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Elements of Quality by Design in Development and Scale-Up of Freeze-Dried Parenterals

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ABSTRACT

A key concept in the Quality by Design paradigm is design space—a multidimensional space that encompasses combinations of product design and processing variables that provide assurance of suitable product performance. This article discusses design space in the context of developing, scaling up, and transferring freeze-dried products to a manufacturing setting. Smooth technology transfer starts with a robust formulation and an appropriate container and closure system. The design space is developed as an envelope in a graph of sublimation rate, shelf temperature, and chamber pressure. One boundary of the design space is established by failure of the formulation under aggressive cycle conditions. Other boundaries of the design space are determined by equipment performance, including refrigeration capacity, condenser capability, heating capacity, or limitations of the dynamics of water vapor flow within the system. Definition of this design space assures a thorough understanding of both the product and the process, and it minimizes the probability of unpleasant surprises in the technology transfer process.

The US Food and Drug Administration's Quality by Design (QbD) initiative is a new regulatory philosophy based on pre-defined quality targets and a deep understanding of how formulations and processes interact to influence critical quality attributes of pharmaceutical products.[1] This understanding is based on: prior knowledge of unit operations used in manufacturing a product, experimental data from development work, and published literature. In contrast, many submissions are based on empirical determination of performance criteria from analysis of experimental data. Table 1 briefly contrasts the Quality by Design paradigm with the current regulatory environment.

The intended benefits of QbD are:

1. Regulatory relief throughout the product life cycle, because post-approval changes don't require prior approval.

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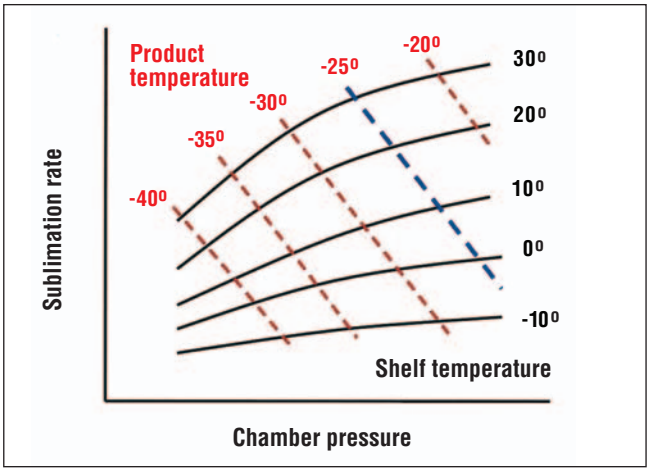
Figure 1. General layout of a proposed design space for freeze-drying, showing general relationships among sublimation rate, system pressure, shelf temperature, and product temperature (temperatures are degrees Celsius).



2. Potential reduction in the volume of data submitted; empirical data replaced by knowledge-based submissions.
3. Facilitation of continuous process improvement, because these process improvements don't require pre-approval.
4. Elimination of a need for current model of process validation.

A key element of QbD is the concept of design space, which is a multidimensional space that encompasses combinations of product design and processing variables that provide assurance of suitable product performance. Product and process changes that fall within the design space can be implemented without prior approval. Design space is proposed by the applicant and is subject to regulatory review and approval.

Although the principle of QbD is simple and appealing, the actual development, scale-up, and commercialization of pharmaceutical products presents a significant challenge to pharmaceutical scientists and engineers. This article will illustrate how the concept of design space might be applied to the development, scale-up, and transfer of freeze-dry processes for injectable pharmaceuticals.

Table 1. Current paradigm compared to the Quality by Design paradigm

Current paradigm	Quality by Design paradigm
Quality is tested into the product.	Quality is designed into the product.
Product specifications are based on batch testing results.	Real-time quality control, based on process analytical technology, is used.
Validation freezes the process.	Product specifications are based on fitness for use and process capability.
Process improvements require pre-approval.	Process changes within the established design space do not require pre-approval. Process validation is redundant.

Process analytical technology is an integral part of Quality by Design, because the paradigm relies on the use of real-time process monitoring and control as a part of an overall control strategy. In addition, a new development in process analytical technology—tunable diode laser absorption spectroscopy (TDLAS)—can be applied to define the design space for a freeze-dry process.[2]

GENERAL FORM OF A DESIGN SPACE FOR FREEZE-DRYING

A paper published by Chang and Fischer in 1995 includes a graph that, although not the point of the article, suggests an approach to establishing a design space for a freeze-dry process.[3] A simplified sketch of this graph is redrawn in Figure 1, with sublimation rate shown on the y-axis and chamber pressure shown on the x-axis, illustrating the functional relationships among sublimation rate, product temperature, and the two independently controlled variables in the process: shelf heat-transfer fluid inlet temperature and chamber pressure.

Chamber pressure has a complex effect on product temperature and sublimation rate, as follows:

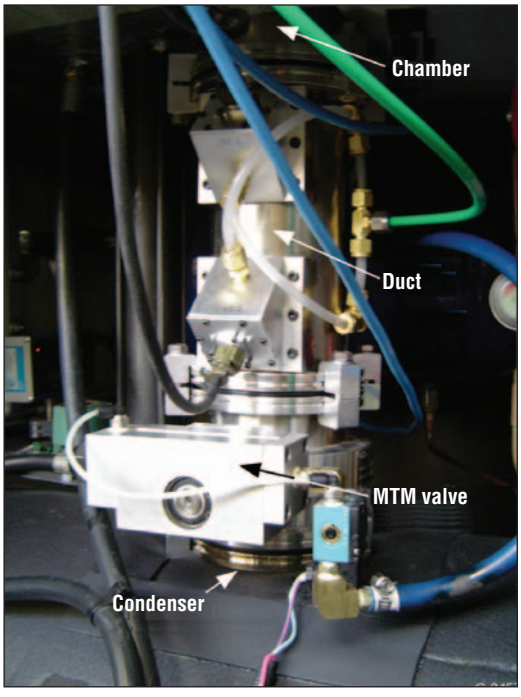
1. Higher chamber pressure decreases the driving force for water vapor transport from the ice interface within the product to the chamber. This driving force is defined as the difference between the pressure at the ice interface within the product and the chamber pressure (Pi-Pc). This effect can be seen by following the lines of constant product temperature in Figure 1, noting the linear increase in sublimation rate with decreasing chamber pressure, as long as product temperature remains the same.
2. Higher chamber pressure increases the rate of heat transfer to support sublimation rate by increasing the thermal conductance of the gas in the narrow gap between the shelf surface and the bottom

of the product vial.[4] This effect increases the product temperature, which in turn increases the vapor pressure of ice in the product, thereby increasing the pressure of water vapor at the ice interface. This condition increases the driving force for flow of this water vapor from the product into the chamber.

Within the range of chamber pressures used for pharmaceuticals and vaccines, the net effect of a higher chamber pressure is to increase the product temperature and sublimation rate of the product. This occurs because the improved heat transfer provided by higher pressure outweighs the negative effect on the sublimation rate of decreasing the driving force for flow of water vapor from the product to the chamber.

Therefore, for the most efficient processing, it is desirable to operate at the highest possible shelf temperature and the lowest chamber pressure that still maintains the target product temperature during primary drying.

Figure 2. Sensor hardware for tunable diode laser absorption spectroscopy (TDLAS) instrument mounted between the chamber and the condenser of an FTS Systems LyoStar II freeze-dryer (MTM = manometric temperature measurement).



HOW IS SUBLIMATION RATE MEASURED?

Traditionally, sublimation rates are measured gravimetrically. A representative number of vials are weighed before beginning the cycle, and the cycle is terminated before the end of primary drying. The average sublimation rate is calculated by re-weighing the pre-weighed vials after partial drying, and by knowing the time interval during which drying took place. Of course, this method is destructive, and weighing the vials can be tedious, but the process information is generally worth the loss of material and the work involved.

There is a new process analytical technology in freeze-drying, however, that provides instantaneous, nondestructive measurement of sublimation rate. Tunable diode laser absorption spectroscopy is a technique in which sensing hardware is placed in the connecting duct between a chamber and a condenser. TDLAS is not applicable to freeze-dryers designed with an internal condenser. A near-infrared beam is directed at an angle to the axis of the duct, and the Doppler shift of the water absorption band is measured by comparison with a sealed reference cell containing water vapor at a known partial pressure. The frequency shift between the two absorption maxima is proportional to the velocity of water vapor in the duct. By measuring the concentration of water vapor by traditional absorption spectroscopy, and by knowing the cross-sectional area of the duct, the instantaneous mass flow rate is determined.

In the laboratories at Baxter Pharmaceutical Solutions, scientists have compared gravimetric measurement of the sublimation rate with the integrated area under the mass flow rate versus time curve, and have generally found agreement within about 3%, which they consider satisfactory.

A photograph of the sensing hardware mounted on an FTS Systems Lyostar II freeze-dryer is shown in Figure 2, and a graph showing sublimation rate during the time course of freeze-drying is shown in Figure 3.

ESTABLISHING BOUNDARIES OF THE DESIGN SPACE

Identify Product Failure Modes

Probably the most common approach to development of a freeze-dry cycle for a given product is to identify, through trial and error, a set of process conditions (shelf temperature profile, chamber pressures, and time) that produce a pharmaceutically acceptable product. Typically, upper and lower limits are placed around these temperatures, pressures, and times; the process is validated and is thus frozen in terms of the inability to make improvements to the process without prior FDA approval. In the Quality by Design approach, the development scientist must gain a superior understanding of a larger map of process conditions that produce an acceptable product. This understanding requires preparing trial batches under increasingly aggressive conditions until the product is unacceptable. Most

Figure 3. Graph of freeze-dry process variables—including shelf temperature, product temperature, and sublimation rate—as measured by tunable diode laser absorption spectroscopy (TDLAS) (g/min = gram per minute)

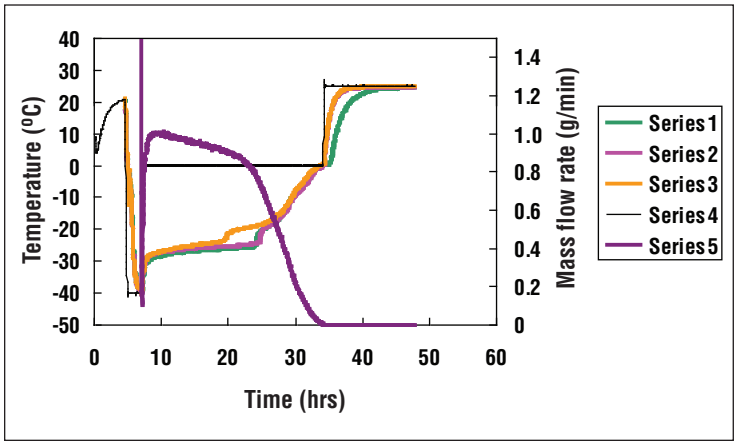
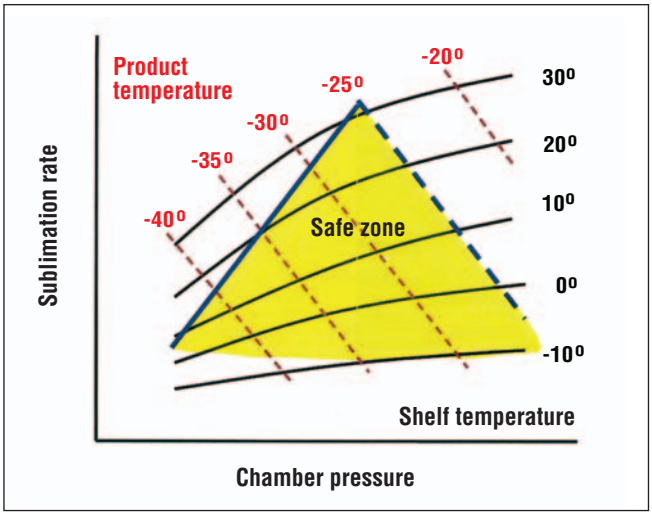


Figure 4. Design space showing boundaries that could be imposed by both product limitations and limitations in equipment capability (temperatures are degrees Celsius)



Collapse is characteristic of amorphous formulations where the upper limit of the product temperature is exceeded during primary drying.

commonly, the product will fail because of collapse. Collapse is characteristic of predominantly amorphous formulations where the upper limit of product temperature (the collapse temperature) is exceeded during primary drying (removal of water by direct sublimation of ice). As the sublimation front recedes, the partially dried solids undergo viscous flow, resulting in the loss of the microstructure that was established by freezing. The collapsed material is characterized by a pharmaceutically unacceptable appearance, high residual water content, and poor reconstitution characteristics.

For predominantly crystalline formulations, the upper product temperature limit during primary drying is the eutectic melting temperature. A eutectic mixture is an intimate physical mixture of two or more crystalline solids that has a sharp melting point. Exceeding this melting point during primary drying causes puffing of the vial contents and loss of pharmaceutical acceptability.

At least one other product-related failure mode is less common than the two mentioned above. For some formulations having a relatively low concentration of total dissolved solids, and particularly for formulations that use a co-solvent system consisting of water and an organic solvent (most commonly t-butanol), solids may be ejected from the vial. This is, of course, unacceptable because of the risk of subpotent product as well as the possibility of compromising the container or closure integrity by the presence of product between the sealing surfaces of the vial and rubber closure.

Identify Product-Imposed Boundary on the Design Space

The upper product temperature limit during primary drying should be determined during characterization of formulations intended for freeze-drying, using low temperature thermal analysis, freeze-dry microscopy, or both. As an example, suppose that characterization of the formulation shows an upper product temperature limit during primary drying of –25 °C. This upper temperature limit is shown by the broken blue line in Figure 1, and it represents the boundary of the design space imposed by the characteristics of the formulation.

For a failure mode involving ejection of solids from vials, the product-imposed boundary on the design space would be a horizontal line corresponding to the sublimation rate above which significant solids ejection takes place.

The heat-transfer system supplying the heat of sublimation of ice is limited in the amount of heat that can be transferred in a given period of time.

Identify Equipment-Imposed Boundaries on the Design Space

In the current culture of increased reliance on third-party organizations for formulation development, manufacture of clinical supplies, and manufacture of commercial product, it is essential to understand the limitations of the performance of laboratory-scale, pilot-scale, and production-scale freeze-drying equipment. To illustrate the potential pitfalls associated with multi-organizational and multi-site product development, consider the following scenario:

A small biotech company enters a joint venture with a large pharmaceutical company. Development scientists in the small biotech company characterize their formulation and determine that it will withstand very aggressive cycle conditions. They develop a freeze-dry cycle accordingly, using laboratory-scale equipment. The development scientists do not take into account the potential performance limitations of equipment at a separate company contracted to manufacture clinical supplies. The first clinical supply lot is manufactured using the cycle developed at the small biotech company, and the batch is rejected because of a failed freeze-dry cycle, resulting in a significant delay in the project.

This scenario is all-too-common. It illustrates the necessity of knowing the capability of equipment at the site where a product will be manufactured, and the need to take into account equipment limitations during initial cycle development.

Equipment limitations can take many forms. For example, the condenser has a limit as to the flow rate of water vapor that can be condensed while keeping the surface temperature of the condenser adequately low. This condition may occur because of limitations in refrigeration capacity at the condenser, because of limited surface area of the condenser, or perhaps because restrictions in water vapor flow around the condenser make some surfaces relatively inaccessible for condensation.

The heat-transfer system supplying the heat of sublimation of ice is limited in the amount of heat that can be transferred in a given period of time. This situation may arise because of limitations in the electrical power that can be provided to heat the silicone oil or other heat-transfer fluid, or perhaps because of limitations in the internal shelf heat-transfer coefficient due to the design of internal flow channels in the shelves and the heat-transfer fluid type and flow rate.

Equipment limitations of the type described above take the form of a maximum sublimation rate that can be supported by the equipment irrespective of the pressure in the system, and they therefore appear as a horizontal line forming an upper boundary on the design space.

There is another, more complicated limitation on the performance of freeze-dryers; this limitation has to do with the dynamics of vapor flow in the duct that connects the chamber to the condenser.[5] Vapor flows through this duct because of the difference in water vapor pressure between the chamber and the condenser. Normally, the higher the pressure difference, the higher the flow rate of water vapor through the duct. The pressure drops continuously across the length of the duct. Because the mass flow rate of water vapor is constant along the duct, the velocity increases. Thermodynamic theory shows, however, that there is a limit to this velocity corresponding to the speed of sound in water vapor—about 400 meters per second—or Mach 1. The speed of sound does not change with pressure. As the velocity of water vapor approaches Mach 1, the flow of water vapor is choked, and further reduction in the downstream pressure has no influence on the mass flow rate through the duct. In freeze-drying, choked flow is characterized by loss of control of pressure in the chamber.

Unlike the equipment limitations described above, the limitation imposed by choked flow depends upon the pressure in the system, where the mass flow rate choke point is directly proportional to pressure. The boundary on the design space imposed by choked

flow would have the general shape shown by the solid blue line in Figure 4. Thus, for the sake of this example, the design space is bounded by the upper product temperature isotherm on the right, and by the line representing the choke point on the left. Any process conditions in the design space would be acceptable. Of course, it is most desirable to operate near the apex of this space, because the apex represents the most efficient process conditions.

Ice Slab Testing for Equipment Qualification

A useful way to identify equipment limitations is to carry out a series of ice slab tests on a freeze-dryer. This is generally done by lining a tray ring with plastic sheeting and adding approximately one-half inch of water to each tray. The water is frozen, the system is evacuated to the desired pressure, and the shelf temperature is increased using a linear ramp rate. At some point, control of chamber pressure will be lost—this corresponds to the choke point. To measure the sublimation rate supported by the equipment at this pressure, it is necessary to repeat the experiment at the appropriate pressure and shelf temperature, carrying out sublimation until a significant fraction of the initial mass of ice has sublimed. This set of experiments is then repeated at a new pressure until enough data points have been determined to define the choke point line illustrated in Figure 4. The choke point data in this graph is based on gravimetric ice slab testing of a production scale freeze-dryer.

Of course, TDLAS capability significantly reduces the labor involved in this type of equipment qualification; it does so by eliminating the need to repeat each experiment after the choke point has been identified. In principle, the entire curve could be generated in one ice slab experiment.

It is also necessary to monitor other aspects of equipment performance during ice slab testing. This monitoring would include checking the condenser to make sure that the temperature remains below, for example, –50 °C. This type of limitation on equipment capability would appear as a horizontal line on the design space.

It is important to view product development for freeze-dried parenterals as an integrated process rather than as a collection of independent activities.

SUMMARY

It is important to view product and process development for freeze-dried parenterals as an integrated process rather than as a collection of independent activities. When doing formulation and initial cycle development, the development scientist must be aware of the type of equipment to which the product will be transferred in the next stage of development. The scientist must also understand the capability of the equipment, and must take it into account as cycle conditions are developed. This approach becomes particularly important for formulations that will withstand aggressive cycle conditions.

To generate a design space similar to the one in this discussion, it is necessary to have a thorough understanding of both the characteristics of the formulation and the capability of equipment. This is the major intent of the Quality by Design paradigm. ◆

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