Coming in from the cold

Zak Yusoff, pharmaceutical freeze-drying applications manager at SP Scientific discusses why a quality by design (QbD) approach is key to achieving optimal lyophilisation of limited and expensive biopharmaceutical drugs.

Historically, scale-up has been accomplished largely empirically, relying on multiple runs and prior experience. Although this approach can result in quicker regulatory approval, it also increases the risk of vial rejection within and between batches leading to increased costs. Difficulties also arise when scaling up the development and manufacturing process. As the demand for better yields and higher quality of biopharmaceuticals intensifies, optimising the lyophilisation process throughout the product's life cycle plays an important role in providing a quality, successful biological product.

The US Food and Drugs Administration (FDA) strongly recommends a QbD approach to drug manufacturing, suggesting quality should not be inspected solely at the end of production but must be designed into the entire manufacturing process. Although implementation of this idea may appear a daunting task, and futile at the earlier stages of product development, controlled lyophilisation in the laboratory that can be transferred to full commercialisation will avoid the need for repeated optimisation of the lyophilisation conditions at each stage. As part of a QbD approach, Process Analytical Technology (PAT) tools can be used to improve the freeze-drying process by defining critical parameters and a range within which an acceptable product is obtained.

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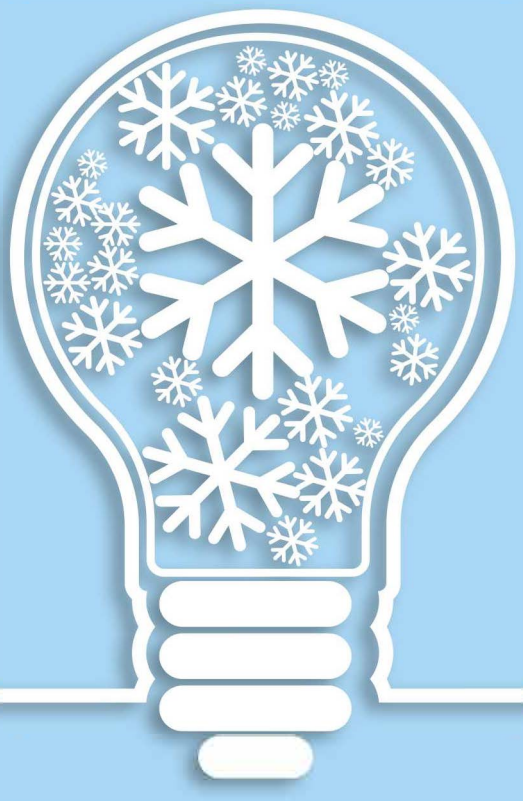

CONSIDERING CRITICAL PARAMETERS OF LYOPHILISATION WHEN SCALING UP

Even after the product formulation has been optimised, using different freeze dryers for each stage of the lyophilisation process can alter the freezing behavior of a product.

One of the biggest freeze-drying scale-up challenges is changes in the degree of supercooling before freezing. The lower the temperature at which the product nucleates (freezes), the higher the rate of supercooling, leading to increased cake resistance and smaller ice crystals. This can result in performance differences and, in many cases, increased drying times.

Another parameter that can differ between lab and commercial scale dryers is the heat transfer coefficient from the heating surfaces to the product creating batch heterogeneity. For the most efficient processing, it is desirable to operate at the highest possible shelf temperature and at a chamber pressure that still maintains the target product temperature during primary drying. Variations in resistance to mass flow during primary drying can occur between lyophilisers due to differences in nucleation temperature and equipment design. Therefore, it is important to optimise the mass flow rates in early primary drying to maintain the heat removal capacity of the condenser.

STRATEGIES FOR OPTIMAL SCALING UP OF FREEZE-DRYING PROCESS

There are several strategies that have been employed to overcome these challenges. The simplest relies on using historical experience of a particular freeze dryer as a product is scaled up. It is also possible to scale down processes to use smaller amounts of initial product. This is especially relevant with biopharmaceuticals that are usually available in limited quantities. A more labour-intensive option is to characterise the lyophiliser for minimum controllable pressure, max sublimation rate and heat transfer coefficient (Kv) measurement.

ACCELERATING SCALE-UP WITH COMPATIBLE EQUIPMENT AND TECHNOLOGIES

Combining many of these scale-up options into a range of equipment that can be used for freeze-drying products from early stages of development to full commercialisation could enable transfer of conditions more easily. SP Scientific's Line of Sight approach consists of a suite of tools (technologies and equipment) that can be employed at each stage of development and production. The Line of Sight strategy has been to use QbD approaches and equipment design to create an expanded design space for products as early as the formulation and cycle development stages enabling better transfer across equipment when scaling-up. Currently, if the raw materials for the lyophilised product are scarce or very expensive, fractional load experiments can be performed using only part of the freeze dryer shelf area: an inefficient utilisation of resources. The introduction of a new generation of small capacity freeze dryer, such as the seven vial LyoCapsule freeze dryer, can overcome these limitations and enable multiple optimisation conditions to be tested on a small number of samples.

Transfer of lyophilisation conditions between freeze dryers is efficient by applying the same methodologies throughout the process. New generation technologies, such as ControLyo technology to control nucleation, SMART-MTM to calculate freeze-dried cake resistance and product temperature, Tempris wireless sensors to measure product temperature, or Tunable Diode Laser Absorption Spectroscopy (LyoFlux TDLAS) to measure water vapour concentration and flow velocity, are enabling organisations to freeze-dry a specific product providing consistent product quality.

CONCLUSION

A QbD approach provides optimal process conditions through greater knowledge of the entire process which enables the development of a design space for the process and product. Once this design space is determined the product should be acceptable within this range under the FDA's QbD definition.

If we view the product and process development for freeze-dried parenterals as an integrated process, rather than as a collection of independent activities, then it makes sense to follow a QbD method even at the early stages of formulation development.