Chapter 11
Contemporary Approaches to Development and Manufacturing of Lyophilized Parenterals

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Abstract This chapter provides a historical reference, covers the progression in the scientific and technological development, highlights the contemporary aspects, and describes the application of the current USFDA guidance to the development through commercial life cycle for lyophilized products. Considerations of designing formulations, including the use of organic solvents, and influence of packaging are noted. Emphasis is placed on the engineering of the lyophilization process, establishing the critical process parameters, and defining of the critical quality attributes. Utility of applying the US FDA process analytical technology initiative, as well as the notion of applying design space principles to the lyophilization process is included, leading into discussions on applying the current USFDA guideline on process validation to the development and manufacturing. Current challenges and unique aspects in development of lyophilized products are also highlighted, including poorly soluble drug substances, novel delivery systems, improving manufacturing capabilities, and reducing unit costs for world wide product distribution. This presentation encompasses the progression of the technological developments, reviews current thinking on the science and technology, and highlights contemporary approaches to the development and manufacturing of lyophilized parenterals.

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11.1 Introduction

11.1.1 Historic Review of Lyophilized Products

Lyophilization came of interest as a novelty in a laboratory setting, later as a method of preservation in hospitals until acknowledged as being a method of commercial manufacturing. A comprehensive review that included a historical, contemporary, and future potential highlights the future growth of lyophilization for parenteral products (Trappler 2011). The preservation of yellow fever virus was reported in the Journal of Experimental Medicine in 1929. In 1938, the Journal of the American Medical Association highlighted developments in the preservation and concentration of human serum for clinical use. The first products to be preserved by this method were human plasma, vaccines, and antibiotics. Early work on developing manufacturing was in collaboration between Max Strumia of Bryn Mawr College and the Sharp and Dohme Company in Philadelphia (Stark 1998).

Naturally derived biological preparations were prominent. Early commercial products included hemin by Abbott and corticotrophin by Parke Davis and Rorer Pharmaceuticals. One of the first antibiotics was penicillin G procaine by Wyeth. Development of antibiotics grew through the 1970s, with aminoglycosides (Tobramycin, Lilly) and cephalosporins (Keflex, Lilly), and cefazolin (Ancef, SKB, Kefzol, Lilly). Other new antibiotics included β-lactams vancomycin HCl, (Vancocin, Lilly) and tetracycline (*doxycycline*, Vibramycin, Pfizer). Continued development of new vaccines included IBV H-52 and H-120 for infectious bronchitis. Dactinomycin (Cosmegen, Merck) and cisplatin (Platinol, BMS) were some of the first lyophilized oncolytics. The Upjohn Company marketed two lyophilized corticosteroids, hydrocortisone sodium succinate (Solu-Cortef) and methylprednisolone sodium succinate (Solu-Medrol).

In the period of the 1980s through the 1990s, new products continued to be introduced to the market, many being anti-infectives to include antivirals. BMS introduced a new β-lactam (Azactam) and Merck developed a combination of a β-lactam and cephalosporin to treat gram-positive and gram-negative infections (imipenem/cilastatin, Merck). Antiviral therapies were also introduced to the market through the 1980s, with acyclovir (Zovirax, GSK) and ganciclovir (Cytovene, Syntex/Roche) and interferons ra-2A (Roferon-A, Roche) and ra-2B (Intron A, Schering). Novel treatments for MS became available with Bayer's Betaseron (interferon rB1b) and treatment for heart attack patients with Genentech's Activase (alteplase). New vaccines continued to be on interest. Treatments for HPV (Cervarix, GSK), DPT + polio and hemophilus influenza b (Pentacel, Sanofi Pasteur), pneumococcal (Prevnar, bulk powder intermediate, Wyeth), and herpes zoster (Zostavax, Merck) were marketed.

Early on as an academic curiosity, the later use in research laboratories and hospitals, and now an important technology, the use of lyophilization has become more commonplace in processing active pharmaceutical ingredients (APIs) as well as finished drug products. Since the inception of lyophilization as a method of

preservation, the number of products and the expanded application to therapeutics, diagnostics, and medical devices has driven the growth as a commercial manufacturing method. The greatest growth has been spurred on by the growth of the biopharmaceuticals.

11.1.2 New Products of Key Interest

Three major product classes continue to be of interest: antibiotics to treat drug-resistant infections, specifically MRSA; oncolytics that also now include biopharmaceuticals such as monoclonal antibodies; and vaccines. Immunomodulators is also a therapeutic class of products that continues to gain attention. Lyophilization is also used for the preservation of conjugated chemical entities, nanoparticles, and liposomes. New promises for treatment using RNA interference (RNAi) for oncology and genetic conditions are a new class of therapeutics that will also likely be lyophilized preparations.

11.1.3 Science and Technology Advancements

Interests in measuring, manipulating, and controlling conditions during lyophilization have led to new directions and developments, and continued studies are warranted to gain a better understanding of the basic principles and mechanisms that apply to freezing along with primary and secondary drying.

Control of freezing, specifically the random nucleation of water and resulting stochastic growth of ice, has long been an ambition. Various potential methods and the interest in controlling freezing drew interest for process and product improvements (Bursac et al. 2009; Patel et al. 2009). More recently, methods suitable for inducing nucleation that promise to be scalable has recently been introduced and is currently being studied by a number of investigators (Konstantinidis et al. 2011). Control of the ice crystal size and employing Ostwald ripening, with the ambition of improving the mass transfer of water vapor through the dried layer above the sublimation front during primary drying, has also been studied (Searles et al. 2001). The use of annealing during freezing has also been investigated for inducing complete crystallization of solutes such as ionic species and amino acids, and may influence the polymorphic form of some solutes. Beyond impacting the physical structure on a macroscopic scale, conditions during freezing can also influence the morphology of the solid form, as illustrated with mannitol (Cannon and Trappler 2000). The effect of excipients on crystallization of active ingredients has also been shown to occur (Korey and Schwartz 1989).

Shelf temperature is a process parameter that has always been recognized to be the principal variable affecting the product temperature and processing rates. Chamber pressure, though currently recognized as a critical process parameter (CPP), received

little attention in the early application of the drying technology: one simply reduced the pressure to as low as the equipment could achieve any given day. Observations to the effect of pressure on processing were reported as early as 1954 at the American Vacuum Society annual meeting (Ginnette et al. 1958). Since 1980, control of the pressure during primary drying by introducing nitrogen into the product chamber has become the convention (Nail 1980). Defined as a CPP, contemporary process engineering approaches has also included pressure control during secondary drying. Still, there remain unanswered questions on the principles and effects involved, with a growing understanding of the mechanisms and direct influences on heat and mass transfer. Influences on the progression during primary drying have received the greatest level of attention.

Increased understanding and improvements in factors that influence secondary drying have been limited. Desorption of water is perceived to be straightforward. The influence of chamber pressure was investigated and, within the nominal pressure range studied, is reported to have little effect (Pikal et al. 1990). Measuring and understanding the factors that influence removal of absorbed vs. adsorbed water has received little attention and warrants further study.

Overall, the most significant area of research has been on methods for the nucleation of water to control uniformity of this stochastic event. It is well recognized that ice formation and solute solidification during freezing has the greatest influence on behavior during processing and for some products, finished product attributes. Endeavors to control nucleation draws significant interest (Bursac et al. 2009). This includes investigation into the use of an "Ice Fog" technique (Patel et al. 2009). Investigations and methods suitable for application in commercial manufacturing have been refined by Praxair (Konstantinidis et al. 2011). Control of the nucleation is gaining great interest, as it shows great promise for improvements in processing and finished product quality with implementation in a commercial manufacturing scale. The advancements in control of freezing promises to be the most significant since the control of chamber pressure was introduced by Nail in 1980.

Other advancements involve the use of organic solvents as adjuncts to formulations. Organic solvents in combination with water have been selected as an aid in improving the dissolution and solubility of a poorly soluble compound, for accelerating the rate of vaporization during primary drying, and for altering the characteristics of the finished product. The most common mixed solvent systems are water and methanol, ethanol, or *t*-butanol. Early investigations focused on using pure organic solvents such as ethanol for low-temperature vacuum drying (Flamberg et al. 1970). Other investigators exploited improvements in processing and the resulting product attributes obtained for combinations of various organic solvents and water (Seager et al. 1985). Interest in the use of combinations of *t*-butanol and water gained greater interest (DeLuca and Kasrain 1995). There are, however, concerns in using organic solvents in the level of residuals and their pharmacologic effect. Process control and safety during lyophilization and toxicologic effects of residual solvents in the finished product are the principal concerns in the use of organic solvents (Teagarden and Baker 2002).

11.1.4 Current Expectations and Drivers for Improvements

Interests in improved control of CPPs for better reproducibility and efficiency and assuring consistent finished product critical quality attributes (CQAs) throughout the batch and from batch to batch are the two key aspects pushing innovation in the field. Driven by economics as the market value of products continue to increase, reduction in losses because of a batch being rejected due to loss of control of the CPPs, or a significant reject rate during physical inspection is receiving more focus and attention.

Product and process understanding is a precursor to achieving greater control for commercial scale lyophilization. It is well accepted that the CPPs throughout the lyophilization process are the independent variables of shelf (inlet) temperature, chamber pressure, and time. Key process parameters are the dependent variables of product and condenser temperatures. Basing the process on product temperature is recognized as inadequate for commercial manufacturing due to influences of temperature probe placement and product location, both of which are directed by the need to follow proper aseptic processing technique. It is well known and accepted that product temperature measurements of the vials containing probes are atypical of the rest of the batch: they are the first to freeze and the first to dry. As well, automated material handling systems for transfer, loading, and unloading the lyophilizer have precluded monitoring product temperature in routine manufacturing, simply because the probes cannot be automatically positioned in a vial. This fosters a reduced reliance on product temperature as an indicator of adequate process control and places greater emphasis on precise, reproducible control of the independent parameters.

In particular, there is a quest for understanding of how different product behavior and finished product attributes result with using the same CPPs in a different lyophilizer when scaling up or transferring a product from one lyophilizer to another or to different manufacturing sites. Investigations into failures in product transfer lead to a greater understanding of gas and vapor flow. Mechanisms and models of flow through the restrictive connection from the product chamber to an external condenser have been identified as a significant influence and a major consideration.

Suitability for the intended use is the rationale by which quality attributes are established. For a lyophilized parenteral specifically, this encompasses dried state storage stability and the ability to readily revert to a parenteral solution for patient administration upon reconstitution. Improved stability for longer shelf life resulting in greater effectiveness of material management and inventory control is becoming more important as market quantities and batch sized continue to increase. Distribution networks are also more extensive as global markets develop. Alleviating returns for product beyond its expiry date can provide significant savings. A long shelf life is also imperative for the increasing number of products used in therapies treating rare conditions: products that have received orphan drug status. Inventory turnover is not as often as products used in therapies for more common conditions.

Improved dried state stability encompasses both an extended expiration date and more importantly suitability for storage at room temperature. As product manufacturing becomes more centralized and distribution becomes more global, product may reside in the distribution chain longer. Manufacturing larger batch sizes is reflected in the number of larger capacity lyophilizers. A common size commercial scale lyophilizer prevalent in the turn of the century may have had the capacity for 60,000 10 cc vials. It is now more common to install capacity for batch sizes of 130,000 10 cc vials. Larger batch sizes allow for a reduction in unit costs with higher throughput in manufacturing.

The need to distribute products that must be maintained at controlled temperature conditions of 5 or −20 °C is becoming more difficult and costly as distribution channels become more extensive and distances greater. This is an important consideration during development and becomes compelling for designing formulations that will stabilize the dried product at more elevated temperatures. Relative to the needs for distribution of commercial product, cold chain distribution for clinical studies is manageable, though not easy, particularly with global product distribution into a wide variety of countries. Product development is not complete when a product is sufficiently suitable for conducting clinical trials. Further work is warranted for developing a suitable commercial product that does not require cold chain distribution. Even in the rare case when cold chain distribution and storage is necessary, stability studies to establish an acceptable duration when the product may be beyond the intended storage conditions for some interval are warranted.

In addition to suitable stability for an extended shelf life, achieving desired finished product quality attributes has also focused on the absence of melt-back and collapse. Product exhibiting any incidence of melt-back or collapse is considered to be a product defect unless proven to have acceptable CQAs. Melt-back or collapse may be proven to be a cosmetic concern when shown to have no effect on dried product attributes, including storage stability, though melt-back and collapse are generally considered to be less desirable.

11.2 State of the Industry in Commercial Manufacturing

Increased market demands as the patient population and market size grows, and global distribution becomes more common, has led to increased batch sizes. As well, with an increase in specialized courses of therapies, treatments for less common conditions and specialized indications driven by development of orphan drugs require a fewer number of smaller batches necessary to supply the focused market. One might expect this to lead to segregation in manufacturing operations: high capacity for large market products and boutique operations for specialty products like orphan drugs.

Manufacturing capabilities and capacity continue to reside within an innovator's operations as well as being outsourced to a Contract Manufacturing Organization (CMO). For some pharmaceutical and biopharmaceutical companies, the

manufacturing may be solely outsourced. For others, in-house capacity may be supplemented using a CMO. The most significant differentiation between an innovator's in-house manufacturing operation and a CMO is that the innovator may have a dedicated manufacturing site while a CMO is a multi-product facility. Control and security of automated control systems and equipment cleaning are prime concerns with such multi-product operations. The increased separation of an operator for decrease exposure to the product widely applied to parenteral manufacturing has also been used for lyophilization operations as well.

Automated control of the lyophilization process has become common and includes lyophilization and support processes. Automated systems are comprised of control capabilities, process monitoring, and data acquisition, as well as batch report generation and historical data archiving. Process control and automation combines the necessary hardware in lyophilizer design and construction and the automated control system. This allows for complete automation of clean-in-place (CIP), steam-in-place (SIP), and nitrogen filter integrity test (FIT) along with the lyophilization process and has become common. These sophisticated automated control systems may stand alone, be able to be accessed remotely, or an integral part of an expansive network. Technical support of automated systems requires staff with knowledge of the control system hardware and software, as well as having a good understanding of the process requirements and how the lyophilizer operates. Control of the applications software as well as the lyophilization process recipe is critical. The operator interface is also important. Security for the system access and confidence that the correct recipe is initiated to begin the process for a specific product is imperative. As for any process step in manufacturing a pharmaceutical, documentation of the step, either manually or electronically, and verification by a second individual is expected.

Automation has also been effectively applied to cleaning of the lyophilizer interior. CIP systems for the product chamber and condenser are routinely included in new production lyophilizers. Although not a direct product contact surface, the lyophilizer interior may be treated as such (Johnson et al. 2012). Expectations for cleaning effectiveness and residual levels used for process equipment such as bulk solution tanks are often applied. Unique to lyophilizers is that the use of any cleaning agent is rare a, most often only as a decontamination agent. Rather, a rinse with purified water, USP, or water for injection, USP is all that is often used. The most effective cleaning verification consists of swabbing surfaces that have been shown to be difficult for the CIP system to effectively clean. This may be the location furthest from the cleaning nozzles or where the spray may be obstructed. CIP of both the product chamber and condenser should be verified.

The combination of increased batch size and the interest in minimizing product exposure to operators has driven continued improvements and frequency of application in high speed automated material handling systems. Approaches have varied between transfer and loading of the lyophilizer in a single row directly off of a conveyor to accumulating a large quantity, often an entire shelf of product at a single time for transport and loading of the lyophilizer. Both approaches have also been used for unloading the lyophilizer.

Restricted access barrier systems (RABS) have also become more common. Application of a passive system, where operator access is achieved by opening the barrier separating the operator from the product, or complete isolation where the enclosure is sealed and sanitized where access for operator activities is provided through gloves in the isolator wall.

11.3 Contemporary Technology

11.3.1 Formulated Product Characterization

Identifying the low-temperature characteristics is imperative for investigating the CPPs during process engineering studies. The shelf temperature intended during the freezing needs to be sufficient to assure adequate solidification. Product characterization and behavior while warming a frozen preparation is crucial for investigating conditions appropriate for primary drying. These temperatures can be determined using common methods of low-temperature thermal analysis (LT-TA). These methods include electrical resistance (ER), low-temperature differential scanning calorimetry (LT-DSC), and freeze-drying microscopy (FDM).

There are various methods available for characterizing the liquid preparation to be lyophilized. Many depend upon the change in physicochemical nature of the formulation. Specifically, it is the change in state that is of interest. Fundamental difference in physical properties including heat capacity and thermal and electrical conductivity are classical methods for determining when a material undergoes a change in state.

Electrical resistance measurements have been used to effectively determine when a material solidifies with cooling of an aqueous system containing a solute that crystallizes from a dilute aqueous solution. It is also effective to indicate at what temperature a melt occurs upon warming a frozen preparation. For an aqueous solution containing a solute that crystallizes, subsequent to nucleation of ice and ice crystal growth, continued cooling will show a sharp increase in electrical resistance when the solution undergoes nucleation and crystal growth of the solute with the coincident solidification of the remaining unfrozen water. Upon warming such a composition, a most highly concentrated solution will form at a distinct temperature as a result of melting. This behavior, occurring at a distinct and reproducible temperature and concentration, reflects the behavior of an eutectic material, referred to as eutectic behavior. The temperature at which the crystalline material and a small amount of ice melts to form a highly concentrated solution is the eutectic temperature. As many lyophilized pharmaceutical preparations solidify as amorphous rather than crystalline compositions, lyophilized preparations exhibiting eutectic behavior are rare and measurements of electrical resistance of limited value. In mixed preparations where there may be a solute, such as an ionized species of an organic compound, the solidification upon cooling and softening upon warming may be revealed by a change in the electrical resistance, though the results would not be considered definitive but rater supportive data when other methods of analysis are employed.

The evolution and consumption of the heat of fusion and a change in thermal conductivity and heat capacity are the basis of LT-DSC. For material that tends to crystallize, an exotherm occurs, reflected in a sudden increase of the sample temperature due to the heat of fusion when nucleation and crystallization occurs during cooling, relative to a reference that does not exhibit eutectic behavior. Upon warming the sample, an endotherm occurs when consuming the heat of fusion with the melt of crystalline material. For material that does not crystallize, but rather solidifies in an unstructured amorphous mass, there is a change in heat capacity, thermal, and of lesser magnitude, electrical conductivity. This change manifests in the different cooling and heating rates due to differences in heat capacity and thermoconductivity of the material in the liquid and solid state, with a sudden shift in that rate occurs when the material progresses from one state to another. It is the sudden shift in the rate that reflects the glass transition, denoted as T_g' for low-temperature analysis of a preparation to be frozen and lyophilized. A sensitive method with the ability to determine solidification of a solution to form ice and solidified solutes, and to distinguish a glass transition and crystalline melt upon warming, LT-DSC is a useful analytical tool. Most often, a glass transition of an amorphous complex occurs and the temperature at which this change occurs is of greatest interest and is the result reported. As many instruments report the change in enthalpy (ΔH), it may also have value as a quantitative method, though these values are seldom reported.

Like LT-DSC, differential thermal analysis (DTA) measures the difference in thermal conductivity and heat capacity relative to the material in the liquid state, and the temperature where there is a change in the heat capacity coincides with the change in state. DTA measures the difference in temperature relative to a reference material when the instrument is cooled and warmed at a constant rate. Measurement of the difference in dielectric measurements correlated to a change in state of a frozen system has also been explored (Evans et al. 1995). These methods are rarely used as commercial instruments are not readily available.

FDM is considered to be the gold standard of the industry. A sample is placed on a specially constructed stage contained within a vessel capable of exposing the sample to low temperatures at a reduced pressure. Commercially available units utilize piezoelectronics for accurate and precise control of the sample stage. Using conventional microscopic techniques, a drop of sample is placed on a coverslip and a second coverslip placed over the droplet to form a thin film of the sample solution. The sandwich of the coverslips and sample is then placed on the stage positioned under a standard microscope. An advantage to this method is that a polarizing microscope may be used to distinguish the development of a crystalline form of a solute upon freezing and the melt upon subsequent warming, along with sometimes vibrant colors. Changes in the physical appearance during cooling and warming may be correlated to the temperature of the instrument stage. Upon cooling, the nucleation of water to form ice and subsequent solute solidification may be observed. Subtle changes in state during cooling are often difficult. With the stage evacuated to a reduced pressure, the stage is warmed, ice begins to sublime, and observations made of the sample. The ice-vapor interface, termed the sublimation front, may be observed as it progresses from the outer edges of the coverslip towards the center of the film. One can observe the growth of a dried layer as sublimation

continues and the material dries with retention of the structure established during freezing. As the solute composition continues to warm, a change in the structure different than previously appearing at lower temperature can be observed: the material has warmed through it's glass transition, has softened, is no longer able to support its original structure, and is becoming sufficiently fluid and a change in the observed appearance occurs. Continued warming leads to catastrophic collapse observed as a complete loss of structure.

Though the common methods of LT-TA described utilize different techniques, all are based on a measurement associated with a change in state. The presence of an ionic species, where transfer of an electrical current with the species being ionized and can effectively carry an electrical current when in the liquid state, is the basis of ER measurements. This is an effective method with the presence of an ionized species and of no value when the composition is amorphous. Measuring the glass transition by LT-DSC is an effective method for many pharmaceutical preparations as the great majority of the products are amorphous. The limitations and the interpretation of the thermogram are somewhat subjective, as some thermal events are difficult to detect and interrupt on the thermogram. There is also no standard reference to reporting the results. For a crystalline melt, the temperature at the onset of the melt or the temperature at half the peak height, or the temperature at the peak of the exotherm may be reported. A glass transition may be difficult to determine, is open to interpretation, and varied in reporting. As there is a shift in the thermal conductivity and heat capacity, the onset of the shift or the point of inflection may be considered more significant. Regardless of the method when interpreting the analysis, the approach should be clear and consistent when reporting the results.

11.3.2 Understanding the Influence of Packaging

Unique in pharmaceutical product manufacturing, the packaging is an integral part and has a significant impact on lyophilization. The vial influences achievable processing rates during freezing and subsequent drying due to its influence on heat transfer during the process as suggested by Pikal et al. (1984). Tubing vials have been shown to be more effective in heat transfer compared to molded vials under the same set of processing conditions. This, however, causes the temperature around the bottom perimeter of the vial to become the warmest location and can lead to product exceeding the threshold temperature in the local region. Molded vials, though having poorer overall heat transfer, tend to provide more uniform heat transfer (Trappler et al. 2012). The bottom curvature, specifically the bottom radius and extent of contact between the vial and the lyophilizer shelf is the most significant factor in the vial geometry for heat transfer (Cannon and Shemeley 2004). For a given volume of product, the diameter of the vial dictates the depth of the product, which has an influence on mass transfer of water vapor from the sublimation of ice and therefore potential drying rates. Mass transfer through the dried layer is well recognized as one of the rate-limiting factors, with different model systems demonstrating varied resistances (Pikal et al. 1983).

Interactions between lyophilized product and glass vials would not be expected to be prevalent since the product is not in contact with the glass in the liquid state for any extended time and the product is in the solid state during storage. Therefore, concerns of leachable and extractable components from the glass vials have not been a significant issue for lyophilized products as compared to liquid preparations. There are instances where a lyophilized product at extremes in pH have undergone a significant pH shift when comparing the bulk solution to the reconstituted product after lyophilization due to interaction with the glass.

The unique stoppers used for lyophilized products are designed to allow water vapor to pass thought the opening provided when the stoppers are partially inserted into the vial during the filling operation. The geometry of the stopper and resulting opening has been shown to have little effect on passage of water vapor though the partially inserted stopper: single, two, and three vent stoppers are comparable. There have been stoppers with more numerous vents that become restrictive to water vapor flow, though such stoppers are not common (Bosch and Shultz 2008).

Improvements in stopper rubber formulations have been made to reduce water and gas permeation through the stopper and the tendency of the stopper to absorb moisture during steam sterilization to subsequently desorb the moisture during product storage. For low dry weight products where even small amounts of moisture remains in the stopper, contribution of moisture from the stopper may increase the moisture in the product, leading to collapse upon storage. Stopper drying processes are critical for some combinations of product and stopper types (Hora and Wolfe 2004). Leachable and extractable materials from the stopper are of growing interest, though more of a concern for liquid products exposed to the stopper during long-term storage.

There is a growing interest in cartridges and syringes as a lyophilized product presentation. Like many lyophilized preparations, cartridge and syringe presentations are often unit dose. The increase in products intended for self-administration makes such a product presentation attractive for ease of administration, improved convenience, and patient compliance. There are also suggestions that the total cost for delivery to the patient is a commercial advantage and self-administration of injectables offers advantages and challenges as they become more prominent (Kaifman et al. 2012). Generally, this presentation is limited to small product dosages for subcutaneous and intramuscular administration where volumes are often 2 mL or less, though bolus injections require larger volumes.

Significant challenges are associated with processing for material handling and lyophilization. Cartridges were first introduced by Wyeth under the Tubex® brand. Cartridge holders for administering the products were as common as stethoscopes for health care practitioners. Dental cartridges have been and continue to be manufactured in large quantities with the use of high speed manufacturing. Cartridges are also available in tubs as a ready-to-use presentation for manufacturing: they are washed, siliconized, and sterilized. Dual chamber cartridges and syringes have been developed and are available as a product presentation with unique designs suitable for reconstitution of a lyophilized preparation. These cartridges are unique in that there is a channel protruding from the side wall of the cartridge that allows the

diluent to pass by a center plunger, and with a unique plunger design, aid in reconstitution of the lyophilized cake upon activation of the cartridge. The manufacturing entails first dispensing the bulk solution into the cartridges held in a frame or magazine, orienting the cartridge vertically. After the product is dried, the product is placed on a filling line, the diluent dispensed into the open end of the cartridge and a second plunger inserted to seal the diluent. Vetter is the prominent CMO that has established commercial manufacturing. Merck manufactures its own cartridges and markets lyophilized polyethylene glycol (PEG) Intron in a dual chamber cartridge as a Redipen® for self-administration.

Limitations and challenges for dual chamber cartridges for lyophilized preparations include the unique material handling required in an aseptic environment. The number of manipulations of an open container increases the opportunity for contamination. As the geometry of the cartridges, complicated by the arrangement in tubs, does not lend to a significant contact with the lyophilizer shelf, heat transfer is a significant rate-limiting factor, particularly during freezing. Because of this, low temperatures sometimes required during freezing for solidifying the product are difficult to attain. With the product to be lyophilized positioned where there is no intimate contact with the shelf, as with vials, efficient and effective heat transfer is even more of a challenge.

The other limitation is the batch size within a given lyophilizer relative to those of products contained in vials. The number of containers for a given shelf surface when processing product in vials is relatively high since the vials can be close packed, referred to as a "nested" configuration, where each vial, except for the edge vials, has six neighbors. For example, approximately 355 of 3 cc vials can be placed within 1 ft^2 (100 cm^2) of the shelf surface. A magazine used for commercial manufacturing of a 3 cc dual chamber cartridge allows for processing only 146 units within the same shelf surface area, and the cartridges stand approximately ¾″ (9 mm) apart from each other. There is also a lack of intimate thermal contact between the product container and the shelf. A shelf clearance of 3″ (76 mm) is sufficient for lyophilizing in a 10 cc vial containing up to 3 cc. For the equivalent syringe or cartridge, 8″ (205 mm) is required to accommodate the cartridges vertically oriented within the magazine. All of these factors present new challenges in understanding the mechanisms for heat and mass transfer; different approaches to processing are warranted.

11.3.3 Identifying Critical Process Parameters

It is well accepted throughout the industry and the US FDA that shelf temperature, chamber pressure, and time are the CPPs as independent variables[1] for lyophilization (Food and Drug Administration 1993). The lyophilization process is described as a series of soaks and ramps of the shelf temperature and soaks of the chamber pressure.

[1] An independent variable is those that are under direct control and are not resulting from influencing factors or dependent upon other processing variables.

A soak is a predefined interval for which the parameters are controlled at the desired target condition. During these soaks a steady state condition can be achieved. A ramp is an average rate of change in temperature from one soak setpoint to another. Target CPPs reflect an ideal set of soaks and ramps for the shelf temperature and soaks for the chamber pressure as the CPPs.

Determining the CPPs suitable for a specific product is dependent upon the formulation characteristics and the product presentation. Formulation characteristics need to be determined and understood early in the development and precedes any process engineering studies. As the volume within the container and the size and type of container has an influence on processing, the final product presentation also needs to be defined.

Contemporary approaches in conducting process engineering explore variables in the CPPs and can commence once the formulation and product presentation are defined. The objective of process engineering is to investigate the effects of altering the CPPs on the resulting behavior during processing and the resulting finished product attributes. The goal of the process engineering is to establish the combination of shelf temperature, chamber pressure, and time for each step of the process that are safe, effective, and sufficiently robust. The preferred combination of the CPPs is verified by correlating the essential CQAs and desired finished product attributes, including sufficient stability during storage. A rigorous approach to development to gain an understanding of the product and process that may include empirical and mathematical data as outlined in the ICH Harmonised Tripartite Guideline on Pharmaceutical Development (Q8R2) (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use 2009).

The validity of the parameters in the process engineering studies during development is dependent on the ability to emulate commercial capabilities. Component preparation needs to yield attributes of cleanliness achieved in a commercial operation. The vials and stoppers should be of the same condition as when producing a product in a commercial operation: clean and essentially particulate free. The bulk solution should be sterilized by filtration. Assembly of the product with dispensing the sterilized bulk solution and transfer and loading of the lyophilizer should be in a class 100 environment: Class A is not required, Class B is sufficient. Each of these factors influences the cleanliness and particulate burden. The cleanliness of the components and product to be lyophilized affects the nucleation of water and the growth of ice. These events during freezing in an uncontrolled environment are different than that which occurs when processing commercial sterile product in an aseptic operation.

To gain confidence in the processing parameters and the lyophilizer is performing as expected, the equipment should be qualified and a preventative maintenance (PM) and calibration program should be in effect. Equipment qualification and proper PM are critical for confidence that the equipment used in engineering the process is operating properly and there is adequate control of the conditions during processing. As in a commercial operation, to have confidence in the measurements and in following sound scientific principles, the instrumentation for controlling and

Table 11.1 Operational qualification test function and parameters

Qualification test	Test parameters		
Shelf cooling	Maximum		Controlled
Shelf heating	Maximum		Controlled
Shelf control	Low temp	Intermediate	High
Condenser refrigeration	Maximum cooling rate		Ultimate low temperature
Vacuum system	Maximum evacuation rate		Ultimate low pressure
Leak rate	Threshold capabilities		
Pressure control	Low	Intermediate	High
Condenser capacity	Threshold capabilities		
Sublimation / Condensation Rate	Maintain CPPs		Maximum rates at predefined conditions

monitoring the process, as well as those used for monitoring the product should be calibrated. The steps in preparing the material under study should be well documented. Utilizing batch records for preparation and processing the batch in a study when conducting the process engineering provides an opportunity to record critical data and documenting observations. This provides many advantages over simply making notes in a laboratory notebook. Such formalized and detailed records provide valuable documentation as part of a development report. It also provides well organized, complete, and comprehensive data, becoming a valuable reference when preparing the chemistry, manufacturing, and controls (CMC) section of a regulatory submission.

In the clinical phase of development, establishing the CPPs need to focus on those suitable to prepare material for clinical studies. Parameters that are safe, effective, and sufficiently robust to accommodate unexpected influencing factors are most appropriate. Experience and expertise in the science and technology are paramount in obtaining this goal in a limited number of studies with a limited amount of API. The goals and expectations should be towards parameters necessary to prepare clinical material rather than those that may be desired for routine commercial operations. Optimal parameters for preparation of clinical material are those that are sufficiently robust and be suitable for differences in characteristics that may occur in the API. As well, it would be appropriate to verify the low-temperature thermal characteristics of each batch of API early in clinical development. This should be a routine practice until the upstream processing has been shown to be reproducible and able to yield API of consistent purity and potency.

Upon achieving favorable clinical results and in parallel to conducting later clinical studies, further process engineering studies to begin exploring process parameters for commercial manufacturing are appropriate. The goal for the studies at the later stages of clinical development is to establish the CPPs suitable for integrating into a commercial product manufacturing operation. Knowledge of the capabilities in the commercial operations as well as for the lyophilization equipment is imperative. A good source of information about such capabilities is the lyophilizer operational qualification study results. Test results listed in Table 11.1 would be appropriate to consider in conducting the studies in process engineering.

Clinical manufacturing and commercial lyophilizer performance provide the guidance in selecting the parameters used in the process engineering studies early in clinical development as well as in the later studies for a process suitable for commercial operations. Executing an engineering study in the clinical and commercial operations would be prudent to assure the lyophilizer can execute the intended parameters prior to processing actual product.

Different approaches may be employed to assess the impact of profiles in the parameters: shelf temperature for loading the lyophilizer and completing the freezing step and combinations of shelf temperature and chamber pressure for primary and secondary drying. The objective during the process engineering studies later in the clinical development phase of bringing a new product to market is to vary the CPPs in order to assess their impact on the resulting product temperature, processing rates, and residual moisture. Key to evaluating any combination of processing variables is knowledge of the product character and behavior during processing. Thermal analysis studies, as described in the earlier section, are the very first study and prior to undertaking any process engineering studies. Implementation of processing parameters based upon mathematical models can also be valuable as an initial trial, gaining experience on the behavior of the product under an initial set of processing conditions.

Shelf temperature has the greatest influence processing rates and the ultimate product temperature at the end of each step. The rate at which heat is removed during freezing, quantified as heat flux, dictates the initial cooling rate, rate at which the ice crystals grow, rate at which the highly concentrated solution cools, and rate at which the final solidification occurs. Annealing during freezing may alter the ice of initial freezing by inducing Ostwald ripening (Searles et al. 2001). During primary drying, the shelf temperature mostly dictates the rate of sublimation (Deluca and Lachman 1965). During primary drying, however, the heat flux is coupled with mass flux, the rate at which the water vapor can traverse through the dried layer above the sublimation front. This achievable mass flux has been studied to a great extent and a term of R_p assigned to the resistance of the dried layer (Pikal et al. 1983). Classically, the greatest direct influence of the chamber pressure is on the pressure differential that develops between the vapor pressure of ice at the sublimation front and the partial pressure of water above the sublimation front. This partial pressure is influenced by the flow of the water vapor through the dried layer above the sublimation front. The resistance, or more directly the pressure differential between the vapor pressure of ice and the chamber pressure dictates the flow rate, affecting the achievable rate of sublimation, ultimately and indirectly, the product temperature. It is important to recognize that the achievable rate of sublimation is dependent upon the relative partial pressure of water vapor above the sublimation front, above the top of the dried material, and in the atmosphere in the lyophilizer. Overall, the greater the difference in the ice vapor pressure in the product and the partial pressure of water that comprises the atmosphere, the greater the rate of sublimation that can be achieved.

Contemporary processing conditions entail control of the shelf temperature and chamber pressure during the secondary drying step. Principles and mechanisms that

effect desorption are the driving force in secondary drying. Classically, heat is the predominant influence to rates of desorption. Some studies have been conducted to evaluate the influence of chamber pressure up to 200 μmHg with no significant effect determined (Pikal et al. 1990).

Initial process engineering studies may focus on holding one variable constant while altering the second. The principal interest in these early studies is in the effect of the various combinations on the product temperature. A suitable and safe threshold temperature may be as close as 2–3° below the indicated collapse temperature measured during the LT-TA studies. Though a general guideline, a safe margin in temperature is selected empirically based on the character of the product gleamed from LT-TA, particularly FDM and during the early process engineering studies.

Though not intended to take the process to the point of causing the frozen material to melt back and form a liquid or the dried layer at and above the sublimation front to collapse, the CPPs should be varied to at least approach, though not necessarily exceed the critical threshold temperature. Results from studies that force the product to approach the critical threshold temperature can be used to identify both a target set of parameters as well as the combinations of parameters suitable for the process boundary conditions of the proven acceptable range (PAR) (Chapman 1984). Depending upon the character of the material and behavior during processing at the various conditions, the most effective combination of shelf temperature and chamber pressure can be identified. A study to evaluate the behavior during processing at the target conditions and the rates at the selected shelf temperature and chamber pressure would identify the time required to complete each step. It is important to consider that the time indicated for reaching the ultimate temperature during freezing and primary drying indicated by the containers monitored using a temperature sensor will be atypical of other containers, due in part to the stochastic nucleation event and resulting ice crystal growth. With uncontrolled freezing, the containers with the temperature sensors are the first to undergo nucleation of water to form ice, generally have larger ice crystals, and will therefore be the first containers to complete the sublimation of the ice. Recognizing this difference warrants consideration in the time selected to complete each process step. In freezing, additional time may be included to assure all the material in all the containers are near or at the same temperature and within an acceptable variation relative to the shelf temperature. During primary drying, all the containers should be near or at the shelf temperature for an amount of time so that the one is assured that all the material in each container and all the containers are at the same condition prior to progressing to secondary drying. The time necessary for secondary drying is easily determined by measuring the residual moisture as time progresses at the target shelf temperature and chamber pressure. Residual moisture can be plotted relative to time to determine how long is required at the target process conditions to achieve the level that correlates to long-term stability in the dried state.

An essential part of verifying the target CPPs is correlating long-term stability at the intended storage conditions for the dried product. Storage at accelerated conditions may also be useful. Dried state stability may utilize the application of Arrhenius equation for predicting stability upon storage. Note, that the Arrhenius

Table 11.2 CPPs for a mAb formulation, 4.1 mL fill, 30 mL type 1 tubing vial, and 20 mm single vent stopper

Process step	Soak (°C)	PAR value (°C)	Duration hours	Ramp rate (° per hour)	Pressure (μmHg)	PAR value (μmHg)
Loading	5	0–10	4		10 psia	
Freezing				15	10 psia	
	−50	−55 to −45	4		10 psia	
Primary drying				30	80	60–100
	−18	−23 to −13			80	60–100
Secondary drying				15	80	60–100
	25	10			80	60–100

activation energy and Arrhenius A factor are intended for calculating rate constants of reactions in solution, and should be considered a first approximation for reactions in the solid state. It is expected that, at a minimum, the ICH guidelines for conducting stability studies be followed. Use of the glass transition (T_g) of the dried material to evaluate the relative temperature difference for the storage condition has also been studied and may be applied to predict the dried state stability (Fitzpartick and Saklatvala 2003). If the product is stored at a temperature above the T_g, molecular mobility, a prerequisite to chemical reactions is possible, thus leading to potential degradation.

Once the target parameters of shelf temperature, chamber pressure, and time are established, data from the early studies in varying the CPPs can be used to identify the parameters for boundary studies to establish the PAR for the process. The boundary conditions are most often selected that they vary equally from the target CPPs. For example, a target parameter for the soak during freezing of −40 °C may have a PAR of ±5 °C, providing an acceptable range from as low as −45 °C to as warm as −35 °C. A description in the Master Batch Record would therefore describe the process in a series of soaks and ramps as in the example listed in Table 11.2.

Studies conducted to verify these conditions that form the PAR demonstrate the product temperatures remain below the threshold temperature and there is sufficient time in each step to take the process to completion. Conducting the Boundary Studies to establish parameters at the PAR creates a window for the process around a set of ideal CPPs. A set of parameters for a PAR for a set of target CPPs, creating the process window is illustrated in Fig. 11.1. This chart can be an effective tool in comparing the parameters achieved during product and process transfer as well as during routine commercial manufacturing.

11.3.4 Establishing Critical Quality Attributes

The goal in the vast majority of applications when lyophilization is used for preservation is the removal of water that may be involved in hydrolysis reactions leading to degradation of the active ingredient. Residual moisture is therefore a CQA as the

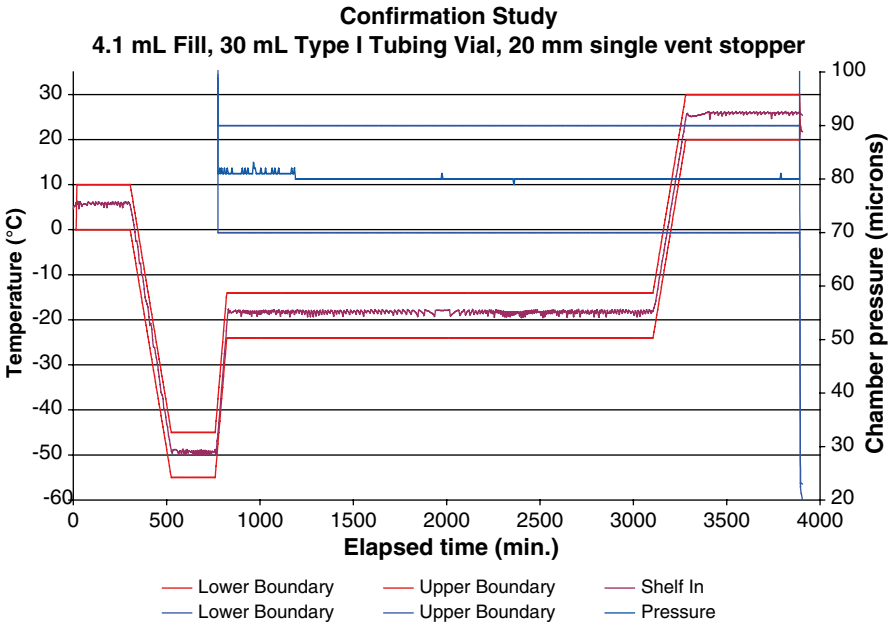

Fig. 11.1 Executed CPPs and process window of a set of conditions defined as the PAR, or boundary conditions

level of residual moisture has a direct correlation to dried state stability. Correlating the CPPs to this CQA is straightforward: drying with retention of the structure during freezing and sufficient time in secondary drying at elevated temperatures yields a product of predictable residual moisture and long-term stability. Later studies in process engineering can include preparation of multiple sublots stoppered at different times during secondary drying to correlate time, residual moisture, and long-term stability.

Complete dissolution is imperative when the product is to form a true solution suitable for parenteral administration. Establishing a specification for reconstitution time is influenced by the intended use of the product. For a product designed as a pharmacy bulk pack for reconstitution and dispensing into syringes for later direct administration addition into an IV solution at the bedside in a prophylactic course of therapy, a reasonably short reconstitution time is more a matter of convenience and is desirable, not a critical product design attribute. For a product designed for treatment in a critical course of therapy and may be on an emergency room crash cart such as tissue plasminogen activator or an operating room crash cart such as dantrolene, when complete dissolution in seconds rather than minutes is imperative, this dried product characteristic becomes a CQA.

Physical form may also be a CQA. Pharmaceutical products are more stable when crystallized during freezing. If so, then such an attribute needs to be characterized and monitored during development, through technology transfer and in routine

Fig. 11.2 A lyophilized cake having desirable level of "pharmaceutical elegance"

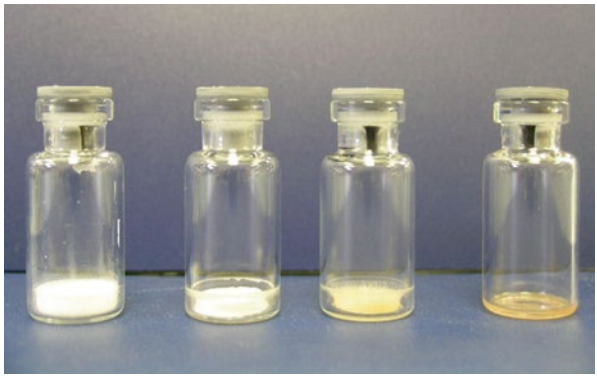

Fig. 11.3 An amorphous solid formulation exhibiting a range in the extent of collapse

manufacturing. If the formulation consists of one or more excipients that tend to and may not crystallize, being impeded because of other excipients, crystallization of these excipients should be monitored as well. For example, a formulation containing glycine, mannitol, phosphate buffer, or sodium chloride in combination with sucrose that do not readily crystallize during freezing may crystallize during storage in the dried state.

Physical appearance is a desirable attribute and not a CQA. A dense, uniform, and white lyophilized cake with the absence of cracking and an irregular cake surface reflects an attribute referred to as "pharmaceutical elegance" as depicted in the photograph of Fig. 11.2.

Such pharmaceutical elegance is strived for in product design and is a desirable finished product attribute, though not always achievable and not a CQA. A desirable physical appearance is also the structure and strength of the dried cake, when the cake structure remains intact without cracking and breaking into pieces or being friable and forming a powder. The retention of product structure established during freezing is also desirable: The presence of collapse of amorphous material, illustrated in Fig. 11.3, or melt-back of crystalline material in Fig. 11.4 is considered a product defect unless proven to have no effect on product stability or reconstitution.

Fig. 11.4 A crystalline formulation exhibiting a range in the extent of melt-back

Melt-back of a crystallized fraction or an amorphous product in the presence of ice with the product reverting to the liquid state is considered to be catastrophic. Melt-back results in a complete loss of structure to at least some portion of the cake and is associated with high residual moisture and inadequate stability, and poor dissolution with a prolonged reconstitution time. Collapse is associated with a loss of the structure achieved during freezing and may be less definitive. Some products may exhibit a slight loss of structure associated with collapse and have no distinguishable differences in their CQAs.

Focus is given to establishing a reproducible process and consistency of finished product quality; an essential aspect of achieving a high level of quality is batch uniformity. As each unit of product provided to the ultimate customer is never tested, verification of quality is based upon sampling of a batch to assess the product quality and the sample tested is expected to reflect the attributes of each unit within the batch. Sampling provides a level of confidence though is not often statistically significant. Sampling for uniformity of dosage form requires 30 units for a sample set, with ten tested and the remaining 20 sequestered for retesting. Assessment of sterility directs 20 units be tested. Residual moisture is commonly evaluated based on three samples. For assessment of each CQA, each test is grounded that each and every sample is representative of the rest of the batch.

Specific to a lyophilized product, sensitive to the time in the presence of water and, for some attributes, influenced by the presence of location in the lyophilizer, assessment of batch uniformity is of two relative perspectives. Evaluating the beginning, middle, and end of the batch is not an unfamiliar concept for assessing quality aspects of a pharmaceutical product. For a lyophilized preparation, it reflects the exposure of a reactant the leads to potential degradation. As a bulk solution the product experiences conditions of high volume and low surface area, perhaps exposed to metal surfaces of the stainless steel holding tank for the duration of the end of compounding and filtration through a sterilizing filter to the completion of the filling operation at the end of the day. Part of the batch is also exposed to glass surfaces with low volume and high surface area ratios, and is dependent on the length of the filling operation. Assessing finished product quality attributes for the beginning, middle, and end of the day encompasses the variability of conditions the product

experiences. Measure of potency and degradation products is prudent to monitor the influence of the time is within a specific environment in the presence of water.

As well, there may be an influence of location within the lyophilizer on critical quality and sometimes desirable quality attributes: residual moisture as it correlated to stability, reconstitution, and appearance. These attributes may be correlated to thermal history through the lyophilization process. Thermal history may be correlated to attributes of a lyophilized preparation and thermal history may be influenced by position within the lyophilizer. It would therefore be prudent to identify and discriminate which are indeed desirable and CQAs. Generally, each is considered desirable and may be useful attributes in assessing the influence of location within a lyophilizer. One approach is introduced as a statistically based critique comparing thermal history throughout the process to finished product attributes (Trappler 2004). The approach evaluates distribution of product temperature at the critical times during the process: the temperature profile within the batch at the completion of a stabilization period upon completing the loading operation, at the end of freezing, primary and secondary drying. These intervals are critical for the process to assure each and every vial is at the same condition prior to proceeding to the next step of the process where the processing conditions change significantly. At the completion of freezing, it is imperative that the product is adequately solidified with sufficient time at the final freezing temperature. Prior to proceeding to secondary drying, all the ice must be sublimed and the product should be within a reasonable range relative to the shelf temperature prior to progressing to warmer temperatures for secondary drying. Removal of residual moisture with the product at warmer temperatures is time and temperature dependent, and therefore should be close to the shelf temperature prior to stoppering the product. Evaluating the variation in product temperature at these critical times in the process can be achieved using a statistical analysis relative to the mean of the temperatures for the entire batch. One approach is by converting the temperature to a relative z-score and evaluating the z-score values at the critical time for each step of the process. If product at the most representative and at the most varying temperature location shows no difference in finished product attributes, then product distributes throughout the lyophilizer will also yield the same finished product properties. Correlation of thermal history to lyophilized product attributes builds a significant body of data for establishing a level of confidence in batch uniformity, independent of location within the lyophilizer.

11.3.5 Attempts in Applying the FDA PAT Initiative

Significant attention has been given to process analysis technology (PAT) since the issuance of the FDA PAT (process analytical technology) initiative. Historically, the progression of the lyophilization process was indicated by the product monitored using temperature sensors. It is well recognized that the presence of a temperature sensor influences processing: the containers with sensors are the first to freeze and the first in which sublimation of ice is complete. This makes these containers atypical of the rest of the batch, and therefore the data a relative indication.

Alternatives for monitoring the product temperature and the progression of the process have long been of interest. Various techniques in monitoring of the progress during primary drying have been investigated. A barometric method where the pressure rise in the chamber is correlated to the amount of ice remaining in the product interrupts the process by isolating the product chamber to the condenser and monitoring the increase in the chamber pressure. An alteration to the technique referred to as the manometric method, correlates the chamber pressure achieved to the product temperature. This technique, coupled with a mathematical modeling, became the basis for application to process engineering techniques in identifying the shelf temperature and chamber pressure during primary drying (Milton et al. 1997). Semiquantitative measurements for the progression of primary drying have also been of interest. Comparison of pressure measurements based on the presence of water vapor comparing the chamber pressure indicated by a thermoconductivity gauge to that of an absolute manometer has also been used to indicate the progression of ice sublimation. Measurement of the water vapor in the atmosphere using a moisture sensor was also explored (Pikal and Roy 1989). Use of mass spectroscopy in the analysis of the composition of the atmosphere during vacuum processes was first of interest in other industries (Landsberg et al. 1956). The technique was later applied to lyophilization, though there have been limited investigations. This semiquantitative method of gas and vapor analysis does, however, provide significant insight to the conditions during processing, principally during primary drying. Implementation of any of the various methods focusing on the progression of the sublimation of ice may lead to greater insight into primary drying (Nail and Johnson 1991). More recent investigations have been into monitoring the flow of water vapor from the product chamber to the condenser measuring relative velocities of nitrogen, and water vapor based on the Doppler effect using tunable diode laser absorption spectroscopy (TDLAS) has gained interest (Gieseler et al. 2007). As these process monitoring techniques have been considered for application in a PAT initiative, none of the technologies provide comprehensive process analysis and there has been no widespread use of any one method.

11.3.6 Incorporating Design Space Principles

Application of the principles of process and quality control entails defining the product quality attributes and identifying the influencing factors that affect the quality attributes. Successful execution of a process involves controlling the inputs reproducibly to yield consistent product attributes. Achieving adequate control and reproducibility requires a target and a defined range for an allowable variation for the inputs to the process. This entails consistent product components, including drug substance, added formulation components, and packaging components, as well as controlled and reproducible processing conditions. Based on this defined range, fixed target processing variables of the CPPs are required. Process design and executing adequate process control are based on allowable input variation; reproducibility of

Table 11.3 Component inputs to consider for design space

Component	Input/factor		Influence/attribute
API	Purity	Final concentration	Potency
Excipients	Assay	Final concentration	Stability
Acid/base/buffer	pH	Final concentration	Solubility/stability
Container: product	Composition	Leachable/extractable	Purity/stability
Container: process	Geometry	Construction	Heat/mass transfer
Closure: product	Composition	Permeability	Gas/moisture content
Closure: process	Geometry	Construction	CCI

the CPPs and consistency of CQAs can be achieved. This requires identifying the inputs and conducting studies to quantify the relationship of those inputs to the process output; the finished product quality. Once quantified, an allowable process input variation can be identified and a range of CPPs established. Such an approach requires greater efforts in development to generate the empirical data, leading to understanding the relationships of the multivariate inputs. During process engineering the inputs that affect the process and resulting CQAs are measured and the CPPs are adjusted accordingly. This approach can be readily implemented for processes with a single variant: It becomes more complex for multi-variant processes.

Product and process knowledge, along with predefined and controlled inputs to a process with allowable process variability around fixed CPPs that influences the CQAs establishes a PAR. Adjusted CPPs according to variation of process inputs to control the CQAs is referred to as the design space. Inputs for lyophilized preparations can be categorized as being components or process. Components include ingredients of the formulation and packaging. Processing entails preparation of the bulk solution, sterilization filtration, dispensing, as well as lyophilization. Interactions between components may be within the formulation components or between the formulation and packaging. The formulation and packaging components may influence behavior during processing, as well as stability during long-term storage. Processing factors encompass preparation of the bulk solution through the completion of lyophilization. Table 11.3 highlights some of the component inputs while Table 11.4 lists process inputs.

The influences of product and process variations need to be assessed during process engineering and development. Early during clinical development, many assumptions are often and need to be made, with potential for an interaction and impact on the final product evaluated. More knowledge and insight into the drug substance and product are gained as the product progresses through the clinical development: success and failures reveal whether the assumptions made earlier in development are correct.

Nominally, the conventional approaches to pre-formulation studies that entail measuring the pH solubility and pH stability characteristics for different acids or bases over a range of pH are necessary. Relative solubility in different solvents is also commonly studied. Consideration also needs to be given to compatibility and the risk of potential interaction of an excipient is also important to assess.

Table 11.4 Process inputs to consider for design space

Process step	Input/factor		Influence/attribute
Compounding	Assay	Purity	Purity/potency
Sterilization (filtration)	Sterility	Endotoxin	Microbiological purity
Bulk storage: chemical	Potency	Purity	Purity/potency
Bulk storage: micro	Sterility	Endotoxin	Microbiological purity
Container preparation	Cleanliness	Residuals	Purity
Closure preparation	Cleanliness	Residuals	Purity
Dispensing	Accuracy	Precision	Potency
Loading	Temperature duration	Thermal history	Purity/uniformity
Freezing	Cooling rate	Thermal history	Stability/purity
Freezing	Temperature duration	Solidification	Stability/purity
Primary drying	Pressure	Product temperature	Retention of structure
Primary drying	Temperature duration	Process rate	Dissolution/purity
Secondary drying	Pressure	Product temperature	Retention of structure
Secondary drying	Temperature duration	Process rate Residual moisture	Stability/purity
Stoppering	Pressure		CCI/dissolution

For example, the amine or carboxylic group, or the R group of an amino acid, may be reactive with part of an active compound. Effects of combinations of excipients also need to be explored as they have been shown to have an effect on physic-chemical aspects of the finished product (Byron et al. 1990; Fang et al. 2012). For solutes in solution, any interaction between the excipients and the API and the excipients with each other should be studied.

Packaging components also need to be selected to be appropriate for their effect during processing as well as post processing. For example, a stopper needs to seat properly during processing in order to provide an adequate opening for the water vapor to travel through during primary and secondary drying. Upon stoppering in the lyophilizer and throughout handling during unloading the lyophilizer, transfer to the capping operation, and until the over-seal is in place, the stopper needs to remain in its fully inserted position and not unseat itself. The geometry and construction of the plunger for a cartridge is also critical for the product and final use. The plunger needs to provide an adequate seal to separate the diluent from the dried product. As well, the geometry and construction can influence the extrusion force required for activation, reconstitution, and administration.

Preparation of the bulk solution and components going into the lyophilization process can have an influence on the product behavior during processing as well as the finished product attributes, initially and during longer-term storage. The chemical and microbiological qualities directly influence the suitability of a sterile lyophilized preparation for its intended use. Conditions during lyophilization, including the thermal history prior to and during solidification in the loading and freezing steps, achieving the required rates while retaining the original structure during primary drying, and achieving the level of residual moisture necessary for

long-term stability, all directly influence the behavior during subsequent processing and finished product attributes.

In considering the use of a design space approach to development, it is important to identify and discriminate which may be likely to vary, which are readily detected, and the magnitude of the impact on finished product quality attributes. In the case of a biological preparation where the ratio of the total protein content relative to the active protein varies, and the concentration of an excipient such as an amino acid is dependent upon the total protein, resulting in a variation in the relative molar ratios, and if that variation may be significant, then a range should be studied and established. For a product where an excipient is weighed according to specifications in the Master Batch Record, and any difference in concentration a rare event, is easily detected, and there is no need to study and establish a range.

For a formulation that does not require a buffer and the Master Batch Record that allows for a pH adjustment within a range, it would be prudent to assess the influence of the extremes in pH on physicochemical properties and behavior during processing, at a minimum the low-temperature thermal properties. Recognizing that pH units are a log function of the hydronium ion molar concentration, if the range is more than fractions of pH unit, it may be prudent to monitor the effect of the range on processing, finished product, and any effect during long-term storage.

Other factors may have less of a direct correlation. An example is the level of residual moisture, dictated by stopper drying as part of the processing method, and residual moisture levels upon storage. The long-term stability would be affected by higher residual moisture, where the moisture is desorbing directly or permeating through the stopper. Such a circumstance can also link to initial product design. Formulations with low total solids after lyophilization are more significantly impacted by small amounts of moisture that may be desorbed from the stopper over the product shelf life.

The amount of active for a lyophilized product is claimed as a quantity per vial basis and the dispensing accuracy and precision needs to be within a narrow range. For products which the fill volume is calculated based on an in-process assay, the range of dispensed solution may have a significant range that times during each step of the lyophilization process needs to accommodate the greatest dispensed volume. This unique combination of multi-variant factors is a set of conditions for which pursuing studies to establish a design space is appropriate, as the factors of dispensed volume and process parameters in this case are linked. The process needs to be engineered such that times during freezing and primary drying would be appropriate for the greatest volume that may be dispensed. For a minimum dispensed volume, the product would be expected to reach a low residual moisture content earlier in secondary drying, resulting in a potentially over-dried product. If a range of dispensed volume, or the concentration of the solutes would vary, the minimum and maximum allowable for the range needs to be taken into consideration in establishing the appropriate CPPs.

Control of the inputs into the process listed in Table 11.3 and the outcomes of the processing steps preceding lyophilization in Table 11.4 is essential to achieving the CQAs at the conclusion of the lyophilization process. Each of the lyophilization

process steps has a distinct influence on the CQAs. If the degradation kinetics are such that the product needs to be maintained at a reduced temperature when the product is a liquid; then conditions of temperature and time for loading product are critical and influence the finished product purity and potency. The resulting thermal history may also influence solidification and therefore the finished product, and as importantly, batch uniformity.

11.4 Application of Current Principles of Process Validation

11.4.1 New Essentials of Process Validation

The FDA process validation guideline "Process Validation: General Principles and Practices" issued January 24, 2011 is a paradigm shift for the industry (Food and Drug Administration 2011). In the guideline published in 1987, the perspective was to generate documented evidence that a process does what it purports to do. In the current guideline, the focus is on process and product knowledge gleamed during development, experience, and empirical data during the technology transfer when integrating the product and process into commercial manufacturing, and concurrent collection and evaluation of adequate data during routine manufacturing. The stated intent is for scientific evidence in demonstrating a reproducible process that consistently delivers product of predefined and consistent quality. The guideline goes on to define process validation in three stages: Stage 1 is process design, Stage 2 is process qualification, and Stage 3 is continuous process verification. The goal is achieving a high degree of assurance that the manufacturing process will produce finished product of known "identity, strength, quality, purity, and potency." Objective information and data from development, pilot scale, and commercial scale studies in order to establish that a commercial manufacturing would yield product of the quality attributes suitable for the products intended use. Two key considerations are apparent in the guidelines: uniformity (homogeneity) and reproducibility (consistency). Emphasis is placed on the lifecycle of the product. This lifecycle begins with development, progresses though integration into a manufacturing environment, and continually assessed throughout commercial manufacturing. The proposed approach is for decisions to be made upon perceived risk based on criticality of a quality attribute. A continual evaluation is also a key part of the proposed approach.

Monitoring and trending the equipment performance and control of the CPPs is also a key part in achieving a high level of process control. At a minimum, the shelf temperature, chamber pressure, and time parameters for the process need to be monitored and trended. Certainly trending these parameters throughout the process for each batch is crucial. There is also value in trending the level of control of these CPPs among batches over time. Other performance indicators including the condenser temperature, shelf outlet, refrigeration units, and vacuum system can also be useful to monitor and trend. Each of these monitored conditions need to be evaluated for potential use in designing an appropriate process control strategy.

As the development studies in Stage 1 are a valuable body of knowledge and become an important resource for future reference, good documentation practices are important. Documenting the objectives, rationale, and study design along with recording the experimental data, compiling the results, and justifying the conclusions provide a useful reference in transferring the product and process to a commercial manufacturing operation in Stage 2. It is also an important reference during process performance qualification and process validation, as well as continued process monitoring in Stage 3.

11.4.1.1 Stage 1: Process Design

Early development activities focus on the product design, quality attributes, and identifying requirements for manufacturing, including the parameters necessary for processing. Sound scientific methods and principles are the benchmark of development activities. The studies need to be conducted in accordance with good documentation principles, consistent with ICH Q10, Pharmaceutical Quality Systems. The guideline recognizes the value of development data as a historical reference for use in commercial manufacturing. Though a process validation guideline, product design of the intended dosage form, CQAs, and manufacturing requirements identifying the CPPs are to be considered in "Building and Capturing Process Knowledge and Understanding" (Food and Drug Administration 2011).

The intended dosage form for a lyophilized preparation, including the product design and formulation dictate the parameters for processing. A product comprised of 0.5 mL in a 3 cc vial for a product consisting of a formulation containing excipients such as sucrose and an amino acid for which the solidified composition is amorphous and has a corresponding low glass transition temperature (T_g'), parameters of a relatively low shelf temperature and chamber pressure during primary drying would be appropriate and the lyophilization process may require 2 to 3 days to complete. Conversely, a product that consists of mannitol and an API that crystallizes may exhibit a eutectic melt at a relatively high temperature. Such product characteristics may warrant a high shelf temperature and high chamber pressure, and for such a product that is a 2.1 mL fill volume in a 10 cc vial the lyophilization process may be completed overnight.

Product design entails considering the intended dosing regimen, API stabilization, and manufacturability. The dosing regimen directs route, volume, and frequency of administration, as well as formulation design. Needs of stabilizing the API include the liquid and dried state. Realizing that the majority of the product life cycle will be in manufacturing and distributing, product stability in the dried state requires and warrants the most extensive study in terms of time, effort, and attention. Development objectives are to explore and establish product design and processing parameters for routine manufacturing of cost effective commercial products having consistent high quality. Knowledge and understanding of these perspectives are key for product design in lyophilized parenteral development.

An essential aspect of product design is also the assignment of CQAs. This too is based on the intended use of the product. Quality attributes of potency and purity are imperative for any product and are established through product knowledge from clinical and chemical/biochemical studies early in development. Attributes unique to lyophilized preparations are established later in development. Critical product attributes are residual moisture and reconstitution. Residual moisture correlates to stability in the dried state during distribution and storage. Reconstitution consists of two aspects: time to achieve complete dissolution and attributes of the constituted solution.

The needs for the addition of excipients for stabilizing the API and that are suitable for the intended route of administration dictates the formulation. This stabilization encompasses the product as a bulk solution during manufacturing, the lyophilized product in the dried state during distribution and storage, and the constituted solution in preparation for administration. Pre-formulation studies to ascertain the effect of pH on the solubility and stability are critical in constructing potential formulations and should be included in the development report. Constructs of a formulation consider the API chemistry and known mechanisms and pathways in order to inhibit or minimize degradation. This knowledge and understanding is crucial for justifying the presence and concentration of an excipient used in the formulation.

A unique aspect of lyophilization is the interrelationship of the finished product attributes and the process. It is widely accepted that the CPPs are shelf temperature, chamber pressure, and time. Developing a process and identifying the specific CPPs correlates manufacturing conditions to finished product attributes, giving the highest priority to the impact of the process on the predefined CQAs. Focused process engineering assesses the impact of varying the CPPs on finished product attributes. It is also well accepted that the formulation and packaging components may influence the behavior during processing and finished product attributes. The magnitude of such variability and impact on the finished product need to be identified and quantified as part of the process engineering in order to establish the level of control necessary during routine manufacturing.

Sound scientific principles to establish a reasonable rationale along with appropriate and controlled methods in generating data that support the conclusions are imperative. This needs to be coupled with a knowledge and understanding of the capabilities in manufacturing.

In order to effectively study and identify the target and allowable ranges for CPPs when engineering a process, the laboratory and pilot plant environment needs to be representative of the commercial unit operations. Packaging and formulation components, methods and procedures, environmental conditions, and the measurement and control during the process engineering studies should emulate those in the intended commercial production operations.

Packaging and formulation components can be a significant variant with an impact on behavior during processing and finished product attributes. Vials of different types and specifications have different heat transfer capabilities that effect product temperature and processing rates. It is well understood that packaging and formulation components may vary within the allotted range of specifications within

a batch and from batch to batch. Excipients may be different in their purity levels and influence behavior during processing and dried state stability. Treatment of the components and handling the bulk solution should also emulate treatment during routine manufacturing. Care should be exercised to achieve the same level of cleanliness of the packaging components and the bulk solution, particularly with respect to particulates. Washing the packaging components, filtering the bulk solution, and processing in a controlled environment are influencing factors. Dispensing methods with desired accuracy and precision are important. Some products may be sensitive to sheer, and fill volume can influence rate-limiting factors such as dried product resistance during primary drying.

Success of process engineering the lyophilizer performance and capabilities, method of monitoring and control of the CPPs and associated process conditions, instrumentation quality and calibration, and equipment preventative maintenance, as in a manufacturing environment. Parameters that can be achieved during studies when engineering the process in a development setting and are not achievable in routine manufacturing requires further engineering studies when integrating a product and process into a commercial product production operation. Instrumentation needs to directly measure processing conditions, be sufficiently accurate and precise. It is well understood that the shelf temperature for a commercial production lyophilizer refers to the temperature of the heat transfer fluid measured by an RTD in the fluid path going to the manifold that supplies the fluid to all of the shelves. Chamber pressure is measured using an instrument that measures the pressure in the product chamber directly and is not influenced by composition of the atmosphere. The equipment needs to be able to execute the critical parameters of shelf temperature, chamber pressure, and time as parameters that are independent of any other process and product variables. The shelf temperature should be able to be controlled in an acceptable range, as shelf temperature dictates processing rates. The chamber pressure, and specifically the composition of the atmosphere within the product, needs to be within a predicted and acceptable range, as it has an influence on product temperature as well as processing rate. A laboratory and pilot unit should utilize the same type of measurements and achieve the same level of control of the CPPs in order to be comparable to a unit used for commercial scale manufacturing.

Consideration has sometimes been given to pushing the process to extremes in order to reach conditions that lead to process and product failure. There are numerous interrelationships between variables that could be used to reach the point of failure, though altering the CPPs is the most direct and controllable. Though possible to execute, the value and benefit has not warranted the widespread pursuit throughout the industry to conduct such studies. Even with well-understood influences such as the formulation and packaging components, and recognized CPPs of shelf temperature, chamber pressure, and time, the use of design of experiment (DoE) principles may be warranted where there are special relationships that need to be explored. DoE is an effective research tool to identify variables that are suspected to have an influence or assess the impact or quantifying a variable known to have an influence. With multiple known variables that may have an impact, a risk assessment can be useful for evaluating the variable's significance. Such evaluation may be an ongoing

activity during development and process engineering. For example, upon concluding the product design, defining CQAs, establishing the target CPPs, the significance of the curvature of the vial bottom radius that influences heat transfer can be evaluated using risk analysis tools in deciding if further studies, perhaps using DoE techniques, are suitable and provide significant data.

The product and process knowledge and understanding are critical for establishing the strategy for verifying process control. Risk assessment used for identifying the variables when evaluating the need and creating approaches to DoE can be an effective tool for establishing approaches to process control. Controlling variation of components that can influence behavior during processing and finished product attributes is an important aspect for achieving a high level of process control. Testing of incoming packaging components for characteristics may need to include measurements of the bottom radius of the vial that influences heat transfer. The quality and purity of formulation components and API which may influence the thermal behavior during freezing and drying are also important. Any materials that can influence the product behavior during processing and comprise the integral parts of the finished product are critical to identify and monitor, and can be useful for predicting and to correlate to processing results and finished product quality.

11.4.1.2 Stage 2: Process Qualification

Technology transfer to commercial manufacturing entails verifying that the process can be integrated into commercial scale operations. Evaluating the capabilities of the lyophilizer to execute the CPPs and achieve the performance required to control the processing conditions are a prudent first step. Data from the operational qualification of the lyophilizer for commercial scale manufacturing can be compared to the process requirements established in Stage 1. Comparison of performance capabilities to the process parameters in the example listed Table 11.2 should be conducted as the first step in qualifying the lyophilizer as being capable of executing the process conditions and adequately controlling the process.

The change control program for the lyophilizer to assess any impact of modifications to the equipment since the execution of the operational qualification should be evaluated for the impact on achieving the process control necessary for the product intended to be manufactured.

A satisfactory comparison and with the confidence that the lyophilizer will implement and control the required process parameters provides that assurance that the integration of the product and process into the commercial operation will be successful. The next step in the sequence in integrating a new product and process into a manufacturing operation to produce commercial product is to conduct process performance qualification studies. The PPQ studies verify the suitability of combined effects and abilities of the components, equipment, procedures, and operations intended for use in manufacturing commercial product. It is the final step in the development pathway of bringing a product to commercial status in a new manufacturing operation. Historically, this is the step in which three successful subsequent batches were produced, upon which the process was deemed to be validated.

Using the established CPPs and assessing the success of processing with quantifying predefined CQAs based on the data, results and conclusions from development in Stage 1, the PPQ studies can be designed. The PPQ is executed with the intent of conducting the studies following the procedures identified in the Master Batch Record, controlling the CPPs established during development, assessing the predefined CQAs, conducting the sampling and finished product testing, and meeting the acceptance criteria identified in the PPQ protocol. This study brings all the aspects, demands, and challenges of commercial product operations together to demonstrate capability of manufacturing the product with assured, consistent quality.

It is intended that process validation is not the period of discovery; results and outcome of the validation study should be known prior to conducting PPQ studies. It is therefore prudent to design a study and execute an engineering batch to confirm the anticipated equipment performance and verify the expected level of process control, as well as assess the attributes of the lyophilized material. The design of the engineering batch should follow the procedures intended to be described in the Master Batch Record, the CPPs controlled as established during development, and the relevant CQAs assessed. The sampling and finished product testing should be according to that intended during execution the PPQ study. This engineering batch may consist of actual product or may use a surrogate specifically developed to emulate the attributes of the actual product.

Designing a surrogate is based on the knowledge and understanding of the product characteristics during processing and the finished product attributes as a lyophilized preparation. Packaging components are to be the same as that for the actual product. Formulation components may be identical and substitutions made if necessary, depending upon the actual formulation for the product. Substitutions necessary for replacing the API are suitable when it has been verified that the surrogate behaves similarly as compared to the actual product during processing. Undertaking the design and development of a surrogate is similar to that of designing and developing a product. Critical characteristics and behavior during processing need to be known and understood. Dried material attributes need to be quantified in order to be useful when evaluating commercial manufacturing operations. In essence, the designed surrogate needs to be qualified as a suitable substitution for the actual product.

Critical characteristics and behavior include total weight of solute and solvent in the container, influence of the solutes on resistance to water vapor transport through the dried layer, and rates of the solvent sublimation. The total weight of the solute and solvent effect the load conditions on the lyophilizer and challenges the systems performance and capacity in implementing the CPPs and achieving the required performance. Influence of the container is on the heat transfer achieved from the shelf to the product, thereby influencing the achievable rates during freezing and sublimation. The total amount of solute and solvent creates a challenge during freezing as the heat load of the total mass, particularly when the heat of fusion is liberated during nucleation and growth of the solvent crystals. This heat load again presents a challenge while the solvent is subliming during primary drying. The effect of the solutes is on the ease of the water vapor traversing through the dried

layer to leave the product. This resistance influences the amount of total water vapor transport through the lyophilizer to be converted back to a solid on the condenser. The effect of this resistance can also be observed for its impact on the ability of the system to control the CPPs and reflected in the resulting product temperature. The overall rates of sublimation and the associated vapor transport through the lyophilizer for the solvent vapor to be condensed and collected on the condenser are reflected in the control of the CPPs and time required for the solvent to be sublimed reflected in the break of the product temperature.

It is also desirable, though not essential that the physical appearance, residual moisture, and reconstitution of the surrogate emulate those of the dried product in order to assess the effect of processing. It is important to recognize that physical appearance may well be different, simply due to the nature of the solutes used in the surrogate formulation. Acknowledging that the physical appearance is subjective, it would be useful in order to discriminate product that may have undergone collapse. Design of the surrogate should, however, possess a similar threshold temperature in order to be indicative of the possibility of melt-back or collapse during processing. This threshold temperature is established based on the T_g' of the surrogate. Though not needing to be identical, it needs to be suitable to justify the same threshold temperature and be predictive of the presence of collapse in the actual product. The residual moisture is useful in evaluating the rate of desorption achieved with the conditions for secondary drying. Though the residual moisture may be different due to the nature of the solutes, it would be useful if the desorption rates for the surrogate relative to the actual product were known in order to compare the effects during processing. Like physical appearance and residual moisture, reconstitution time is dependent on the nature of the surrogate formulation. More quantitative than physical appearance and more subjective than residual moisture, it is useful information when compared to the values established during the qualification of the surrogate.

Replicating the attributes unique to lyophilized preparations also allows for the evaluation of batch uniformity relative to the location within the lyophilizer. Based on adequate knowledge and understanding of the product and surrogate, the surrogate can be used to assess the influence of position within the lyophilizer and predict the batch uniformity relative to the unique attributes of a lyophilized product: physical appearance, residual moisture, and reconstitution. Temperature during processing may be correlated to finished product attributes at selected locations within the lyophilizer to determine the most representative and extreme locations within the lyophilizer. This may be accomplished by monitoring product temperature and sampling in proximity of the monitored material for evaluation of the dried material attributes for the corners and center of each shelf. Analysis of the temperature data at the end of each process step of loading, freezing, primary and secondary drying, and assessment of the unique attributes of a lyophilized preparation can be used to justify two locations for sampling product during the process performance qualification studies for the product.

Processing an engineering batch provides an opportunity to evaluate the performance of the equipment, control of the CPPs, and assess the attributes of the lyophilized material. Successful results during the engineering batch provide an increased level of assurance that the equipment is capable of controlling the CPPs and the product will meet the CQAs relative to the influences of the equipment and process. It also reduces the risk of loss of product when conducting the subsequent PPQ studies.

With the experience of the engineering batch, any final refinements to the procedures and process parameters for the PPQ studies using actual product can be implemented. Additional sampling would be warranted for evaluating the variation that may occur due to the processing of the actual product. This may include the locations identified as being the most representative and most extreme during the engineering study. In addition, batch uniformity and any influence of lyophilization may be assessed when comparing the bulk solution to the final lyophilized material. The potential for variation of the bulk solution and filled product over the time interval required for the filling operations may be evaluated. This sampling may entail the beginning, middle, and end of the batch. If material is sampled and tested as a solution prior to lyophilization and shown to be no different when compared to lyophilized material from the beginning, middle, and end of the batch, it is shown that there is no change during the course of filling and product difference due to lyophilization.

The more extensive sampling of the PPQ batches provides the data that supports the conclusion of assured batch uniformity. Data from the sampling liquid product at the beginning, middle, and end quantifies any change in potency and purity over the duration of the filling operation. Sampling the lyophilized material at the beginning, middle, and end of the batch quantifies any change in potency and purity, and the effect such changes may have on the behavior during processing and attributes of the lyophilized product attributes of appearance, residual moisture, and reconstitution. Sampling at the most representative and extreme locations in the lyophilizer identified during the engineering study quantifies any variation in the appearance, residual moisture, and reconstitution attributes of the lyophilized product.

Completing the PPQ studies using the sampling plan with eight sample sets of data for each quality attribute described above for three samples for each sample set provides 24 data points that can be compared for each batch. Statistical analysis of the 24 data points can be a useful tool in evaluating batch uniformity, process reproducibility, and finished product consistency. A statistically sound analysis is more easily accomplished for attributes where quantifiable values are measured, such as potency, purity, and residual moisture. Evaluation of semiquantitative and subjective attributes such as reconstitution time, completeness of dissolution, and physical appearance is less rigorous. For physical appearance, a catalog of photographs as visual evidence is very effective in recording results and supporting conclusions of the PPQ studies. Such a catalog can be created during the later stages of product and process development. The catalog of expected product appearance is also valuable for future reference during routine manufacturing.

11.4.1.3 Stage 3: Continuous Process Verification

Historically, process and product is assessed through a commercial product stability study for a single batch and during an annual product review. Assurance of product quality is also supported through the change control program. Stage 3 of the process validation guideline consists of continuous and more rigorous monitoring. Trending of process data can be an effective tool in assessing the level of control of the CPPs in routine processing. Trending may entail a comparison of the actual and or range of CPPs of shelf temperature, chamber pressure, and time for each batch. A statistical analysis may be comprised of the variation from the target setpoints of the shelf temperature, chamber pressure, and time throughout the process or the minimum, maximum, and average CPP for each part of the process or the entire process. Alternatively, analysis may be based on the trend of instances where alarm levels or action levels have been exceeded. Multiple batches may be identified and scheduled for periodic evaluation of the process data and include additional sampling. This sampling program may duplicate that used in the PPQ studies and the finished product assessed and compared to the finished product results for the PPQ studies. Data from these selected batches may also be trended. The number of batches selected for increased sampling and analysis may be based on frequency of product manufacturing and may be adjusted based on results of such sampling and the historical manufacturing experience. For any approach selected, development and assessment of the trending program warrants an interdisciplinary team consisting of representatives from development, manufacturing, quality, and a statistician.

11.5 Current Challenges in Development of Lyophilized Products

Opportunities for providing lyophilized preparations have created new challenges in product development and commercial product manufacturing. Investigations into use of cosolvent and aqueous/organic solvent systems have led to reconsideration of compounds that have limited solubility. Following the trend for liquid, ready-to-use preparations in product presentations not limited to an ampule or vial, lyophilized products are available in more diverse delivery presentations, including cartridges and syringes. In addition, there has been more attention to expanded capabilities and gaining efficiencies in commercial manufacturing.

11.5.1 Poorly Soluble Drug Substances

The classical approach to converting a poorly soluble chemical entity to a more soluble form is to create a salt form of the compound: Converting a free acid or base to a salt improves the solubility. The salt form also impacts stability of the compound.

Lyophilized preparations being administered by injection, bioavailability of various salt forms is less of a concern compared to other dosage forms. Other techniques for designing an injectable have included the use of a cosolvent, encapsulating the active in a liposome, and creating a conjugated form.

Cosolvents can be categorized into two main types: solvents and those that will vaporize and be removed with the water during the process and those that will remain as part of the formulation to also solubilize the API upon reconstitution. Those utilized to increase API concentration and are removed during lyophilization are the organic solvents ethanol, methanol, and tertiary butyl alcohol. Solubility in the various molar ratios of the organic and aqueous solvents warrants a specific preformulation study, as the solubility may be different than in each solvent alone. Testing as part of product batch release and specifications for a residual organic solvent are warranted.

In combination with water, ethanol and methanol remain as a liquid through the freezing step and vaporize directly from the liquid state at high rates during primary drying. Use of any organic solvent should be kept to a minimum, as they create challenges during processing because of the high rate of vaporization from the liquid state. The design of lyophilizers is based on requirements for processing purely aqueous-based formulations and not well suited to accommodate high levels of such organic solvents.

Tertiary butyl alcohol has received growing interest as it solidifies during freezing when in combination with water. Although solid at room temperature, the solidification for aqueous compositions occurs at temperatures commonly used for lyophilization. The unique characteristic of forming multiple eutectic solutions and the behavior during processing has been studied and reported in the literature (DeLuca and Kasrain 1995). There have also been circumstances where product has been lyophilized directly from tertiary butyl alcohol alone, as in the case of alprostadil for injection (prostaglandin E1) by Pfizer.

Agents used to solubilize the API and the final drug product has been used since the early 1970s. Amphotericin B was combined with desoxycholic acid to yield the desoxycholate form and a colloidal dispersion, initially developed by Squibb Institute of Medical Research. Amphotericin B for injection has also been prepared as a liposome and lipid dispersion. Though lyophilized lipid preparations are rare, liposomes encapsulating lipophilic compounds have provided an alternative for drug entities having poor solubility in water and mixed organic solvents. Lupron Depot® is formulated as a dispersion consisting of the leuprolide acetate salt as lyophilized microspheres to form a suspension upon reconstitution, having the benefit of sustained release of the active.

Conjugating a drug entity has been pursued where an active is combined with a polymer or protein for improving the solubility. PEG has proven to be an effective agent. Covalently connecting an API to PEG is known as PEGylation. PEGylation combines PEG to a small molecule, peptide, protein, antibody, or oligonucleotide with the use of a linker. The new entity exhibits different characteristics, including solubility of the active. Vaccines such as hemophilus b protein conjugate have been shown to be effective.

11.5.2 Delivery Systems for Parenteral Products

Classic product design approaches have been to package a lyophilized product in a vial. This approach continues for market entry of a new entity, partly because commercial manufacturing operations are geared towards a vial packaging system. Innovations in delivery systems include dual chamber syringes. As home health care becomes more common, there will be a growing need for self-administration of lyophilized products. Opportunities for errors associated with the multiple steps required for reconstitution is a driving factor for development of new delivery systems. Auto-injectors using a syringe are currently available for liquid, ready-to-use preparations such as Humira, a leading treatment for rheumatoid arthritis (RA) with nearly 1.5 million prescriptions across all its indications, and predominantly a self-administered therapy. Such systems for lyophilized preparations would improve the safety and aid in patient compliance. Implantable devices where the active ingredient is embedded in a polymer, allowing sustained release would also provide benefits for therapy regimens in the treatment of chronic conditions.

11.5.3 Improving Manufacturing Capabilities

Increased volume of lyophilized preparations requiring leading to larger batch sizes has also resulted in reducing unit costs. A larger batch size requires higher speed filling lines and larger lyophilizers. Typical commercial manufacturing lyophilizers are 450–570 ft^2 (42–53 m^2) of usable shelf surface area, processing up to 200,000 of 3cc vials. High speed filling systems and automated material handling for loading and unloading the lyophilizer have also provided increased efficiencies and the potential for greater yield. Reduced unit costs are realized through greater utilization of personnel, facilities, and capital equipment. The number of samples and overall batch release testing costs are also lower, decreasing the costs on a per vial basis for each batch.

There have also been improvements in the understanding of lyophilization science and technology. This leads to more safe, effective, and robust processes used in manufacturing. There is no doubt that the time required to complete the lyophilization process is important, influencing the number of batches necessary to meet market demand. It is also important to acknowledge that there is less likelihood of a batch failure with a robust process. There is a balance between the processing time conducive to high throughput in a manufacturing operation and a robust process making a product less susceptible to slight variations in processing conditions and providing greater assurance that all batches produced can be released. A batch failure has an impact on throughput of an operation as well as the direct and indirect costs. These costs are attributed to material consumed to manufacturing the batch, lost revenue from the sale of the batch, and the costs of conducting an investigation into the failure.

11.5.4 Reducing Unit Costs of Products for World Distribution

Realizing impact on reduced unit costs from increased manufacturing capacities contributes to greater global accessibility to lyophilized pharmaceuticals. As well, focusing on the actual cost to deliver a product to the patient is also imperative. Certainly, reducing the costs to manufacture a lyophilization preparation, such as increased batch sizes and more robust processes is beneficial. Reducing the cost of the lyophilized preparation alone will be insufficient. The cost to deliver a product to a patient also includes the cost of the diluent, syringe, needles, and alcohol wipes. In addition, there is also the cost of the clinician in assembling the product, diluent, and components; completing the reconstitution and administering the product to the patient. In markets where labor is not a significant factor, there may be a nominal cost for the preparation and administration, though there are still the material costs. Cost of product and administration needs to be compared to the cost of a delivery system with all the materials combined, minimizing the need for all the individual components and product preparation for administration.

Achieving reduced costs, greater safety, and improved patient compliance requires innovation in packaging systems paralleling the innovations made in auto-injectors for liquid injectables. These systems will have an influence on packaging design and the formulation. These will all drive the needs for manufacturing of lyophilized preparations. Vials and special stoppers, now conventional packaging systems for lyophilized preparations will someday be replaced by improved packaging having reduced component and manufacturing costs along with benefits of improved patient safety and compliance.

11.6 Summary

The initial interest in lyophilization was as a method of preserving products known to be unstable upon storage as a liquid ready-to-use presentation. This technology, not well understood and cumbersome in integrating into a commercial manufacturing operation, was initially used in a hospital setting and then expanded into larger scale commercial manufacturing for a limited number of products, principally antibiotics, blood products, and vaccines. With an increased number of products and the development of biopharmaceuticals that require preservation for suitable long-term storage, the utilization of lyophilization in manufacturing has grown. Greater knowledge and understanding of lyophilization science and technology has paralleled the growth in its application. Current interests are in commercializing cost effective and user friendly product presentations, efficient and robust processes, and greater level of control. All of these are driven by the continued expansion in the application of the science and technology to meet the needs of future generations of new products.

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