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3.2.P.3.4 Controls of Critical Steps and Intermediates

This section contains the controls of critical steps and intermediate including: (1) acceptance criteria and test results for the exhibit batches; (2) comparison of controls and equipment between the exhibit and commercial-batch manufacture; and (3) information about hold time study for Clobetasol Propionate Foam, 0.05% bulk liquid. Aucta Pharmaceuticals, Inc. (Aucta) is the applicant and Pharmasol Corporation (Pharmasol) is the drug product manufacturer.

1.0 Acceptance Criteria and Test Results for the Exhibit Batches

In-process release acceptance criteria are set in the Specification 100-5-760 for Clobetasol foam bulk solution(concentrate). The same analytical procedure provided in Section 3.2.P.5.2 is utilized for the drug product release and in-process testing.

Split fill was performed on all exhibit batches of Clobetasol Propionate Foam, 0.05% with 50g pack size, and 100 pack size. The acceptance criteria and analytical procedures are the same for both exhibit batches and commercial batches. The testing results for bulk solution compounding and filling operation of exhibit batches are provided in Table 1.

Table 1 Bulk Solution (Concentrate) Release Testing Results for Exhibit Batches

Test	In Process Control	Results		
		31982	32595	32598
Appearance (at 45°C)	Clear solution with no visible particles	Confirms	Confirms	Confirms
ID by HPLC	The retention time of the clobetasol propionate in the test sample solution shall correspond to the retention time of clobetasol propionate in the standard solution for the assay chromatogram	Confirms	Confirms	Confirms
ID by UV	UV spectrum matches that of standard	Confirms	Confirms	Confirms
pH	5.0-7.0	5.9	6.0	6.0
Assay by HPLC	No less than 90.0% and no more than 110.0% of the labeled amount of clobetasol propionate	Top: 97.4% Mid: 96.5% Bot: 98.1%	Top: 102.7% Mid: 99.9% Bot: 100.2%	Top: 100.6% Mid: 100.4% Bot: 97.5%
Ethanol Content	90.0-110.0%	Top: 99.8% Mid: 99.6% Bot: 99.8%	Top: 99.9% Mid: 100.0% Bot: 99.7%	Top: 99.9% Mid: 100.1% Bot: 100.2%

The in-process controls of filling and packaging operation are the same for both exhibit batches and commercial batches as listed in Table 2. The results of exhibit batches are also presented in the same table.

Table 2 In-Process Control Results for Exhibit Batches

Test	In Process Control	Results					
		31982-50g	31982-100g	32595-50g	32595-100g	32598-50g	32598-100g
Concentrate Filling Weight (gram)	50g can: 50.0-51.0 100g can: 100.0 – 101.0	50.50 50.47 50.45 50.41 50.51 50.50	100.59 100.46 100.54 100.41 100.57 100.51	50.36 50.50 50.52 50.40 50.46 50.53	100.54 100.56 100.48 100.48 100.51 100.47	50.51 50.56 50.61 50.66 50.53 50.60	100.62 100.68 100.59 100.57 100.66 100.55
Gasser Filling Weight (gram)	2.46g – 2.86g for 50g can 5.09g – 5.49g for 100g can	2.67 2.65 2.64 2.67 2.68 2.68	5.30 5.32 5.29 5.32 5.29 5.30	2.67 2.69 2.63 2.65 2.66 2.67	5.28 5.30 5.31 5.32 5.30 5.31	2.68 2.70 2.67 2.67 2.68 2.68	5.32 5.29 5.29 5.27 5.29 5.31
Crimp Depth (in.)	0.190”-0.200”	0.195	0.195	0.195	0.195	0.195	0.195
Crimp Diameter (in.):	1.065”-1.075”	0.170	0.171	1.070	1.070	1.070	1.070
Vacuum (inHg)	NLT 15 inHg	16	16	16	16	16	16
Pressure at 25°C (psi)	50 -75	68 68 70 70 68 68	70 70 70 72 72 70	66 66 67 66 66 70	72 72 71 72 72 72	66 66 66 66 66 64	72 73 72 72 72 71
Extrusion (gram)	50g can: NLT 50 100g can: NLT 100	52 51 53 52 52 52	104 103 104 104 104 104	52 51 51 51 53 52	104 103 104 104 104 103	51 52 52 52 51 52	103 104 104 104 104 104

2.0 Comparison of Controls and Equipment between Exhibit Batches and Proposed Commercial-Scale Batch Manufacture

The commercial scale process contains the same unit operations and utilizes equipment of the same design and operating principles as used to produce the exhibit batches. The manufacturing equipment used for lab batches, exhibit batches, and proposed commercial batches are summarized in Table 3, including the operating targets and control ranges of the identified critical process parameters and in-process control parameters for critical unit operations.

Justifications for the operation ranges and in-process controls are provided in Section 2.3 and 2.7 of Module 3.2.P.2 "Clobetasol Propionate Foam,0.05%, Quality by Design Development Report".

Table 3 Control Strategy for Generic Clobetasol Propionate Foam, 0.05%

Factor	Attributes or Parameters	Range Studied (Lab scale)	Actual Data for the exhibit batch (Pilot Scale)	Proposed range for commercial scale[1]	Purpose of Control
Raw Material Attributes					
Clobetasol Propionate PSD	D90	6.05µm -9.32µm	D90 less than 10 µm	D90 less than 10 µm	To ensure quick dissolving of the API
Alcohol Phase Process Parameters					
Mixing Tank 1	Equipment	Glass Beaker (250ml – 5L)	Tank 604 (60-gallon tank)	Tank 250J (250-gallon tank)	To ensure enough working capacity
	Mixing Temperature	45° ± 5°C	45° ± 5°C	45° ± 5°C	To ensure material dissolving and prevent degradation
	Mixing Speed	90-450 rpm	100 ± 10 rpm	Center Propeller 90 ± 5 rpm Side Scraper 20 ± 10 rpm	To ensure sufficient mixing
Alcohol Phase In-Process Controls					
Appearance	Solution is clear, material completely dissolved				
Aqueous Phase Process Parameters					
Mixing Tank 2	Equipment	Glass Beaker (250ml – 5L)	Tank 13J (13-gallon tank)	Tank 80J (80-gallon tank)	To ensure enough working capacity
	Mixing Temperature	45° ± 5°C	45° ± 5°C	45° ± 5°C	To ensure material dissolving and prevent degradation
	Mixing Speed	90-450 rpm	250 ± 30 rpm	250 ± 50 rpm	To ensure sufficient mixing
Aqueous Phase In-Process Controls					
Appearance	Solution is clear, material completely dissolved				

Factor	Attributes or Parameters		Range Studied (Lab scale)	Actual Data for the exhibit batch (Pilot Scale)	Proposed range for commercial scale[1]	Purpose of Control
Main Phase Process Parameters						
Mixing Tank 1	Equipment		Glass Beaker (250ml – 5L)	Tank 604 (60-gallon tank)	Tank 250J (250-gallon tank)	To ensure enough working capacity
	Order of Addition		Transfer aqueous phase into alcohol phase	Transfer aqueous phase into alcohol phase	Transfer aqueous phase into alcohol phase	To ensure quick dissolving of two phases
	Recirculation		Not necessary	Collect 5kg solution form the bottom of the tank and add to the top. Repeat three times	Collect ~5kg solution form the bottom of the tank and add to the top. Repeat three times	To ensure sufficient mixing and no dead spot
Bulk Solution Homogeneity Process Parameters						
Mixing Tank 1	Mixing Temperature		Not necessary	45° ± 5°C	45° ± 5°C	To ensure solution in liquid form
	Mixing Speed		Not necessary	90 ± 10 rpm	Center Propeller 80 ± 10 rpm Side Scraper 20 ± 10 rpm	To ensure homogeneity
Bulk Solution Homogeneity In-Process Controls						
Appearance at 45°C	Clear solution with no visible particles					
ID by HPLC	Retention time corresponds to standard					
ID by UV	Spectrum matches standard					
pH	5.0-7.0					
Assay	90.0% - 110.0%					
Ethanol Content	90.0% - 110.0%					
Primary Packaging Process Parameters						
Crimping	Crimp Depth		0.190” – 0.200”	0.190” – 0.200”	0.190” – 0.200”	To ensure good packaging integrity
	Crimp Diameter		1.065” – 1.075”	1.065” – 1.075”	1.065” – 1.075”	
	Crimp Vacuum		NLT 15 inHg	NLT 15 inHg	NLT 15 inHg	To ensure vacuum is created in cans
Concentrate Filling	Concentrate fill weight	50g	50.5 ± 0.5 g	50.5 ± 0.5 g	50.5 ± 0.5 g	To ensure minimum fill and delivery amount are met
		100g	100.5 ± 0.5 g	100.5 ± 0.5 g	100.5 ± 0.5 g	
Gassing	Propellent fill weight	50g	2.66 ± 0.2g	2.66 ± 0.2g	2.66 ± 0.2g	To ensure product delivery rate and pressure are met
		100g	5.29 ± 0.2g	5.29 ± 0.2g	5.29 ± 0.2g	

Factor	Attributes or Parameters		Range Studied (Lab scale)	Actual Data for the exhibit batch (Pilot Scale)	Proposed range for commercial scale[1]	Purpose of Control
Primary Packaging In-Process Controls						
Crimp Depth	1 can per station every 60 min		0.190" – 0.200"			
Crimp Diameter	1 can per station every 60 min		1.065" – 1.075"			
Crimp Vacuum	1 can per station every 60 min		NLT 15 inHg			
Leak can and valve	100% of the units		No formation of a constant stream of bubbles from the can when submerged in the heat tank			
Pressure	1 can per station every 30 min		50 – 75 psi			
Extrusion	100% of the units	50 g	NLT 50 g			
		100g	NLT 100 g			
Concentrate fill weight	1 can per station every 60 min	50g	50.5 ± 0.5 g			
		100g	100.5 ± 0.5 g			
Propellent fill weight	1 can per station every 60 min	50g	2.66 ± 0.2g			
		100g	5.29 ± 0.2g			
Product total weight	100% Cans	50g	(52.46g + low end of packaging component weight) - (53.88g + high end of packaging component weight)			
		100g	(105.09g + low end of packaging component weight) - (106.49g + high end of packaging component weight)			

1. The proposed operating range for commercial scale will be qualified and continually verified

The test results of exhibit batch samples collected throughout the production met the predetermined acceptance criteria as shown in Table 1 and Table 2. Therefore, the process parameters are appropriate for the product.

The manufacturing process parameters used for the exhibit (registration) batches are summarized in Section 2.3.8 of Module 3.2.P.2 "Clobetasol Propionate Foam, 0.05%g, Quality by Design Development Report".

3.0 Hold Time Study for Clobetasol Propionate Foam Bulk Solution

A 150 kg bulk batch (Batch #32598) was manufactured at Pharmasol Corporation using the pre-approved batch record (Compounding Record 8112010E). Prior to the commencement of the filling operation, 12 kg of the bulk was stored in a 5-gallon, stainless steel container with a tightly closed lid at ambient warehouse conditions (20°C – 25°C, ambient RH). Based on the data generated, the maximum bulk holding time was determined to be 71 days when stored at ambient conditions. Appearance, identification, pH, assay and ethanol content were tested for bulk samples. As shown in Table 4, all results for final bulk solution of Clobetasol Propionate Foam 0.05% at 71 days met the acceptance criteria when stored in the bulk container, thus the final bulk solution is stable for 71 days holding period.

Table 4 Holding Stability for bulk Clobetasol Propionate Foam, 0.05%

Test	Specifications	Results	
		Day 0	71 Days
Appearance (at 45°C)	Clear solution with no visible particles	Top: Conforms Middle: Conforms Bottom: Conforms	Top: Conforms Middle: Conforms Bottom: Conforms
Identification by HPLC	The retention time (RT) of Clobetasol Propionate in the test sample solution shall correspond to the retention time of Clobetasol Propionate in the standard for the assay chromatogram	Top: Conforms Middle: Conforms Bottom: Conforms	Top: Conforms Middle: Conforms Bottom: Conforms
Identification by UV	UV spectrum matches that of standard	Top: Conforms Middle: Conforms Bottom: Conforms	Top: Conforms Middle: Conforms Bottom: Conforms
pH	5.0-7.0	Top: 6.0 Middle: 6.0 Bottom: 6.0 Ave.: 6.0	Top: 6.0 Middle: 6.0 Bottom: 6.0 Ave.: 6.0
Assay by HPLC	No less than 90.0% and no more than 110.0% of the labeled amount of Clobetasol Propionate	Top: 100.6% Middle: 100.4% Bottom: 97.5%	Top: 101.7% Middle: 101.4% Bottom: 101.2%
Ethanol Content	90.0-110.0%	Top: 99.9% Middle: 100.1% Bottom: 100.2%	Top: 99.5% Middle: 99.4% Bottom 99.6%