

plays an important role in the primary drying time due in large part to the difference in the fraction of edge vials as load changes. The vapor tube dimension is also an important factor to be considered in terms of the potential for choked flow leading to loss of pressure control at high sublimation rate.

QbD application in lyophilization development is becoming popular due to the potential flexibility in regulatory filing. A key feature of this approach is that it combines prior knowledge, a formal risk assessment process, and well-designed experiments. Prior knowledge can come from published literature, preliminary experiments, and past experience. The well-established theory in lyophilization makes cycle development much more efficient. Mathematical modeling of the primary drying step is extremely critical in the QbD paradigm. Blind usage of factorial DoEs in freeze-drying development should be avoided, as long as the modeling produces accurate prediction of product temperature profiles as a function of cycle conditions, a condition normally met and easily proven with a few key experiments. Establishment of a design space for primary drying is straightforward when applying this modeling strategy, where simulations of various shelf temperature and chamber pressure conditions may be conducted using a simple excel-based computer program. As demonstrated in the case study, some experiments are needed to evaluate K_v and R_p and to verify accuracy of the simulation results. For cases where the model gives a narrow range based on the collapse temperature, a scale-down model approach may be needed to expand the primary drying design space, and further establish the robustness of other process parameters such as secondary drying, freezing rate, etc. In addition, the combination of mathematical simulation and this scale-down model can be used to facilitate the continuous lyo process validation, and also support investigations to understand if a change in material (e.g., drug substance source, container, etc.) or lyo-process will have any product impact.

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