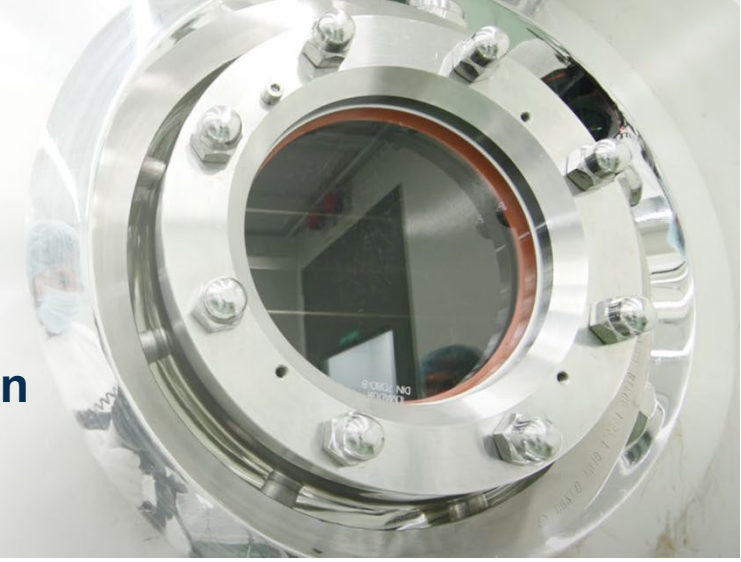

How a CDMO Achieves Finished Product Lyophilization with Limited & Expensive API

By Bryan Braxton, Senior Director, Aseptic R&D

Stability is an inherent challenge in the early stages of development for both solid and liquid pharmaceutical ingredients. Lyophilization may the answer needed to complete formulation development and advance your candidate to Phase I clinical trials.

Lyophilization, or freeze drying, is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes: freezing, primary drying (sublimation), and secondary drying (desorption). Products are manufactured in the lyophilized form due to their instability when in solution and the impact of a solution on the container closure system.[1]

But lyophilization can be challenging, expensive, and time-consuming. Agile, cost-effective lyophilization services can accelerate the development of complex drug candidates that present stability challenges. Partnering with an agile CDMO that recognizes these obstacles, and can still formulate a finished product with limited and expensive active supply, is critical.

Lyophilization Development Starts in the Lab

A CDMO should offer lyophilization services at early-stage product and cycle development and then be able to scale up to GMP. Successful development of lyophilization cycles in the R&D laboratory will de-risk the scale-up for GMP/clinical production, thus reducing cost and shortening timelines.

Product and cycle development depend on scientists who are skilled at producing data quickly and proficiently. Formulation development and lyo cycle development are interdependent. The formulation stage is when bulking agents and salts will be chosen to ensure a stable, freeze-dried product. Lyo development involves creating appropriate processing parameters that produce an acceptable and stable cake for the finished product.

At the start of the lyo process, products must be formulated in such a way that they can be suitable for freeze drying. During the development of a lyophilization cycle, or when optimizing a

known lyophilization cycle, understanding thermal and physical characteristics is essential, as no two products are alike. Scientists will study the thermal characteristics of the product and processes, with a particular focus on critical process parameters, such as freezing point and eutectic temperatures. This will bridge the product's physical properties through the use of Differential Scanning Calorimetry (DSC) and Scanning Electron Microscopy (SEM). Chemical and related stability characteristics should also be evaluated, focusing on reconstitution time, moisture content, assay, degradation products or impurities, as well as other critical quality attributes.

Note that changes to Critical Quality Attributes (CQAs) during the scaling process from lab bench to small batches in a GMP facility is not a one-size-fits-all approach. Some R&D teams may default to the traditional one-factor-at-a-time (OFAT) approach. This can be an effective method to reduce the multitude of potential critical parameters, but this method is not ideal in cases of limited API. Instead, Design of Experiment (DoE) should be considered to understand the key parameters and the relationships with CQAs. These experiments should start by investigating what others have documented in the pharmaceutical literature for similar dosage forms as well as leverage learnings across the technical teams at your facility. DoEs should be performed on equipment that supports scaling, including efforts to understand the equipment engineering and design constraints. Also, an understanding of the potential interactions of the formulation with the container closure system and processing components required for manufacture is essential before risking the use of large amounts of API.

Lyophilization Cycle Development & Optimization

Developing a finished product that meets target specifications suitable for dosing is critical. With limited and expensive API, a CDMO can only perform so many runs in a lyophilizer – and obtain as much information as possible from each of those runs. The heat mass transfer relationships from each run in the R&D lab lyophilizer are key for developing a cycle that will work in the finished product.

Lyophilization cycle development should begin with understanding the formulation component chemistry, including the basics associated with how the dosage form will be used to serve patients: the route of administration, required stability of the compound, and expected dose (if known). The route of administration is important to understand as it impacts the choice of excipients and the conditions needed to stabilize the dosage form.

It is important to note here that lyophilization is not an independent activity. The process of development is a collaboration between CDMO scientist and the sponsor. The drug sponsor should provide the CDMO with as much information as possible to ensure a more successful formulation and API stability as well as to de risk scale-up.

Once the basics are understood about how the product will be used, the CDMO will work to understand the options that exists for formulating a successful dosage form. This is done by understanding the solution-phase chemistry, including concentrations and degradation. Critical

temperatures (Tg) will be measured using differential scanning calorimetry (DSC), which provides valuable information when designing a lyophilization cycle. Once a cycle is developed, the CDMO should evaluate reconstitution time and other CQAs.

Ultimately, the R&D lyophilizer provides key features for optimizing, developing, and scaling a lyophilization cycle:

- End of Primary Drying (EOPD) – Utilizing convergence of Pirani gauge and capacitance monometer to control primary drying time;
- AutoDry Function – Utilizing critical product parameters (configuration, formulation, thermal conductivity, etc.) to execute a lyophilization cycle;
- Total Measured Heat from Shelf – Determine the enthalpy proportion of various sources of heat transfer to further optimize lyophilization performance; and
- Sample Thief – Optimize secondary drying by removing samples during operation for moisture analysis.

Ultimately, the R&D lyo equipment can de-risk the product development process by conducting experiments at an R&D scale. For example, a lyophilizer that supports small quantities of vials in development enables minimum amounts of costly API to be used during R&D as a cost-effective risk mitigation step.

Agile Scale Up

During cGMP scale-up, the parameters established during development are verified. Many factors influence this process of lyophilization, including formulation, vacuum profile, and product temperature during drying. In some cases, it is possible to scale up from a laboratory-sized lyophilizer to small production equipment in a single stage. Scale-up processes often occur in two stages: laboratory to pilot production and then pilot production to full commercial volumes.[2] The pilot stage is required to produce sufficient product under relevant GMP conditions for clinical validation.

A skilled and experienced CDMO will use the same lyophilization technology and equipment in the lab that translates directly to the production lyophilizer to create critical and scalable synergies for scale-up and transfer activities. This capability permits minimum amounts of costly API during R&D as a cost-effective risk mitigation step, and also establishes the conditions for agile scaling for larger development and commercial batches.

This establishes the conditions for de-risking as product is scaled for both clinical and commercial production. A systematic and scalable process from concept to clinic to commercialization saves API, decreases costs, and shortens timelines.

References

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2. Scale-up of industrial microbial processes, Jason S Crater and Jefferson C Lievense , FEMS Microbial Lett. 2018 Jul; 365(13): fny138, National Institutes of Health.

About Pii

Pharmaceutics International, Inc. (Pii) is a US-based contract development and manufacturing organization (CDMO) located in Hunt Valley, Maryland. The experienced scientists, engineers, and staff at Pii pride themselves on adroitly employing a phase appropriate method of drug development for the prudent use of their client's resources as they solve challenging problems. In addition to offering end-to-end development services, Pii manufactures a variety of dosage forms to include complex parenteral drugs and has a wealth of analytical testing capabilities. Its Hunt Valley campus has four aseptic suites with lyophilization capabilities. Our talented professionals stand ready to help!

About the Author

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Bryan Braxton joined Pii in October 2018 as Senior Director of Aseptic R&D. Bryan has 30+ years of experience in the pharmaceutical industry.

Bryan held roles of increasing responsibility in sterile products at both Unither, AMRI, Pfizer, Abbott, and Glaxo, in the areas of Formulation Development, Process Transfer, Quality by Design, Technical Services, Contract Services, and Project Management.

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