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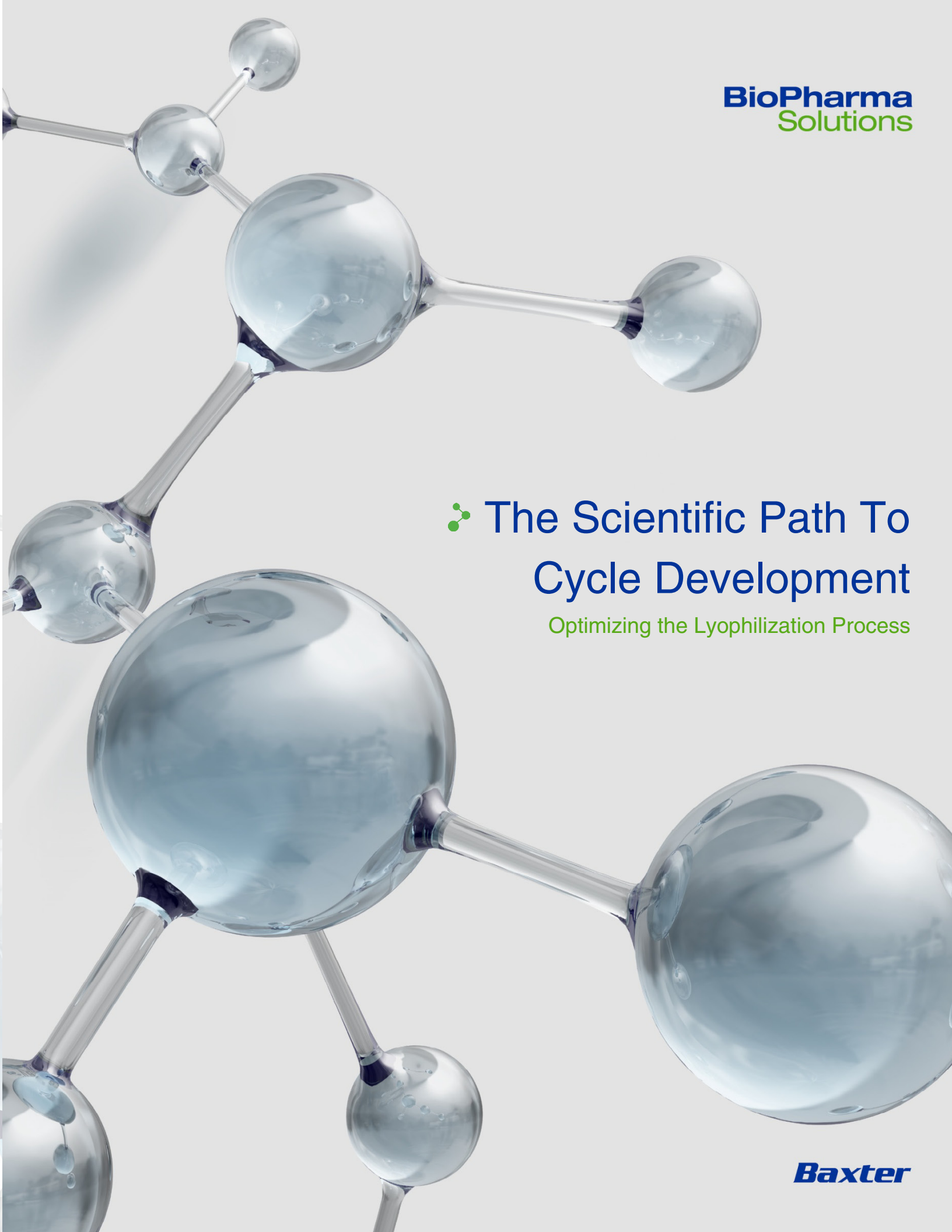

The Scientific Path To Cycle Development

Optimizing the Lyophilization Process

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The Scientific Path to Cycle Development

Management of medication delivery through lyophilization - freeze-drying - is a crucial enabling process technology for many important parenteral drugs. Close to 50% of biopharmaceuticals, including enzymes, proteins and monoclonal antibodies, must be lyophilized as these therapeutic agents are insufficiently stable for ready-to-use solution dosage forms. A small but growing number of small-molecule drugs are also prepared in this manner. It is a safe bet that without lyophilization, the majority of these products would not be available.

In solution, many drug substances are susceptible to even modest changes in temperature and chemical environment. These complex molecules undergo hydrolytic, oxidative, and aggregation reactions, compromising both potency and safety. Consequently, parenterals must often be distributed "cold-chained" - refrigerated or maintained frozen from manufacturing line to patient. Even then, freezing and/or thawing may cause some proteins to aggregate. Lyophilization overcomes poor stability by rendering labile drugs and proteins in a solid form more tolerant of long-term product storage.

Science-Based Vs. Trial and Error

Lyophilization requires extensive experimentation during its development phase. Knowing what has worked in the past on similar molecules or formulations can greatly reduce the trial-and-error aspect of developing a robust freeze-drying product and process. However, best practices in product and process development require statistically-valid experimental design approaches to select optimal formulations, packaging systems, and resultant lyophilization cycles.

Many lyophilization processes employ cycles that are not optimal; that is, the cycle is either too aggressive (temperatures are too high or cycle times too short) or too conservative (cycle times are too long). Typically, cycles are too long because research and development efforts did not take the time to optimize the formulation and fine-tune the cycle. Without the data, conservative cycles that are used are usually "safe" (the product meets quality parameters), but the same quality product could be produced with much shorter cycles if appropriate studies are performed.

Instead, a scientific approach utilizes advanced analytical and experimentation methods to arrive at the optimal temperatures and pressures during lyophilization that are dependent on the properties of the API and its formulation. Part of that learning curve involves thermal analysis, X-ray powder diffraction, and freeze-dry microscopy to determine the solid physical state and critical temperature properties of the product in the final formulation.

How Dry is Dry Enough?

In general, for small organic molecules, the drier, the better. While complete dryness is unattainable, typically, a goal of less than two percent residual moisture in the final lyophilized product is obtained. For large biopharmaceutical molecules, it is possible to over-dry. Even in the lyophilized state, proteins depend on small quantities of water to help maintain higher-order structure, so some biopharmaceutical lyophilized products may have a range of residual moisture in the final product, e.g. 0.5 percent to 2.5 percent.

When determining a dryness endpoint, the potential for moisture desorption from the rubber closure must be recognized. Rubber closures are steam sterilized, and the closure will absorb a certain amount of moisture that potentially can desorb into the product and cause an increase in powder residual moisture over time. Water desorption can be minimized by thoroughly drying stoppers and by using stopper materials that do not readily absorb water.

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Avoiding Potential Roadblocks During Lyophilization

Power outage or equipment failure problems are always a possibility. However, many problems occur because of poorly designed formulations and cycles. Robust formulations can be designed to withstand modest ranges in product temperatures or pressure. Even the most sensitive products can withstand slight variances, which inevitably occur when using large, complex equipment. By designing the formulation and freeze-dry cycle properly up front, excellent results are obtained despite minor process parameter excursions.

What must be kept under strict control are the endpoints of the three lyophilization stages - freezing, primary drying (removing solvent) and secondary drying (removing solute water to an acceptable level) - all of which determine the quality and stability of the final product. Product quality and stability for lyophilized products may be more easily seen or predicted, because excess residual moisture content normally results in inelegant or defective-looking finished product cakes.

Too much water can result in product defects known as collapse, partial collapse, meltback, or other physical phenomena that can result in chemical instability. Another defect includes product layering. This is when various parts of the lyophilized cake look different because the freezing stage was improperly designed, resulting in variations in ice crystal size. Similarly, formulation or process deficiencies include top layer crusting (a crumbly coating in the top cake layer) or splotches on the side of the vial and underneath the rubber closure.

Ironically, freezing and/or drying stages used in lyophilization processing may themselves cause stability issues with some biopharmaceutical products. These problems can be overcome with appropriate use of formulation stabilizers and appropriate design of cycle parameters. This includes altering temperature, pressure, and rates of freezing and drying.

Conclusion

Optimizing formulations, as well as cycle parameters, can minimize the effects of freezing and drying conditions on sensitive biopharmaceutical molecules. Lyophilization process validation not only includes assurance of meeting all physical and chemical requirements of the lyophilized dosage form, but also includes the maintenance of sterility in

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transferring product and during the freeze-drying cycle itself.

Using science-based approaches versus trial and error can, in effect, help you navigate potential roadblocks on your molecule's pathway to commercialization.

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