Title: Cycle Validation for Freeze Drying					
Guidance Number: 054					
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Checked by:		Date:		Date Issued:	
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Introduction:
This document provides guidance on cycle validation for freeze drying, also called lyophilization. The information contained in this document is supplemental to Guidance 108 ñLyophilizationò.

This guidance 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 guidance 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

Cycle validation

Due to the sensitivity of the process to variations, scale-up of the lyophilization cycle can be very difficult. Products that have multiple strengths, vial sizes and different batch sizes will often have different cycles for each combination.

It is recommended that each specific product and specific freeze dryer combination is considered separately. Bracketing of equipment can be considered where equivalence of the equipment has been demonstrated, for example, during equipment qualification. However, due to the sensitivity and criticality of the process, the bracketing strategy for multiple, identical freeze dryers should consider evaluation of the cycle in each dryer (for example, placebo runs, engineering or demonstration lots).

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.

Differences when transferring a product between freeze dryers that may be expected to have an impact on the process include:

- Å Equilibrium product temperature during primary drying
- Å Chamber dimensions, capacity
- Å Differences or limitations in pressure control, e.g. Pirani (thermal-conductivity gauge) vs. MKS gauge (capacitance manometer)
- Å Limitations in temperature control (setpoints, achievable ramp rates)
- Å Shelf configuration and/or tray type (materials, dimensions)
- Å Condenser efficiency/capacity
- Å Batch size
- Å Load configuration

Lyophilization cycles need to be validated. Typically, this will consist of at least 3 runs using the worst case load. Key acceptance criteria include:

- Moisture content,
- Cake appearance, and
- Reconstitution properties.

Validation of the cycle should also include the establishment of validated loading patterns. It is recommended that the load configurations are described and diagrammed and include the following:

- Description of container design, shape, size, and fill volume for drug products;
- Description of the loading configuration within the chamber; and
- Identification of the number and placement of temperature probes, if used, in drug product containers and throughout the load for APIs.

Identification of ñworst caseò locations in the load Temperature mapping of the empty chamber (across and between shelves) is performed during qualification for the freeze dryer.

During cycle validation, temperature probes should ideally be placed at the ñworst caseò locations (coolest and warmest) in the load based on the empty chamber data. The location of the probes should

