Process Validation

TRADITIONAL DP PROCESS VALIDATION

1. Introduction

The <INN> commercial drug product process was validated at <site> by demonstrating that the process, when executed within defined process parameter ranges, met pre-defined acceptance criteria for performance indicators.

Pre-defined validation acceptance criteria were established based on manufacturing development data derived from process characterization studies, pilot scale, and commercial scale production. Based on process and product understanding, it was determined that <number> PPQ runs (validation batches) were required to qualify the <INN> drug product manufacturing process. In the remainder of this section, the term "process validation" refers to PPQ.

Results obtained during process validation provide evidence that the drug product process is validated and consistently produces <INN> drug product that meets pre-defined criteria. All process validation studies were performed using approved protocols, manufacturing procedures, and standard operating procedures. Details of the <INN> commercial drug product manufacturing process are provided in 3.2.P.3.3 .(Description of Manufacturing Process and Process Controls).

The <INN> drug product manufacturing activities at <site> included the following processing steps:

- Compounding
- Sterile Filtration
- Filling
- Lyophilization
- Capping and Sealing

A summary of the drug product process validation batches are provided in the sections below. Data obtained supports the <INN> commercial drug product manufacturing process described in 3.2.P.3.3 (Description of Manufacturing Process and Process Controls).

2. <INN> Process Validation Batches

The batches used in support of validation of the <INN> drug product manufacturing process are included in Table 1. The formulation, primary container, and manufacturing process are identical for all X drug product strengths. The only difference is the volume

delivered to the X mL vial during aseptic filling of the filtered formulated drug product. Equipment differences between manufacture of the dosage strengths include working volumes of associated formulation, holding, and filling equipment. The <INN> drug product validation batches were designed to provide data across the range of equipment volumes utilized for all dosage strengths. The validation batches provided data at minimum and maximum batch size ranges for the X mg/vial and X mg/vial dosage strengths. Additional details around the determination of number of validation batches and the bracketing strategy justification is included in 3.2.P.3.5 (Process Validation and/or Evaluation, Process Evaluation).

Process Validation

Table 1. Batches Used in <INN> Drug Product Process Validation

Drug Product Batch Number	Date of Manufacture	Strength (mg/vial)	Batch Designation	Vessel Volume (L)		Drug Substance Batch Number	Batch Size (kg)		Target Fill Weight (g)	Number of Vials
				Formulation Mixing Bag	Receiving Tank		Formulated Drug Product	Filtered Formulated Drug Product		
XXXXX	XXXXX	XX	Maximum	XXX	XXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXX	XXXXX	XX	Minimum	XXX	XXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXX	XXXXX	XX	Maximum	XXX	XXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX
XXXXX	XXXXX	XX	Minimum	XXX	XXX	XXXXX	XXXXX	XXXXX	XXXXX	XXXXX

Process Validation

3. Validation Program at <site>

The validation program at <site> includes a comprehensive evaluation of the adequacy and reliability of the system maintenance programs, installation qualification, operational qualification, and performance qualification for individual equipment. Validation is performed using a prospective approach for each system prior to initiation of process validation batches.

All major equipment used for the <INN> drug product manufacturing process was successfully qualified prior to use in the process validation batches. These qualifications include installation and operational qualification of preparation and hold vessels, qualification of sterilization and other preparation processes for stoppers, vials, and other equipment used in the manufacturing process.

3.1 Compounding

The compounding process, including dissolution, homogenization and solubilization of <INN>, pH adjustment, clarification filtration and dilution steps, has been validated. The following tests and controls were conducted:

- pH (adjustment of pre-clarification bulk solution): Target pH ensures solubility and solution stability.
- pH (post-dilution bulk solution): Target pH ensures solubility and solution stability.
- Assay (pre-clarification filtration): Solubility of <INN> is verified to assure that the target formulation concentration of X mg/mL can be achieved at the dilution step.
- Assay (post-dilution bulk solution): The assay result is used to determine the fill weight. This step impacts quality (% label claim) of the drug product.

In-process test results for the compounding process met the acceptance criteria and are provided in Table 2. All results met the acceptance criteria.

Table 2. In-Process Testing for the Compounding Steps

Test	Acceptance Criteria	Lot XXXXX	Lot XXXXX	Lot XXXXX
pH (adjustment of pre-clarification bulk solution)	XX to XX	XX	XX	XX
pH (post-dilution bulk solution)	XX to XX	XX	XX	XX
Assay (pre-clarification filtration) (mg/mL)	≥ XX	XX	XX	XX
Assay (Post-dilution bulk solution) (mg/mL)	XX to XX	XX	XX	XX

Process Validation

3.2 Sterile Filtration and Filling

A sample was withdrawn for in-process bulk bioburden testing prior to sterile filtration.

The target fill volume was calculated from the in-process assay. The bulk solution was sterile filtered through a 0.XX µm sterilizing filter into a sterile hold tank. At the start of filling, sterile filtered drug solution was then filtered through a second 0.XX µm sterilizing grade filter to an automatic filler for sterile filling. The hold time and the processing time have been validated and established from the process validation batches of the drug product.

The in-process results for the critical steps and the filter integrity test are provided in Table 3. All results met the acceptance criteria.

Process Validation

Table 3. Testing for the Filling Steps for Process Validation Batches

Test	Acceptance Criteria	Lot XXXX	Lot XXXX	Lot XXXX
TAMC[a]	≤ 10 CFU/100mL	XX	XX	XX
TYMC[a]	≤ 10 CFU/100 mL	XX	XX	XX
Fill Weight Average (g)	N/A	XX	XX	XX
Target (g)	N/A	XX	XX	XX
Actual Avg. Weight from Target	± X% target (%)[b]	+0.X	+0.X	+0.X
Hold Time[c]	≤ XX (hours)	XX hrs XX min	XX hrs XX min	XX hrs XX min
Hold Time[d]	≤ XX (hours)	XX hrs XX min	XX hrs XX min	XX hrs XX min
Hold Time[e]	≤ XX (hours)	XX hrs XX min	XX hrs XX min	XX hrs XX min
Hold Time[f]	≤ XXX (hours)	XX hrs XX min	XX hrs XX min	XX hrs XX min
Filter Integrity Test	≥ XX (psi)	XX psi	XX psi	XX psi

CFU = colony forming units; psi = pounds per square inch; TAMC = total aerobic microbial count; TYMC = total yeasts and molds counts
[a] Bioburden samples collected from bulk solution prior to sterile filtration.
[d] Start of sterile filtration to start of filling.
[e] Start of filling to end of filling.

3.3 Lyophilization and Capping

Lyophilization

Filled, partially stoppered vials are loaded into the freeze dryer and lyophilized. To ensure the drug product vials are lyophilized uniformly, samples from various locations, trays and shelves in the lyophilizer were tested for assay, water content, reconstitution time, total related substances, impurity XXXX, impurity XXXXX, and all other individual related substances. In addition to the standard non-routine lyophilization uniformity testing for PPQ batches, on batch XXXXX a statistically determined non-routine lyophilization homogeneity sampling plan was implemented for two critical attributes, assay (main peak) and water content. This homogeneity sampling plan allows for a multiple linear regression model to be fitted to the data of each assay in order to assess lyophilization homogeneity across shelves and sample locations. Where statistically significant effects were shown to exist, these data were evaluated against a statistically derived homogeneity equivalence acceptance criteria. The complete batch results are summarized in Table 4, and the homogeneity analysis results are summarized in

Table 5. The testing results demonstrate that the process validation batches met all acceptance criteria.

Capping: Dye ingress testing confirmed that the integrity of the container closure system was maintained by the capping process.

3.4 Drug Product Release Specification Testing

Test results from the process validation batches demonstrates that drug product of acceptable quality is produced using the <INN> drug product manufacturing process and equipment meeting the acceptance criteria defined in the specifications in Table 6.

The outcome of the process validation campaign is summarized below:

1. XXX consecutive process validation batches were successfully produced meeting acceptance criteria defined in the process validation protocol.
2. Results from specified additional testing and studies met the acceptance criteria.
3. No new impurities were observed for any of the XXX process validation batches.

The complete testing results are provided in 3.2.P.5.4 (Batch Analyses).

3.5 Conclusion

The successful production of XXX process validation batches of <INN> manufactured at <site> confirms that the production process yields consistent and reproducible drug product.

All validation data met acceptance criteria demonstrating consistency and reliability of the process to meet its predetermined quality requirements. The lot release results are summarized in Table 6.

Process Validation

Table 4. Process Validation Batches Lyophilization Results

Parameter	Acceptance Criteria	Lot No.					
		No. of Locations	Lot XXXX [a]	No. of Locations	Lot XXXX	No. of Locations	Lot XXXX
Lyophilizer Number		N/A	XXX	N/A	XXXX	N/A	XXX
Assay (% Label Claim)	XX% to XX% of label claim	XX	XX	XX	XX	XX	XX
Assay RSD	N/A	XX		XX		XX	
Water Content	≤ X% w/w	XX	XX	XX	XX	XX	
Reconstitution Time	≤ XX minutes	XX	XX	XX			
Total Related Substances	Not more than X% area	XX	XX	XX			
Impurity XXXX	Not more than X% area	XX	XX	XX			
Impurity XXX	Not more than X% area	XX	≤ XX	XX			
Other Related Substances	Not more than X% area	XX	XX	XX	0		

n = number of locations; RSD = relative standard deviation.

Process Validation

Table 5. Additional Homogeneity Analysis Results

		Lot Number XXXX			
Test Parameter	Homogeneity Acceptance Criteria	Do statistically significant effects exist?	Lower one-sided 95% confidence limit of Max Difference	Upper one-sided 95% confidence limit of Max Difference	Was Homogeneity demonstrated?
Moisture (%)	± XX % (w/w)	Yes	XXXX %	XXXX %	Yes
Assay by HPLC (% Main Peak)	± XX %	No	Not calculated [a]	Not calculated [a]	Yes

[a]. The multiple linear regression analysis reveals there are no statistically significant effects of shelf or position on Assay by HPLC results. Therefore, homogeneity is demonstrated and it is not necessary to calculate the two one-sided confidence limits for maximum difference.

Process Validation

Table 6. Release Performance Parameters for Process Validation Batches

		Lot Number		
Test Parameter	Acceptance Criteria	XXXXX	XXXXX	XXXX
Appearance (Product Container, visual)	1) Clear glass vial sealed with a gray rubber stopper and a flip-off overseal	Conforms	Conforms	Conforms
	2) No visible damage or breach of vial container or closure	Conforms	Conforms	Conforms
Appearance (Lyophilized, Visual)	White to off-white cake or powder, essentially free from evidence of contamination with no visible foreign particulates	Conforms	Conforms	Conforms
Appearance (Reconstituted, Visual)	Clear, colorless to slightly yellow solution, essentially free of visible particulates	Conforms	Conforms	Conforms
Identification	Conforms to reference standard	Conforms	Conforms	Conforms

μm = micrometer; EU = endotoxin unit; mOsm = milliosmole; n = number; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia

Process Validation

Table 6. Release Performance Parameters for Process Validation Batches

Test Parameter	Acceptance Criteria	Lot Number		
		XXXXX	XXXXX	XXXX
Assay	XX% to XX% of label claim	XX	XX	XX
Total Related Substances	Not more than XX% area	XX	XX	XX
Impurity XXXX	Not more than XX% area	XX	XX	XX
Impurity XXXX	Not more than XX% area	≤ XX	≤ XX	≤ XX
All Other Individual Related Substances	Not more than XX% area	XX	XX	XX
Reconstitution Time (Time Measurement, Visual)	≤ X minutes	X	X	X
Water Content	Not more than X% (w/w)	XX	XX	XX
Uniformity of Dosage Units, Weight Variation	Meets USP / Ph. Eur. requirements (% label claim), n = XX Acceptance Value (AV) ≤ XX	n = X AV = XX	n = X AV = XX	n = X AV = XX
pH (reconstituted)	XX to XX	XX	XX	XX

μm = micrometer; EU = endotoxin unit; mOsm = milliosmole; n = number; NA = not applicable; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia

Process Validation

Table 6. Release Performance Parameters for Process Validation Batches

		Lot Number		
Test Parameter	Acceptance Criteria	XXXXX	XXXXX	XXXXX
Osmolality	XX ± XX mOsm/kg	XX	XX	XX
Particulate Matter USP <788>, Ph. Eur. 2.9.19	Meets USP / Ph. Eur. Requirements	Conforms	Conforms	Conforms
Particulate Matter ≥ XX μm	Not more than XXXX particles/container ≥ XX μm	XX	XX	XX
Particulate Matter ≥ XX μm	Not more than XXX particles/container ≥ XX μm	X	X	X
Sterility	Sterile	Conforms	Conforms	Conforms
Bacterial Endotoxins	≤ XX EU/mg	< X	< X	< X

μm = micrometer; EU = endotoxin unit; mOsm = milliosmole; n = number; NA = not applicable; Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia

Process Validation

4. Sterility Assurance Validation

The information specific to the validation of sterility assurance for the <INN> drug product is provided in this section.

The manufacturing systems are designed for producing sterile products for human use by sterile filtration and aseptic processing. The building, facilities, manufacturing rooms, equipment, and floor plans are designed to prevent contamination from the environment or personnel. The manufacturing process is designed, controlled, and validated to maintain a high degree of sterility assurance for manufacturing drug product.
A summary is presented below.

4.1 Overall Sterile Operations

Aseptic processing consists of sterile filtrations in a closed system, filling and partial stoppering, lyophilization, and capping. The environments where preparation of components, and manufacture of drug product takes place, are controlled and monitored to ensure compliance with the required cGMP standards appropriate to the individual unit operations.

4.2 Critical Operations

The critical operations for sterility assurance include sterilization and depyrogenation of container closures, sterilization of filters, sterilization of product contacting equipment, aseptic filling and stoppering, transferring and loading filled vials into the freeze dryer, lyophilization, stoppering, and sealing. The sterile filtration is conducted in a closed system to prevent the exposure of sterile <INN> solution to exterior environments.

4.2.1 Stopper Sterilization Validation

Stoppers are sterilized using a processor with an attached, closed, sterilized transfer unit (C/D) container. Validation of stopper sterilization in the processor consisted of XX successful runs with the XX mm lyophilization stoppers using thermocouples and biological challenges. The production parameters are set based upon the validated parameters with a longer sterilization time.

4.2.2 Revalidation

Revalidation for the sterile process is conducted periodically under a revalidation program to ensure the sterilization processes are maintained within a validated state.

4.3 Media Fills

Media fills are conducted routinely and for initial qualification. When media fills are conducted to qualify a new process or requalify a specific process, operations and

components of the media fill are designed to mimic the process as closely as possible. The media fill for each filling room is performed for XX hours, supporting the proposed maximum filling duration (hold time), and are repeated at least XX times per year.

Each media fill is performed by filling a broad spectrum culture medium. Incubation is conducted at XX°C to XX°C for ≥ X days followed by incubation at XX°C to XX°C for ≥ X days, after which they are inspected for macroscopic evidence of microbial growth. Any suspect unit is identified by tray number, providing traceability within the fill.

Lyophilization media fills are designed to simulate the entire process of manufacturing, filling, loading, pulling a vacuum, stoppering, venting (using sterile filtered air rather than nitrogen), unloading, etc.

Three media fills were performed using the <INN> change parts, filling pumps/needles, components and the XXX ft^2 freeze dryer, during the initial introduction of <INN> drug product XX mg/vial. One additional media fill run using the <INN> XX mg/vial commercial closure system (vial, stopper, and equivalent overseal) was performed to support <INN> XX mg/vial. All media fills were successfully executed. The results from the environmental monitoring met the acceptance criteria, and no vial showed positive growth. The testing results from the original XXX media fills and the one confirmation media fill are listed in Table 7 and Table 8.

Process Validation

Table 7. <INN> Drug Product Container Closure Media Fill Results for Line 1

Media Fill Lot No.	Container SIze	Filling Date	Filling Duration	Freeze Dryer Shelves Loaded with Filled Vials	No. of Integral Filled Vials	Positive Units	Disposition
XXXXX				XX	XXXX	X	Pass
XXXXX				XX	XXXX	X	Pass
XXXXX				XX	XXXX	X	Pass

Table 8. <INN> Drug Product Container Closure Media Fill Results for XX mg/vial Container Closure System

Media Fill Lot No.	Container Size	Filling Date	Filling Duration	Freeze Dryer Shelves Loaded with Filled Vials	No. of Integral Filled Vials	Positive Units	Disposition
XXXXX				XX	XXXXX	X	Pass

Process Validation

5. Cleaning Validation

During introduction into the manufacturing facility, <INN> was assessed under the manufacturing site's procedures for cleaning. The appropriate equipment cleaning cycles were designed and validated based on <INN> formulation and concentration. The appropriate analytical methods were selected for <INN> including both non-product specific testing (total organic carbon, endotoxin, bioburden, and visual inspection) and and product specific testing (HPLC analysis for <INN>).

6. Conclusion

Drug product manufacturing process validation for the XX mg/vial was successfully completed at the commercial batch size at the commercial site. The process validation results demonstrated that all steps are controlled, consistent, and reproducible.