Validation of Supporting Processes

1. Washing of Components
The washing of components will be validated for each load configuration in the vial washer. Cycle Development Testing and Performance Qualification testing will qualitatively each washing process. A separate performance qualification and cycle development testing report will be written for each load configuration. The processes will be considered validated when the acceptance criteria is met for three (3) successful consecutive runs.

Cycle Development Testing
Perform one or more cycle development test runs with vials to determine appropriate time for each cycle (wash and rinse), temperature for each cycle, load size, WFI supply pressure, and air supply pressure.

Performance Qualification Test Functions
1. Identify and document the quantity and placement of vials in the load configuration. Determine load configuration from Cycle Development Test studies.
2. Prepare a full load of vials spiked with dye. Wash the vials as per the proposed operating procedure. Inspect each vial for dye residue.
3. Spike three (3) sets of vials with NaCl solution. Allow vials to dry and then wash them per the proposed procedure. Baseline data will be established using unwashed, NaCl-spiked vials. Test the washed vials for conductivity (NaCl) and particulate count (WFI).

Acceptance Criteria
1. No dye residue is detected at >1 ppb in any of the washed vials.
2. The rinse solution from each washed, NaCl-spiked vial must have a conductivity <2 µmho.
3. The rinse solution from each washed, NaCl-spiked vial must have no precipitate when tested per USP Monograph for Sodium Chloride.
4. Both the rinse solutions from the NaCl-spiked and unspiked vials must have particulate counts that meet the specifications listed in USP Monograph for Physical Test, and Particulate Matter in Injections.
5. The rinse solutions from the NaCl-spiked and unspiked vials must meet the specifications for Water for Injection listed in USP Monograph for Water for Injection.
6. The rinse solutions from the unspiked vials must have no more than 0.25 EU/ml.

2. Sterilization of Components
The sterilization of components and equipment will be validated for each load configuration using the cGMP autoclave. Cycle Development Testing and Performance Qualification Testing will qualify each sterilization process. A separate Performance Qualification and Cycle Development Testing Report will be written for each load configuration. The process will be considered validated when the acceptance criteria is met for three (3) successful consecutive runs.

Cycle Development Testing
Perform one or more cycle development test runs used in the load configuration to determine appropriate cycle type, temperature and dwell period, hard-to-heat items or areas, load item preparation, and minimum and maximum load configurations.

Performance Qualification Test Functions
1. Identify and document the quantity, placement, and physical description of each component to be included in the load configuration. Determine load configuration from Cycle Development Test studies.
2. Perform load and chamber temperature mapping and verify that the temperature distribution in the chamber is uniform for the load configuration, and that all measured points within the load configuration receive thermal treatment sufficient for sterilization. Perform three (3) runs on the maximum load and a minimum of three (3) runs on the minimum load.
3. Perform microbiological challenge studies using the Overkill Approach Sterilization Validation. Place Bacillus stearothermophilus spores throughout the load configuration, at points where steam penetration may be incomplete, and at hard-to-heat locations. Perform a minimum of three (3) runs on the maximum load configuration and a minimum of three (3) runs on the minimum load configuration. Perform spore quantification verification on each manufacturer’s lot of spore strips or suspensions. Perform microbiological challenge studies simultaneously with loaded chamber heat penetration and distribution studies.
4. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during cycle Development and Performance Qualifications testing.

Acceptance Criteria
1. During load and chamber temperature mapping, the maximum load configuration, the mean of the \( F_0 \) values from the single slowest-to-heat point from each of the three (3) test runs minus 3 standard deviations of the these three \( F_0 \) values must be greater than 20 min.
2. During load and chamber temperature mapping, the minimum load configuration, the mean of the \( F_0 \) values from the single slowest-to-heat point from each of the three (3) test runs minus 3 standard deviations of the these three \( F_0 \) values must be greater than 20 min.
3. During microbiological challenge studies, all Bacillus stearothermophilus spore strips/suspensions must show negative test for the growth of B. stearothermophilus.
4. During microbiological challenge studies, positive controls for the *B. stearothermophilus* spore strips/suspensions must test positive for the growth of *B. stearothermophilus*.

5. During Microbiological Challenge studies, spore strips/suspension quantification test must indicate that the population of each manufacturer’s lot of spore strips/suspensions is within ±50% of their labeled population.

### 3. Depyrogenation of Components

The depyrogenation of components will be validated for each load configuration using the depyrogenation hot air sterilization tunnel. Cycle Development Testing and Performance Qualification Testing will qualify each depyrogenation process. A separate Performance Qualification and Cycle Development Testing Report will be written for each load configuration. The processes will be considered validated when the acceptance criteria is met for three (3) successful consecutive runs.

#### Cycle Development Testing

Perform one or more cycle development test runs with item used in the load configuration to determine appropriate cycle type, temperature and dwell period, hard-to-heat items or areas, load item preparation, and minimum and maximum load configurations.

#### Performance Qualification Test Functions

1. Identify and document the quantity, placement, and physical description of each component to be included in the load configuration. Determine load configurations from Cycle Development Test studies.

2. Perform load and chamber temperature mapping and verify that the temperature distribution in the chamber is uniform for the load configuration, and that all measured points within the load configuration receive thermal treatment sufficient for depyrogenation. Perform three (3) runs on the maximum load and a minimum of three (3) runs on the minimum load.

3. Perform pyrogen challenge studies and verify through laboratory testing that the endotoxin contents of all indicators in each load are reduced by a minimum of 3 logs. Endotoxin reduction of 3 logs or greater will also ensure a greater than 12 log reduction of biological organisms.

4. Record the range of all process or equipment parameters (set points, flow rates, timing sequences, concentrations, etc.) verified during Cycle Development and Performance Qualifications Testing.

#### Acceptance Criteria

1. Temperature distribution thermocouples in the heat penetration and distribution test studies for three (3) consecutive runs must be within ±5°C of the mean chamber temperature during the dwell period at any one print interval.

2. During heat penetration studies, all thermocouples must receive a minimum temperature of 250°C. F_H (250°C) must be calculated.

3. The endotoxin content of all endotoxin indicators must be reduced to levels of <0.025 EU (or undetectable), or at least demonstrate a minimum of 3 log reduction for three (3) consecutive runs at half-cycle.

4. Positive controls for endotoxin indicators must yield a minimum of 1000 EU.

5. Negative controls for endotoxin indicators must be <0.03 EU/ml.

### 4. Aseptic Filling Validation (Media Fill Studies)

Protocols will be developed to demonstrate that the product is aseptically filled into a final dosage container. These studies will consist of exposing media capable of supporting a broad spectrum of microbiological growth to all operations and procedures normally performed during the manufacturing process. Vials will be filled at the normal working volume. Each study will include filling approximately 3000 vials/ampoules. The vials/ampoules will be incubated at 20 to 25°C for 14 days.

“Worst-case,” challenges such as personnel breaks, equipment adjustments, and additional personnel in the fill room will be incorporated into all media fill studies. Stoppers and vials or ampoules will be sterilized. The time between sterilization and the start of the first media fill will be the maximum validated storage time for sterile stoppers, vials, and ampoules, provided the media fills meet all other acceptance criteria.

All environmental monitoring supplies will be growth promoted on the release date and fill date. Agar strips will be growth promoted after being exposed to the same environmental conditions as those experienced during the fill. Growth promotion will be performed for organisms required by USP Monograph for Indigenous Organisms and Anaerobes using vials/ampoules collected during the fill and upon completion of the 14-day incubation period.

The protocol will include acceptance criteria for sterility assurance level and growth promotion.

Also included will be details of data collection, growth promotion sampling, environmental and personnel monitoring schedule, personnel movement documentation, incubation time and temperature, etc.

#### Acceptance Criteria

Upon successful completion (end-point contamination level of not more than 0.1%) of three (3) consecutive media fills for the vial/stopper combination and ampoules, the aseptic process will be considered validated.

### 5. Cross-Contamination Control

#### Test Functions

1. Verification of HVAC design, zoning of air handling units, airlocks, room pressure differentials, recirculation vs. once-through air handling systems, room air distribution, use of HEPA filters on main return ducts to air handling plants, supply and return duct work, fresh air intakes and exhaust for buildings A, B, and C.

2. Verification of materials and product dispersal around manufacturing facility in buildings A, B, and C.
3. Verification of spread of materials and products during maintenance and cleaning of environmental and process air handling plant and equipment.
4. Verification of containment of materials and products during processing.
5. Verification of dust collection system as per design.
6. Verification of movement of personnel, gowning, and laundry as per design.
7. Verification of utilities design, mix-up, identification, check valves, and back-flow prevention.
8. Verification of facility design, architectural finishes, and room layout.
9. Verification of equipment design, construction materials, clean in-place (CIP) units where possible, and cleaning out-of-place practice.
10. Verification of cross-contamination prevention by performing air sampling and machine swabs.
11. Verification of prevention of cross-contamination by cleaning system validation.
12. Verification of prevention of cross-contamination through residual analysis of finished products.
13. Verification of pallets transfer and interlocks as per design.

Acceptance Criteria
1. The system is installed in accordance with design specifications based on manufacturer recommendations and cGMP guidelines and documented.
3. Spread of materials and products during maintenance and cleaning of environmental and process air handling plant and equipment is maintained and demonstrated through environmental monitoring.
4. Containment of materials and products during processing is demonstrated through environmental monitoring.
5. Dust collection system operates in accordance with design specifications throughout the operating range or range of intended use.
6. General control of movement of personnel, gowning, and laundry is demonstrated through SOP compliance and training.
7. General controls, alarms, identification, and interlocks operate in accordance with design specifications.
8. Facility construction and architectural finishes demonstrate adherence to specifications and cGMPs.
9. Equipment design, construction materials, CIP, and cleaning out-of-place practice are in compliance with cGMPs.
10. Air sampling and machine swabs results meet the acceptance criteria established.
11. Area/equipment cleaned in accordance with the written SOPs and meet the acceptance criteria.
12. The pallet transfer units and interlocks operate as per design and in accordance with the written SOPs.

6. Computerized Pharmaceutical System

Test Functions
1. Perform Installation Qualification.
2. Confirm that hardware and software descriptions are available.
3. Confirm that the documentation is appropriate, up-to-date, relevant, and complete.
4. Verify the digital transmission inputs and outputs as appropriate.
5. Verify analog transmission inputs and outputs as appropriate.
6. Verify data entry and boundary testing as appropriate.
7. Verify access control testing as appropriate.
8. Verify SOPs for operation, maintenance, and change control.
9. Verify training records.
10. Verify system recovery procedure.

Acceptance Criteria
1. The system is installed in accordance with design specifications based on manufacturer recommendations and cGMP guidelines. Instruments are calibrated, identified, and entered into the calibration program.
2. Hardware and software systems are verified as per manual.
3. The documentation is appropriate, up-to-date, relevant, and complete as per protocol.
4. The digital transmission inputs and outputs are verified.
5. The analog transmission inputs and outputs are verified.
6. The data entry and boundary testing meets the specification design.
7. The access control testing meets the specification design.
8. SOPs are available for operation, maintenance, and change control.
9. Training records are available.
10. System recovery procedure is available.