatives at the site, and to familiarize the team with the available equipment. This collaboration and sharing of knowledge contributes to successful transfers of new processes.

Location	Bloomington, IN			Halle, Westfallen, Germany			
Production Area	**R&D Lab**	**Bldg C**	**Bldg D**	**PPB**	**PPC**	**PPE**	
Model	LyoStar II and 3	LyoMax20 x 3	LyoMax20 x 2 LyoMax9 x 1	GT6750	GT6750	GT5/6	GT1
Manufacturer	SP Scientific	IMA Life	IMA Life	Optima Pharma	Klee	Hoff Sonderanlagenbau	Hoff Sonderanlagenbau
# Shelves	3	11	11 and 5	11	8	16	7
Total Shelf Area	0.4 m^2	20 m^2	20 m^2 and 9 m^2	31.9 m^2	14 m^2	40 m^2	17 m^2
Condenser Type	External	External	External	External	External	External	External
Pressure Measurement	MKS or Pirani	MKS	MKS	MKS and Pirani	MKS and Pirani	MKS and Pirani	MKS and Pirani
Lowest Attainable Shelf Temperature	-70°C	-50°C	-50°C	-50°C	-50°C	-60°C	-60°C
Heat Transfer Fluid	Chlorotrifluroethylene Methylsiloxanes	Silicone Oil	Silicone Oil	Silicone Oil	Silicone Oil	Silicone Oil	Silicone Oil
Max Ice Capacity of Condenser	30 L	548 L	548 L	500 L	200 L	940 L	300 L
Vacuum Pump Type	2-Stage Rotary Vane	Edwards dry vacuum, mechanical booster	Edwards dry vacuum, mechanical booster	2 Rotary Vane + R2 Booster	2 Rotary Vane + R1 Booster	2 Rotary Vane + Roots Pump	2 Rotary Vane + Roots Pump
Controlled Wall Temperature	No	No	No	Yes	Yes	Yes	Yes

Table IV. Comparison of Lyophilizers Available at the Baxter Bloomington, IN, and Halle, Germany, Manufacturing Sites.

Summary

Lyophilization cycles are typically developed using a laboratory-scale freeze dryer. The process is transferred to full-scale freeze dryers that can be 10 times the size of the laboratory-scale equipment. The size differences and differences in the designs of the lyophilizers will affect the transfer of heat within the dryers and the flow of water vapor through the equipment. Therefore, it is important to have a detailed comparison of the equipment and, if possible, understand the capability of the lyophilizer. In most cases, the capability of the lyophilizer is defined by the maximum sublimation rate that it can support. This can be affected by the design of the lyophilizer which may include the duct through which vapor flows and the capacity of the condenser. Considering the differences in equipment design and capability will aid in the scale-up and technical transfer of new processes from laboratory-scale to full-scale and in transfers between manufacturing sites.

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