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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

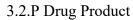
In-process release acceptance criteria are set in the Specification 100-5-760 for Clobetasol foam bulk solution(concentrate). The same analytical procedure provided in Section 3.2.P.5.2 is utilized for the drug product release and in-process testing.

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

Tank	In Dunning Control	Results			
Test	In Process Control	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	
pН	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%	

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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

	I D	Results					
Test	In Process Control	31982- 50g	31982- 100g	32595- 50g	32595- 100g	32598- 50g	32598- 100g
		50.50	100.59	50.36	100.54	50.51	100.62
	<u>50g can:</u>	50.47	100.46	50.50	100.56	50.56	100.68
Concentrate Filling	50.0-51.0	50.45	100.54	50.52	100.48	50.61	100.59
Weight (gram)	100g can:	50.41	100.41	50.40	100.48	50.66	100.57
	100.0 - 101.0	50.51	100.57	50.46	100.51	50.53	100.66
		50.50	100.51	50.53	100.47	50.60	100.55
		2.67	5.30	2.67	5.28	2.68	5.32
	2.46g - 2.86g	2.65	5.32	2.69	5.30	2.70	5.29
Gasser Filling	for 50g can	2.64	5.29	2.63	5.31	2.67	5.29
Weight (gram)	5.09g - 5.49g	2.67	5.32	2.65	5.32	2.67	5.27
	for 100g can	2.68	5.29	2.66	5.30	2.68	5.29
		2.68	5.30	2.67	5.31	2.68	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
		68	70	66	72	66	72
		68	70	66	72	66	73
Pressure at 25°C (psi)	50 -75	70	70	67	71	66	72
riessure at 25 C (psi)	30 - 73	70	72	66	72	66	72
		68	72	66	72	66	72
		68	70	70	72	64	71
		52	104	52	104	51	103
	50g can:	51	103	51	103	52	104
Extragion (gram)	NLT 50	53	104	51	104	52	104
Extrusion (gram)	100g can:	52	104	51	104	52	104
	NLT 100	52	104	53	104	51	104
		52	104	52	103	52	104



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

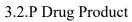
The commercial scale process contains the same unit operations and utilizes equipment of the same design and operating principles as used to produce the exhibit batches. The manufacturing equipment used for lab batches, exhibit batches, and proposed commercial batches are summarized in Table 3, including the operating targets and control ranges of the identified critical process parameters and inprocess 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 P	rocess Parameters					
	Equipment	Glass Beaker (250ml – 5L)	Tank 604 (60-gallon tank)	Tank 250J (250-gallon tank)	To ensure enough working capacity			
Mixing Tank 1	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 $90 \pm 5 \text{ rpm}$ Side Scraper $20 \pm 10 \text{ rpm}$	To ensure sufficient mixing			
		Alcohol Phase Ir	n-Process Controls					
Appearance	Solution is clear, mate	rial completely dissol	ved					
	_	Aqueous Phase P	rocess Parameters					
	Equipment	Glass Beaker (250ml – 5L)	Tank 13J (13-gallon tank)	Tank 80J (80-gallon tank)	To ensure enough working capacity			
Mixing Tank 2	Mixing Temperature	45° ± 5°C	45° ± 5°C	45° ± 5°C	To ensure material dissolving and prevent degradation			
	Mixing Speed	90-450 rpm	$250 \pm 30 \text{ rpm}$	$250 \pm 50 \text{ rpm}$	To ensure sufficient mixing			
	Aqueous Phase In-Process Controls							
Appearance	Solution is clear, mate	rial completely dissol	ved					

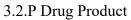
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Factor	Attributes or Parameters	,	Range Studied (Lab scale)	Actual Data for the exhibit batch (Pilot Scale)	Proposed range for commercial scale ¹	Purpose of Control		
Main Phase Process Parameters								
	Equipment		Glass Beaker (250ml – 5L)	Tank 604 (60-gallon tank)	Tank 250J (250-gallon tank)	To ensure enough working capacity		
Mixing	Order of Addi	tion	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		
Tank 1	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		
		Bu	lk Solution Homoge	neity Process Param	neters			
Mixing Tank 1	Mixing Temp	erature	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		
		Bu	lk Solution Homoger	neity In-Process Cor	ntrols			
Appearance at 45°C								
ID by HPLC	Retention time	e corresp	onds to standard					
ID by UV	Spectrum mat	ches star	ndard					
pН	5.0-7.0							
Assay	90.0% - 110.0	1%						
Ethanol Content	90.0% - 110.0	0%						
			Primary Packaging	Process Parameter	·s			
	Crimp Depth		0.190" – 0.200"	0.190" – 0.200"	0.190" – 0.200"	To ensure good		
Crimping	Crimp Diameter		1.065" – 1.075"	1.065" – 1.075"	1.065" – 1.075"	packaging integrity		
	Crimp Vacuum		NLT 15 inHg	NLT 15 inHg	NLT 15 inHg	To ensure vacuum is created in cans		
	Concentrate	50g	$50.5 \pm 0.5 \text{ g}$	$50.5 \pm 0.5 \text{ g}$	$50.5 \pm 0.5 \text{ g}$	To ensure		
Concentrate Filling	fill weight	100g	$100.5 \pm 0.5 \text{ g}$	$100.5 \pm 0.5 \text{ g}$	$100.5 \pm 0.5 \text{ g}$	minimum fill and delivery amount are met		
	Propellent	50g	$2.66 \pm 0.2g$	$2.66 \pm 0.2g$	$2.66 \pm 0.2g$	To ensure		
Gassing	fill weight	100g	$5.29 \pm 0.2g$	$5.29 \pm 0.2g$	$5.29 \pm 0.2g$	product delivery rate and pressure are met		

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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 state every 60 min	ion	0.190" – 0.200"					
Crimp Diameter	1 can per state every 60 min	ion	1.065" – 1.075"					
Crimp Vacuum	1 can per state every 60 min	ion	NLT 15 inHg					
Leak can and valve	100% of the 1	ınits	No formation of a constant stream of bubbles from the can when submerged in the heat tank					
Pressure	1 can per state every 30 min	ion	50 – 75 psi					
Extrusion	100% of the	50 g	NLT 50 g					
	units	100g	NLT 100 g					
Concentrate	1 can per	50g	$50.5 \pm 0.5 \text{ g}$					
fill weight	station every 60 min	100g	$100.5 \pm 0.5 \text{ g}$					
Propellent	1 can per	50g	$2.66 \pm 0.2g$					
fill weight	station every 60 min	100g	5.29 ± 0.2 g					
Product total weight	100% Cans	50g	(52.46g + low end of packaging componer	of packaging component weight)	ent weight) - (53.88g	+ high end of		
	an anatin a nan aa f	100g	packaging compone	of packaging component weight)		9g + high end of		

^{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%

T4	S	Results		
Test	Specifications	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	
рН	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%	