

## Guidance 108 Lyophilization

- Sealing of product containers under vacuum or with an inert gas overlay;
  - Effect of partial meltback on product performance and stability;
  - Container/closure compatibility;
  - Acceptable residual moisture level in finished product;
  - Range of critical parameters;
  - Appearance of the cake; and
  - Reconstitution properties.
3. Commissioning and Qualification of Lyophilizers should include the following:
- Vacuum leak rate, maximum vacuum level, chamber pressure control, and condenser capacity are verified;
  - A minimum of three temperature distribution studies on an empty chamber are conducted to confirm shelf temperature control and uniformity at three temperature ranges representing the three phases of the lyophilization cycle (i.e., freezing, primary drying, and secondary drying);
  - At least one product study is conducted using simulated or actual product; and
  - Media Fills are performed.
4. Microbial Retentive Filters should be integrity tested before and after use.
5. Shelf Temperature Control and Uniformity Studies should be conducted simultaneously. Documentation should include:
- Temperature uniformity of each shelf, including corners, center, and heat transfer fluid inlet and outlet pathways;
  - Placement of temperature probes;
  - Maximum and minimum cooling and heating rates;
  - Thermal gradient across the shelf at cooling and warming setpoints; and
  - Shelf temperature control to within  $\pm 3^{\circ}\text{C}$  at three setpoints (e.g., cold at  $-25^{\circ}\text{C}$ , intermediate at  $0^{\circ}\text{C}$ , and warm at  $25^{\circ}\text{C}$ ).
6. Lyophilization Qualification should include:
- Media fills simulating lyophilization processes;
  - Cleaning of chamber, condenser, and trays;
  - Cleaning validation of the chamber and trays and
  - Sterilization validation of the chamber, condenser, and trays.
7. Product Performance Qualification (PQ) Studies should include a minimum of 3 consecutive, successful lyophilization runs on the Worst Case load configuration with acceptance criteria for lyophilization meeting product specifications for:
- Moisture content,
  - Cake appearance, and
  - Reconstitution properties.