
Regulatory Aspects of Lyophilized Pharmaceuticals Drugs

Lisa L. McChesney-Harris, PhD
Regulatory Affairs
APP Pharmaceuticals, LLC

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Outline for Presentation

- Product Life Cycle – Lyophilized Drugs
 - Location of Lyophilization Information in CTD/eCTD
 - Primary Application Components
 - 505(j) ANDA or AADA
 - 505(b)(1) NDA
 - 505(b)(2) NDA
 - Nuances Specific to Lyophilized Drug Products
 - Postapproval Change Strategies and Examples
 - Prior Approval Supplements (PAS)
 - Changes Being Effected 30 Days (CBE30)
 - Changes Being Effected (CBE0)
 - Annual Reportable Changes

Location within eCTD Application

- Information specific to Lyophilization
- Common Technical Document Structure
 - 3.2.P DRUG PRODUCT
 - 3.2.P.3 Manufacture
 - 3.2.P.3.3 Description of Manufacturing Process and Process Controls

CMC Content per FDA Guidance

- Validation summary of the Lyophilization Process to include:
 - Narrative description of the validation
 - Certification that IQ / OQ have been completed
 - Validation summary data
 - Explanation of all excursions or failures
 - Deviation reports and results of investigations of all excursions or failures

Installation Qualification (IQ)

- IQ procedure predicates a design review and physical inspection of the installed lyophilization system
 - Design specifications
 - Drawings and diagrams
 - Manufacturer's recommendations for installation
 - Results of the inspections against the stated system requirements

Operational Qualification (OQ)

- OQ is the procedure executed to demonstrate that the system will perform reproducibility and consistently within its full dynamic range of operation according to the manufacturer's specifications and to assure that the system performance is adequate to support the process by which the system is intended.

Operational Qualification (OQ)

- Test elements of OQ
 - Chamber and condenser pump down rate tests
 - Leak rate tests
 - Condenser cooling rate and minimum temperature tests
 - Shelf-to-shelf temperature uniformity studies
 - Sublimation rate / condenser capacity and defrost studies
 - Steam sterilization cycle studies
 - Product-specific cycle simulation studies

Lyophilizer Cart Validation

- Carts used to transfer product from the fill line to the lyophilizer chamber are validated by evaluating the following:
 - Surface monitoring of the interior of the transfer cart
 - Media fills simulating the lyophilization process (inclusive of cart use)
 - Validation of sanitization procedures and duration of maintenance of “clean”
 - Integrity of supporting HEPA filtration system

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Stability Considerations

- Powder remains adhered to bottom of vial
 - May be able to justify minimal Inverted orientation testing for exhibit batches, i.e., Upright and Inverted testing only at study end
 - May be able to justify Upright orientation only for stability of commercial production lots
- Reconstitution stability
 - Chemical stability (data to match labeling)
 - Microbial integrity (date to match labeling)

Compositional Considerations

- Nitrogen utilized during the lyophilization process
 - Agency may request that N₂ be included in the description of the drug product composition

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 - Other Nuances Specific to Lyophilized Drug Products
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Reporting Categories for Changes

- Major Change
 - **Substantial** potential to have an adverse effect on the strength, quality, identity, purity, or potency (SQIPP) of a drug product (PAS)
- Moderate Change
 - **Moderate** potential to have an adverse effect on SQIPP (CBE30, CBE0)
- Minimal Change
 - **Minimal** potential to have an adverse effect on SQIPP (Annual Reportable)

Prior Approval Supplements (PAS)

- Major Change in Manufacturing Site
 - Newly constructed or refurbished lyophilization processing facility or area
 - Existing facility that has NOT previously been approved for lyophilized drug products
 - Existing facility that has been approved for lyophilized drug products using different container types and/or sizes
- Major Change in Manufacturing Process
 - Replacement or addition of lyophilization equipment of a different size that uses different operating parameters or lengthens the overall process time

Changes Being Effected in 30 Days (CBE30)

- Moderate Change, Expansion at Mfg Site
 - Facility expansion of areas supporting the lyophilized drug product
 - Addition of equivalent lyophilizers to a facility with existing lyophilizers
 - Existing facility that has been approved for lyophilized products using same container types and/or sizes
- Moderate Change in Manufacturing Process
 - Changes in lyophilization equipment of the same design and operating principles and/or changes in production scale

Facility Expansion – CBE30 Documentation

- Proposed facility diagrams indicated anticipated expansion; to include flow of components, personnel, and filled product
- Validation Master Plan of the facility expansion
- PQ Protocol and Report for WFI System
- PQ Protocol and Report for Medical Air
- PQ Protocol and Report for Environmental Monitoring; to include Monitoring of Nonviable Airborne, Viable Airborne, and Surface Viable
- Summary of Smoke Study Challenges
- Summary of Media Fill Data

Lyophilizer Addition – CBE30 Documentation

- Side-by-side comparison of old to new lyophilizer
- IQ, OQ, PQ Protocol and Report for new LYO
- Product-specific PQ Protocol and Report
- Media fill data for new LYO and any associated transfer carts used for the process
- Revised Master Batch Records reflecting the use of the new LYO with table of changes
- Product-specific COAs demonstrating drug product conformance to previously used LYO
- Stability data summaries demonstrating conformance to previously used LYO

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Thank You!

- Questions

