

## Cycle Validation for Freeze Drying

### **Regulatory Basis:**

FDA Quality Systems Regulations

Reference: FDA CFR - Code of Federal Regulations Title 21

### **General Discussion:**

This document provides document on cycle validation for freeze drying, also called lyophilization. The information contained in this document is supplemental to Document 108 “Lyophilization”.

This document is applicable for sterile drug product; however, the general principles described would be equally applicable to freeze drying of non-sterile drug product or bulk API.

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.

It is recommended that cycle validation studies shall include a minimum of 3 consecutive, successful lyophilization runs on the worst case load configuration.

This document provides an overview of freeze drying and considerations for establishing the cycle validation strategy for the lyophilization cycle developed for a given product. Cycle validation may also be described as product Performance Qualification for a lyophilization cycle.

### **Recommendations and Rationale**

Freeze drying is commonly used to improve the stability of thermally labile molecules. Some active ingredients or drug substances are only stable for a few weeks in liquid formulation but can be stored for years when freeze-dried with the appropriate excipients. Examples of such molecules include peptides, polysaccharides, proteins or even live viruses.

### ***Freeze drying process***

A typical freeze drying process consists of the following stages:

- Filling
- The solution is aseptically filled into loosely stoppered vials
- Loading into freeze dryer chamber
- Freezing
- Shelf temperature is reduced at a defined rate and kept for a defined time in order bring the formulation in the solid state
- Primary drying - the chamber pressure is reduced and the shelf temperature is ramped to one or more predefined settings, to allow removal of water vapour by sublimation. At this stage all free water is removed.
- Secondary drying - at reduced pressure the shelves are heated to a specified temperature to remove bound water
- Stoppering – the chamber may be filled with an inert gas (if required for product stability) and then vials are fully stoppered by moving the shelves up or down to push the stoppers into the vials
- Unloading and capping

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measured to determine the areas in the dryer where sublimation is occurring fastest and slowest (usually edges and centers of shelves, respectively).

### ***Partial Loads***

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. It is recommended that a risk-based evaluation of the impact of running a partial load is included in the protocol. In the majority of cases a full load will be the worst case – that is, the water load is heaviest.

The evaluation should include whether the cycle parameters used for the full-load can be applied to the partial load without significant impact on the product.

However, in the event that partial loads are foreseen and the load is evaluated as “worst case”, the load must be defined and validated.

### ***Assessment of Normal Operating Ranges***

It is recommended that the cycle validation runs be performed at the target control values. However, an approach that can be considered is to perform the cycle validation runs across the allowable range for temperature and pressure, as defined in the regulatory filing. The cycle validation would then include one run each of low temperature/low pressure, high temperature/high pressure, and the target temperature and pressure for the primary drying phase. If this approach is taken it is recommended that the secondary drying phase is performed at the target values for temperature and pressure, as it is the primary drying process that is most sensitive to variation in cycle parameters.

If the allowable ranges for pressure and/or temperature are comparable to the known performance capability of the freeze dryer, only the target values should be used during cycle validation. It is recommended that assessment of more than one lot of API is included in the cycle validation, where practical.