

Summary - Cycle Validation for Freeze Drying

There are three elements to achieving successful validation of a freeze drying cycle:

1. A well defined and understood formulation,
2. A qualified freeze dryer and a freeze drying cycle that provides the link between a specific formulation and
3. A specific freeze dryer.

The design of the formulation is based on the characteristics of the molecule to be freeze dried. Stabilizing agents are chosen and tested. The collapse temperature, or eutectic temperature, is identified and experiments are designed to determine a robust combination of the solution composition and the primary drying temperature. At this stage, the primary packaging (for example, vials, stoppers) are also defined.

A typical freeze drying process consists of the following stages:

- Filling
- Loading into freeze dryer chamber
- Freezing
- Secondary drying - at reduced pressure the shelves are heated to a specified temperature to remove bound water

A freeze dryer is mainly composed of two chambers, the chamber where the product is freeze-dried and the condenser that stores removed water.

- Shelf temperature monitoring and control
- Chamber pressure monitoring and control

The appearance of the freeze-dried cake or plug, is a key indicator of whether the freeze dry process has been successful.

It is recommended that each specific product and specific freeze dryer combination is considered separately.

- Equilibrium product temperature during primary drying
- Chamber dimensions, capacity
- Load configuration

Transferring a product to a new freeze dryer should include an evaluation of whether the existing cycle parameters are appropriate for the new combination. A science and risk-based approach may be taken to determine whether any trial batches are required or whether there is sufficient confidence in the applicability of the original cycle parameters that cycle validation may be initiated without trials. Cycle validation requirements for the transfer of an existing commercial cycle, including the number of runs needed, should be based on science and risk. Considerations should include the magnitude of the change, the process history, the robustness of the cycle and the complexity of the formula/container.

Batch sizes for freeze-dried products are generally defined by the capacity of the freeze-dryer. Cycle times are typically long and therefore the processing of partial loads is inefficient and unusual.

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