AUCTA PHARMACEUTICALS

Improve Delivery Better Medicine

CLOBETASOL PROPIONATE FOAM 0.05%

FOR TOPICAL USE

QUALITY BY DESIGN DEVELOPMENT REPORT

AUCTAPHARMA APPROVAL

NAME	TITLE & FUNCTION	SIGNATURE	DATE
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1.1 Executive Summary

This pharmaceutical development report summarizes the development of Clobetasol Propionate Foam, 0.05%, a generic version of the reference listed drug (RLD), Olux® Clobetasol Propionate foam, 0.05%. The RLD is a solution for aerosolization, indicated for treatment of moderate to severe plaque psoriasis of the scalp and mild to moderate plaque psoriasis of non-scalp regions of the body excluding the face and intertriginous areas in patients 12 years and older. Applicant, Aucta Pharmaceuticals Inc. utilized the Quality by Design (QbD) approach to develop generic Clobetasol Propionate Foam that is pharmaceutically equivalent to the RLD.

Initially, the quality target product profile (QTPP) was defined based on the properties of the drug substance, characterization of the RLD, and consideration of the RLD label and intended patient population. Identification of critical quality attributes (CQAs) was based on the severity of harm to a patient (safety and efficacy) resulting from failure to meet that quality attribute of the drug product. Our investigation during pharmaceutical development focused on those CQAs that could be impacted by a realistic change to the drug product formulation or manufacturing process. For Aucta's Generic Clobetasol Propionate Foam, these CQAs included assay, related substance, pH, delivery rate and ethanol content.

Risk assessment was used throughout the development to identify potentially high or medium risk formulation and process variables and to determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated after development to capture the reduced level of risk based on our improved product and process understanding.

For formulation development, solubility study was conducted on Clobetasol Propionate drug substance in alcohol at ambient temperature, and drug substance has sufficient solubility in alcohol. The same types and grades of excipients as the RLD product were chosen. Excipient binary mixture compatibility studies identified no potential interaction between drug substance and excipients.

The following formulation development studies were conducted. The first experiment investigated the impact of drug product chemical stability while using propylene glycol from different suppliers. The study showed that propylene glycol source had no significant impact on drug product impurities. The second experiment studied the level of citric acid and potassium citrate on drug product CQAs. The formulation composition was finalized based on the knowledge gained from these two formulation studies, and the formulation was recommended

for Waiver option by the agency, as described in the draft guidance on Clobetasol Propionate by Office of Generic Drugs (OGD) through Q1 and Q2 assessment.

For the foam solution manufacturing process, mixing temperature in the tank was identified as critical process parameter (CPP) and acceptable range was identified through the process development phase. Within the temperature range, the drug product was a clear homogeneous solution with no significant generation of degradation products. During the primary packaging process, the propellant fill weight, vacuum crimping, crimping diameter and crimping depth were identified as CPPs, and acceptable ranges were identified during process development. Within the range, the drug product achieved similar delivery rate, pressure, and foam appearance with the RLD, and no leak was observed.

Scale-up principles and plans were discussed for scaling up from lab (0.1-12.0 kg) to pilot scale (150.0 kg) and then proposed for commercial scale (500.0 kg). Three 150.0 kg cGMP exhibit batches were manufactured at pilot scale and demonstrated bioequivalence in the performance studies indicated in the drug specific guidance. The operating ranges for identified CPPs at commercial scale were proposed and will be validated and continually verified during routine commercial manufacture.

Finally, we proposed a control strategy that includes the material attributes and process parameters identified as potentially high or medium risk variables during the initial risk assessments. Our control strategy also includes in-process controls and finished product specifications. The process will be monitored during the lifecycle of the product and additional knowledge gained will be utilized to make adjustments to the control strategy as appropriate.

1.2 Analysis of the Reference Listed Drug Product

The reference listed drug (RLD) is OLUX (Clobetasol Propionate) Foam, 0.05% for topical use. OLUX (clobetasol propionate) Foam, 0.05% contains 0.5 mg of clobetasol propionate, USP per gram. OLUX Foam is a white thermolabile hydroethanolic aerosol foam. Each gram of OLUX Foam contains 0.5 mg clobetasol propionate, USP. The foam also contains cetyl alcohol, citric acid, ethanol, polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol pressurized with a hydrocarbon (propane/butane) propellant. OLUX Foam is supplied in two packaging configurations: 50 g aluminum can, and 100 g aluminum can. OLUX Foam is a corticosteroid indicated for treatment of moderate to severe plaque psoriasis of the scalp and mild to moderate plaque psoriasis of non-scalp regions of the body excluding the face and intertriginous areas in patients 12 years and older.

OLUX Foam has pH around 6.13 under room temperature. The weight to volume ratio of OLUX Foam is around 0.082. The delivery rate of OLUX Foam is around 3.82 gram per second. The pressure measured from the valve of the OLUX Foam Can is around 64 psi. The foam discharged from can is hard to break under 30°C, which stays intact over 30 minutes, but the foam breaks quickly at temperature above 33°C.

1.2.1 Clinical

The reference listed drug (RLD) is OLUX (Clobetasol Propionate) Foam, 0.05% for topical use. The RLD was approved in the United States in 2000, with NDA #021142 and is indicated for treatment of moderate to severe plaque psoriasis of the scalp and mild to moderate plaque psoriasis of non-scalp regions of the body excluding the face and intertriginous areas in patients 12 years and older. The foam contains active ingredient Clobetasol Propionate, which is a corticosteroid; however, the precise mechanism of action in corticosteroid-responsive dermatoses is unknow. OLUX Foam should be used twice daily, by applying a thin layer of foam to the affected skin areas. The treatment needs to be limited to 2 consecutive weeks, since OLUX foam is a super high potency topical corticosteroid. No great than 50 grams or 21 capfuls per week shall be used by patients, due to the potential for the drug to suppress the hypothalamic-pituitary-adrenal (HPA) axis. The label specified that patients should avoid use OLUX Foam on the face, groin, or axillae, or if skin atrophy is present at the treatment site.

1.2.2 Pharmacokinetics

Topical corticosteroids can be absorbed from intact healthy skin. The extent of percutaneous absorption of topical corticosteroids is determined by many factors, including the product formulation and the integrity of the epidermal barrier. Occlusion, inflammation, and/or other disease processes in the skin may also increase percutaneous absorption. Once absorbed through the skin, topical corticosteroids are metabolized, primarily in the liver, and are then excreted by the kidneys. Some corticosteroids and their metabolites are also excreted in the bile.

Based on OLUX Foam label, a controlled pharmacokinetic trial was performed using OLUX foam, and 5 of 13 subjects experienced reversible suppression of the adrenals at any time during the 14 days of therapy with OLUX Foam applied to at least 20% of involved body surface area. Of the 13 subjects studied, 1 of 9 with psoriasis was suppressed after 14 days and all 4 of the subjects with atopic dermatitis had abnormal cortisol levels indicative of adrenal suppression at some time after starting therapy with OLUX Foam.

1.2.3 Drug Release

Clobetasol Foam is available as a solution for aerosolization in the pressurized can, and the foam solutions do not contain any excipients that significantly affect drug absorption. Therefore, the efficacy of clobetasol foam shall be considered as self-evident. No in vivo testing is necessary.

Foam performance studies such as microscopic birefringence, time to break analysis under varying temperatures and weight per volume study for OLUX Foam (RLD) were evaluated. The microscopic birefringence test can rule out the presence of foreign matter or undissolved crystals in the bulk or final foam product. The foam quality could be characterized by weight per volume study of un-collapsed foam. The time to break analysis is used to confirm the thermolabile property of OLUX Foam. No crystals were observed in collapsed RLD foam as illustrated in **Figure 1**, and the dispensed RLD foam collapsed rapidly once temperature reaches 33°C or above, as indicated in **Figure 2**. The weight per volume of un-collapsed RLD foam is around 0.082.

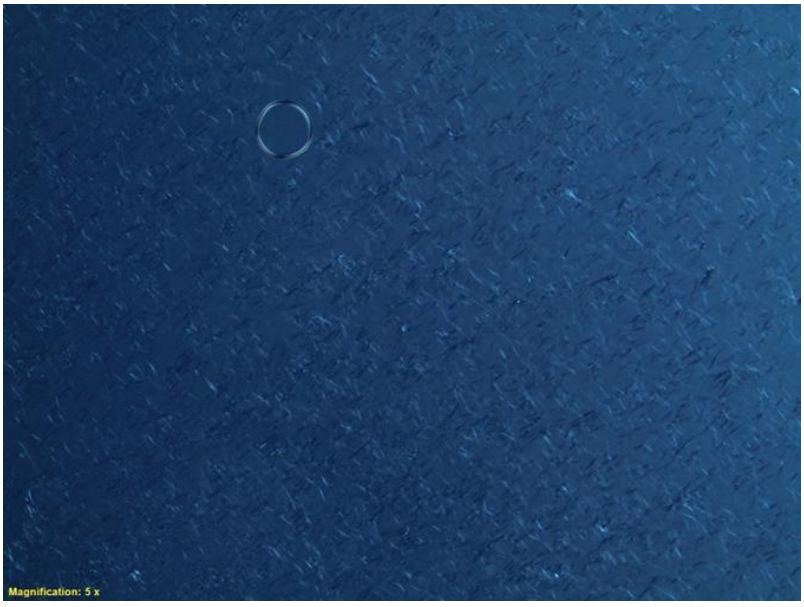

Figure 1 Microscopic birefringence snapshot for RLD

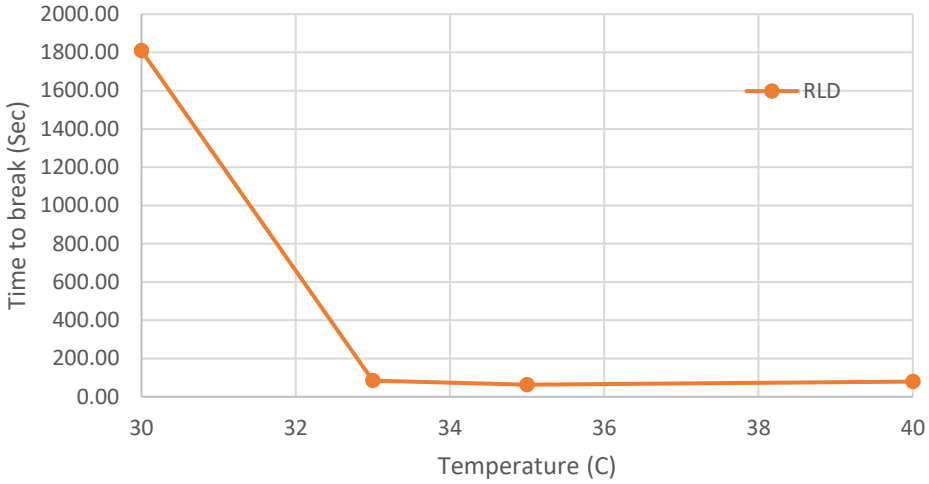

Figure 2 Time to break analysis for RLD under 30°C, 33°C, 35°C and 40°C

1.2.4 Physicochemical Characterization

The physicochemical characterization of OLUX foam is summarized in **Table 1**.

Table 1 Physicochemical Characterization of OLUX foam, 0.05%

Name of the product	OLUX® (Clobetasol Propionate) Foam 0.05%			
API	Clobetasol Propionate, USP			
Description	A white thermolabile hydroethanolic aerosol foam			
Strength	Each gram of OLUX Foam contains 0.5 mg clobetasol propionate, USP			
Batch No.	KNEB-2	MHDK	MDBK-4	NNEN-2
Expiry date	05/2019	02/2020	10/2019	05/2021
Birefringence	No birefringence/ crystal observed	No birefringence/ crystal observed	No birefringence/ crystal observed	No birefringence/ crystal observed
Foam weight to volume ratio	0.082	0.094	0.095	0.094
Time to break at 30°C	27m 22s	30m 3s	30m 16s	30m 02s
Time to break at 33°C	33s	1m 17s	1m 30s	1m 19s
Time to break at 35°C	25s	55s	56s	59s
Time to break at 40°C	46s	54s	67s	76s
pH	6.13			
Pressure	64 psi			
Discharge Rate	3.82 g/sec			
Assay (API)	100.3%			100.3%

Ethanol Content	60% of total drug product			
Total impurity at expiry		2.9%		

1.2.5 Composition

Based on the RLD labeling, public information, product features and reverse engineering, **Table 2** lists the composition of OLUX Foam, 0.05%. The reverse engineering report for the ingredients of clobetasol propionate foam, 0.05% could be referenced. The level provided for each excipient is consistent with previous experience and the IID level previously FDA-approved for topical aerosol foam dosage forms.

Table 2 Composition of OLUX Foam, 0.05%

Ingredient	**Function**	**Composition** (%w/w)	**IID Limit**
Clobetasol Propionate	Active	0.05	N/A
Cetyl Alcohol NF	Emulsifier, Foam Stabilizer	1.14	3.23%w/w
Stearyl Alcohol NF	Emulsifier, Foam Stabilizer	0.51	1%w/w
Polysorbate 60 NF	Emulsifier	0.41	0.43%w/w
Dehydrate Alcohol USP	Solvent	60.71	68.5%w/w
Purified Water USP	Solvent	34.88	N/A
Propylene Glycol USP	Solvent, Humectant	2.09	21.05%w/w
Citric Acid Anhydrous USP	Buffering Agent	0.08	0.11%w/w
Potassium Citrate USP	Buffering Agent	0.13	0.17%w/w
Total	N/A	100.0%	N/A
Propellant AP-70* (Butane/Propane)	Propellant	5.0 %	N/A

* The propellant is listed as an inactive ingredient; however, it does not have to be calculated in the composition of the formulation since it evaporates immediately upon dispense. Nonetheless, the MDE is calculated under the worst-case scenario to demonstrate that Aucta's generic product is safe. The components of the propellant are listed in the GRAS list, the composition specification sheet and the manufacturer document for GRAS and Residual Solvents statements are provided in 3.2.P.4.4 Propellant AP-70.The RLD foam container is pressurized with about 5% (w/w) of propellant for different sized container. For Aucta's generic 50g cans, the target propellant fill weight is 2.66 g, and for 100 g packaging configuration, the target propellant fill weight is 5.29 g.

1.3 Quality Target Product Profile for the ANDA Product

Based on the clinical and pharmacokinetic characteristics of OLUX Foam given in the product label as well as the physicochemical characteristics of the branded drug, a QTPP was defined and

justified as shown in **Table 3** to guide the development of Aucta's generic Clobetasol Propionate Foam that are therapeutically equivalent to the RLD.

Table 3 Quality Target Product Profile for Aucta's Clobetasol Propionate Foam, 0.05%

QTPP Elements		**Target**	**Justification**
Dosage form		Aerosol, Foam	Pharmaceutical equivalent requirement
Dosage design		Foam	Match RLD
Route of administration		Topical (applied to scalp)	Pharmaceutical equivalent requirement
Dosage strength		0.05% w/w	Pharmaceutical equivalent requirement
Stability		At least 24-month shelf-life at 20°C to 25℃ storage condition	Equivalent or better than the shelf life of RLD
Drug product quality attributes	Appearance/Packaging Inspection	Pharmaceutical equivalence requirement: Must meet applictable USP general chapters and hold similar physicochemical properties.	
	Product/Packaging Interaction		
	Identification		
	Assay		
	Related Substances by HPLC		
	pH		
	Minimum Fill		
	Microbial limits		
	Ethanol Content		
	Residual Solvents		
	Delivery Rate		
	Delivery Amount		
	Pressure test		
	Leakage test		
Container closure system		Aluminum can with valve and actuator; Identical or similar to primary packaging to RLD	Needed to achieve target shelf-life, to ensure dosage form integrity and to comply with the method of dosage administration.
Administration		Applied a thin layer of foam to affected skin twice daily.	Labeling indicates dosage form given topically for local therapeutic effects, no significant systemic effects
Alternative methods of administration		None	None

Table 4 summarizes the quality attributes of generic clobetasol foam and indicates which attributes were classified as drug product critical quality attributes (CQAs). For this product, assay, related substance, pH, leakage test, ethanol content, and delivery rate are identified as the subset of CQAs that have the potential to be impacted by the formulation and/or process variables and, therefore, will be investigated and discussed in detail in subsequent formulation and process development studies.

On the other hand, CQAs including identification, packaging inspection, residual solvents and microbial limits which are unlikely to be impacted by formulation and/or process variables will not be discussed in detail in the pharmaceutical development report. However, these CQAs are still target elements of the QTPP and are ensured through a good pharmaceutical quality system and the control strategy.

Table 4 Critical Quality Attributes (CQAs) of Generic Clobetasol Propionate Foam, 0.05%

Quality Attributes of Drug Product	Target	Is this a CQA	Justification
Appearance	A white to off white colored foam when dispensed from the can.	No	Description, color and appearance of the product are not directly linked to safety and efficacy. Therefore, it is not critical. The target is set to ensure patient acceptability.
Packaging Inspection	A white aluminum can, white actuator attached to can with a transparent cap and no visible traces of the product (leakage) on the outside of either actuator or can.	Yes*	Leakage may affect related substance, delivered amount, delivered rate, and pressure of the drug product. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Product/Packaging Interaction	No visual evidence of corrosion shall be observed at the valve/can	No	The degree of concern for product/packaging interaction is low because the target dosage form is topical aerosol foam, and the dosing period is not chronic. The packaging extractable study will be used to verify the product packaging interactions.
Identification	The retention time of the major peak of the sample solution corresponds to that of the standard solution as obtained in the assay, and the UV spectrum matches that of standard.	Yes*	Though identification is critical for safety and efficacy, this CQA can be effectively controlled by the quality management system and will be monitored at drug release. Formulation and process variables do not impact identity. Therefore, this CQA will not be discussed during formulation and process development.
Assay	90.0-110.0% label claim	Yes	Assay variability will affect safety and efficacy. Process variable may affect the assay of the drug product.
Minimum Fill	USP <755> The net weight of the contents of each of the 10 containers shall be NLT the labeled amount	No	Minimum fill is not directly linked to safety and efficacy. It will be controlled by Quality Management System.
Related Substance	EP Impurity A (RRT 0.63): NMT 0.5%; EP Impurity B (RRT 0.74): NMT 0.5%; EP Impurity D (RRT 1.12): NMT 0.5%; EP Impurity J (RRT 1.05): NMT 0.5%; Unknown Impurity 1 (RRT 0.27): NMT 0.5%; Unknown Impurity 2 (RRT 0.37): NMT 0.5%; Unknown Impurity 3 (RRT 1.19): NMT 0.5%;	Yes	Related substance can impact product safety and must be controlled based on compendial/ICH requirement or RLD characterization to limit patient exposure. Formulation and process variables may affect the impurities and degradation products.

	Any Unspecified Impurity: NMT 0.5%; Total Impurities: NMT 3.0%		
pH	5.0 - 7.0	Yes	Variability in pH will affect efficacy, safety. Formulation and process variables may affect the pH values of the finish products.
Delivery Rate	NLT 3.5 g/sec	Yes	Delivery rate is directly linked to safety and efficacy.
Delivery Amount	USP <603> NLT the labeled amount	No	Delivery amount is not directly linked to safety and efficacy
Microbial limits	USP <61>, <62>; USP <1111> TAMC: NMT 200; TYMC: NMT 20; Pseudomonas aeruginosa: Absent; Staphylococcus aureus: Absent; Escherichia coli: Absent; Salmonella species: Absent	Yes*	Non-compliance with microbial limits will impact safety. However, in this case, the risk of microbial growth is low due to high alcohol content of the formulation. This CQA will be monitored at drug release, Therefore, this CQA will not be discussed in detail during formulation and process development.
Pressure Test	50-75 psi	No	Pressure test is not directly linked to safety and efficacy.
Leakage Test	Meet Current USP <604> Leak Rate	Yes*	Leakage will affect related substance, delivered amount, delivered rate, and pressure of the drug product. Formulation and process variables do not impact this quality attribute. Therefore, this CQA will not be discussed during formulation and process development.
Ethanol Content	90.0 – 110.0% of target ethanol amount	Yes	Ethanol content can affect safety and efficacy by affect raw material solubility. The formulation and process variables may affect the ethanol content of the final product.
Residual Solvent	Complies with USP <467> option 2	Yes*	Residual Solvents will impact patient safety and efficacy. Formulation and process variables do not impact this quality attribute. Therefore, this CQA will not be discussed during formulation and process development.
Elemental Impurity	Complies with USP <232> and ICH Q3D	Yes*	Elemental Impurities will impact patient safety and efficacy. Formulation and process variables do not impact this quality attribute. Therefore, this CQA will not be discussed during formulation and process development.

*Formulation and process variables are unlikely to impact the CQA. Therefore, the CQA will not be investigated and discussed in detail in subsequent risk assessment and pharmaceutical development. However, the CQA remains a target element of the drug product profile and should be addressed accordingly.

1.4 Dissolution Method Development and Pilot Bioequivalence Studies

1.4.1 Dissolution Method Development

This section is not applicable. Clobetasol Foam is a solution-based product under pressure for topical application, and all ingredients are in solubilized form. Also, the solutions do not contain any excipients that significantly affect drug absorption. Therefore, the pharmaceutical and bioequivalence of clobetasol foam shall be considered as self-evident since Aucta's generic formulation is qualitatively and quantitatively equivalent to the reference listed drug product. No dissolution test is necessary.

1.4.2 Waiver of Bioequivalence Study

Based on the Product-Specific Guidance for clobetasol propionate foam, 0.05%, Aucta's clobetasol propionate foam, 0.05% qualifies for a waiver of the in vivo bioequivalence (BE) study requirements under 21 CFR 320.22(b)(3). Aucta's generic Clobetasol Propionate Aerosol, Foam/Topical, 0.05% is a solution for aerosolization, and has the same active ingredient in the same concentration and dosage form as the reference listed drug product (RLD). Aucta's generic clobetasol propionate foam, 0.05% do not have inactive ingredient or other change in formulation from the RLD that may significantly affect systemic or local availability. The request for clobetasol propionate foam Q1Q2 formulation assessment (Control Correspondence # 15457592) was submitted to agency. The correspondence from Agency indicated that OGD recommended I. Waiver option described in the draft guidance on Clobetasol Propionate with one of the proposed formulations.

To support the waiver request, data from the following comparative in vitro studies of test vs. reference were performed on 3 different lots of the RLD and 3 lots of the test product (with each lot manufactured separately):

- Microscopic Birefringence Analysis on the dispensed foam after complete collapse to determine whether any crystals of undissolved clobetasol propionate form during dispensing.
- Time to Break Analysis, conducted at 30ºC, 33ºC, 35ºC, and 40ºC. Time to break is the time from dispensing to complete foam collapse (break).
- Weight per volume of un-collapsed foam.

This study was performed with Aucta Clobetasol Propionate Foam 0.05% 32595 (50g), 31982 (100 g) and 32598 (100g) selected from the available lots and the RLD OLUX (Clobetasol Propionate) Foam 0.05% MHDK (50g), MDBK-4 (100g) and NNEN-2 (100g). Ten canisters of products of each lot were tested.

Microscopic Birefringence Analysis

Method 100-3-088 Microscopic Birefringence was used to test for the RLD and Aucta's generic foam. The detailed method could be reviewed in the BE waiver report in Module 3.2.P.2 Microscopic Birefringence, Time to Break and Weight per Volume Summary Report. The results

for Aucta's clobetasol propionate foam 0.05% was listed in **Table 5**, and the results for reference product OLUX foam, 0.05% was listed in **Table 6**. No birefringence or crystals were observed for both Aucta's products and RLD products.

Table 5 Summary of Birefringence Results for Aucta Clobetasol Propionate Foam 0.05%

Lot – Can #	Acceptance Criteria	Specificity	Precision (Analyst 1)	Intermediate Precision (Analyst 2)
API seeded sample	Birefringence observed in collapsed foam seeded with API crystals	Birefringence observed		
32595_50g	No birefringence/crystals observed for unseeded sample (Conforms)		Conforms	Conforms
31982_100g	No birefringence/crystals observed for unseeded sample (Conforms)		Conforms	Conforms
32598_100g	No birefringence/crystals observed for unseeded sample (Conforms)		Conforms	Conforms

Table 6 Summary of Birefringence Results for RLD Clobetasol Propionate Foam 0.05%

Lot – Can #	Acceptance Criteria	Specificity	Precision (Analyst 1)	Intermediate Precision (Analyst 2)
API seeded sample	Birefringence observed in collapsed foam seeded with API crystals	Birefringence observed		
MHDK – 1	No birefringence/crystals observed for unseeded sample (Conforms)		Conforms	Conforms
MDBK-4 – 1	No birefringence/crystals observed for unseeded sample (Conforms)		Conforms	Conforms
NNEN-2– 1	No birefringence/crystals observed for unseeded sample (Conforms)		Conforms	Conforms

Time to Break Analysis

Method 100-3-089 Time to break analysis under 30°C, 33°C, 35°C and 40°C was used to test for the RLD and Aucta's generic foam. The detailed method could be reviewed in the BE waiver report in Module 3.2.P.2 Microscopic Birefringence, Time to Break and Weight per Volume Summary Report. The average results for Aucta's clobetasol propionate foam 0.05% and RLD was listed in **Table 7**. **Figure 3** illustrated the time to break results for all tested lots performed by both Analysts. Comparable results between RLD and Aucta's clobetasol foam were indicated under all temperature conditions. Time to Break study demonstrated that both RLD and Aucta foam products would not break at 30℃ up to 30 minutes, however, the products would break around 1 minutes at 33, 35 and 40℃ which are higher than skin temperature.

Table 7 Averages of Time to Break Results for RLD and Aucta's Clobetasol Propionate Foam 0.05%

Lot	Acceptance Criteria	30°C		33°C		35°C		40°C	
		Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2	Analyst 1	Analyst 2
32595_50g	Average results obtained at each temperature are comparable between analysts.	30m 05s	30m 03s	1m 06s	1m 19s	1m 08s	0m 45s	1m 01s	0m 35s
31982_100g		30m 11s	30m 13s	1m 30s	1m 17s	1m 06s	0m 50s	1m 04s	0m 43s
32598_100g		30m 40s	30m 11s	1m 32s	1m 26s	1m 05s	0m 52s	1m 21s	0m 45s
MHDK		29m 59s	30m 04s	1m 18s	1m 15s	1m 06s	0m 43s	1m 11s	0m 36s
MDBK-4		30m 12s	30m 19s	1m 31s	1m 28s	1m 02s	0m 50s	1m 22s	0m 51s
NNEN-2		30m 02s	30m 01s	1m 26s	1m 12s	1m 09s	0m 48s	1m 25s	1m 06s

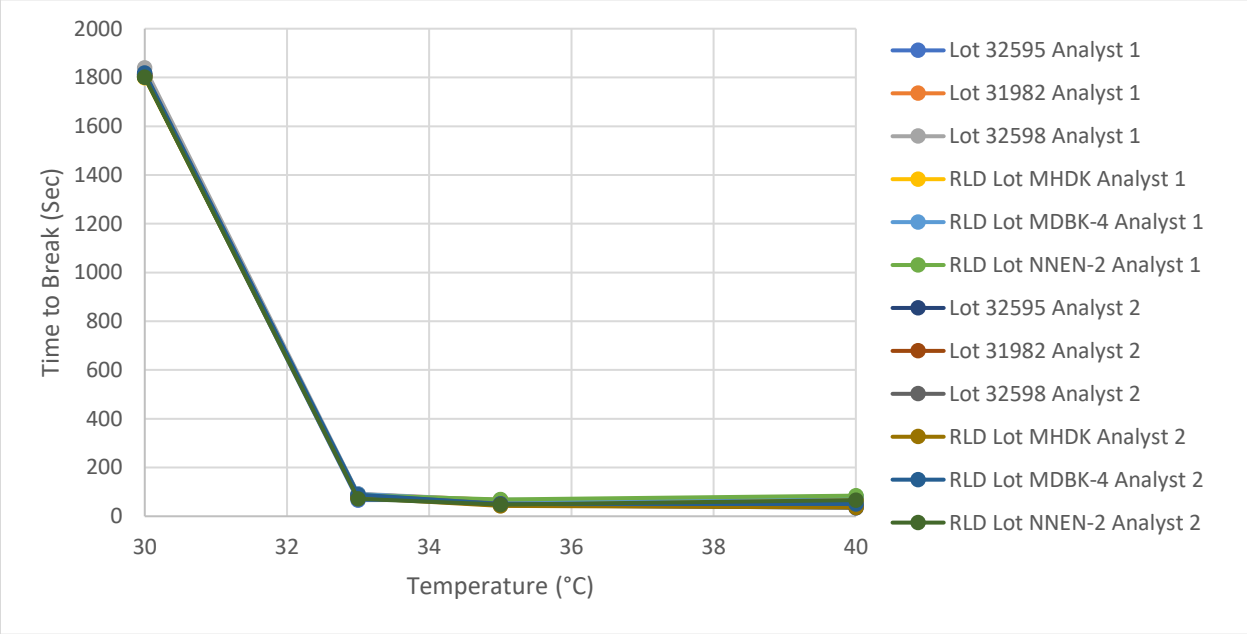

Figure 3 Time to break analysis results under 30°C, 33°C, 35°C and 40°C

Weight per Volume of uncollapsed Foam

Weight per Volume of un-collapsed Foam (Method 100-3-212) was used to test for the RLD and Aucta's generic foam. The detailed method could be reviewed in the BE waver report in Module 3.2.P.2 Microscopic Birefringence, Time to Break and Weight per Volume Summary Report. The average results regard to weight per volume ratio for RLD and Aucta's clobetasol propionate foam 0.05% was listed in **Table 8**. Comparable results between RLD and Aucta's clobetasol foam were indicated for all products.

Table 8 Averages of Weight Per Volume Results for RLD and Aucta Clobetasol Propionate Foam 0.05%

Lot	Acceptance Criteri`1a	25°C	
		Precision (Analyst 1)	Intermediate Precision (Analyst 2)
32595_50g	Average results obtained at each temperature are comparable between analysts.	0.0894	0.0687
31982_100g		0.0937	0.0653
32598_100g		0.0969	0.0771
MHDK		0.1005	0.0878

MDBK-4		0.1006	0.0902
NNEN-2		0.0975	0.0902

Based on the data from Microscopic Birefringence Analysis, Time to Break Analysis, and Weight per volume test, the performance of Aucta's Clobetasol Propionate Foam 0.05% is comparative to that of the RLD OLUX^{TM} Clobetasol Propionate Foam 0.05%. Aucta's clobetasol propionate foam, 0.05% shall be qualified for a waiver of the in vivo bioequivalence (BE) study requirements under 21 CFR 320.22(b)(3).

2.1 Components of Drug Product

2.1.1 Drug Substance

Clobetasol Propionate drug substance manufactured by Symbiotec Pharmalab Private Limited was used throughout the studies. The drug substance manufacturer's FDA establishment identifier number is 3005122933, and the cGMP statement is available.

2.1.1.1 Physical Properties

Physical description:
Appearance: White to cream, crystalline powder

Particle Size:
Tested by Malvern using dry method:
d90 – NMT 10µm
d99 – NMT 20µm

Solid State Form:
Clobetasol Propionate is a salt form of the drug substance. Polymorphism was not observed in the case of Clobetasol propionate manufactured by Symbiotec Pharmalab Private Limited. The confirmatory test, comparing the XRD histogram with USP reference standard is essentially similar, conclusively proved that the Clobetasol propionate produced by Symbiotec shows single crystalline isomorphic form.

Melting range: 194°C to 200°C

Specific Rotation: Between +98° to 104°, calculated on the dried basis

Solubility:
Water: Practically insoluble
Benzene and Diethyl Ether: Slightly soluble
Ethanol: Sparingly soluble
Acetone, Dimethyl sulfoxide, Chloroform, Methanol, and Dioxane: Soluble

Hygroscopicity: Clobetasol propionate is non-hygroscopic in nature.

2.1.1.2 Chemical Properties

pKa: 12.88±0.70 (Condition: Most Acidic Temp: 25 °C)

Chemical stability in solid state and in solution:

The chemical stability in solid state and in solution was summarized in **Table 9**. A maximum of 20.50% degradation is observed when Clobetasol Propionate, USP is treated with 1M NaOH. When it was exposed oxidizing and reducing agent, the degradation is 16.18%. The drug substance chemical stability is robust under UV radiation, heat, and acidic conditions.

Table 9 Drug Substance Chemical Stability in Solid State and Solution

Conditions	Results	
	% Assay	Degradation %w/w
Untreated API	99.65	-
UV Radiation 254 nm 24 hours	98.30	1.35
Heat ~105°C 24 hours	98.05	1.60
1M NaOH 10 minutes at RT	79.16	20.50
1M HCl 30 min at 70°C	97.74	1.91
5% w/v H_2O_2 30 minutes at 50°C	83.48	16.18

2.1.1.3 Biological Properties

Partition coefficient: Log P 3.142±0.572

Biopharmaceutics Classification: BCS Class II

2.1.1.4 Risk assessment of Drug Substance Attributes

A risk assessment of the drug substance attributes was performed to evaluate the impact that each attribute could have on the drug product CQAs. The outcome of the assessment (**Table 11**) and the accompanying justification **(Table 12)** is provided as a summary in the pharmaceutical development report. The relative risk that each attribute presents was ranked as high, medium or low. The high risk attributes warranted further investigation whereas the low risk attributes required no further investigation. The medium risk is considered acceptable based on current knowledge. Further investigation for medium risk may be needed in order to reduce the risk. The same relative risk ranking system was used throughout pharmaceutical development and is summarized in **Table 10.**

Table 10 Overview of Relative Risk Ranking System

Low	Broadly acceptable risk. No further investigation is needed.
Medium	Risk is acceptable. Further investigation may be needed in order to reduce the risk.

High	Risk is unacceptable. Further investigation is needed to reduce the risk.

Table 11 Initial risk assessment of the drug substance attributes

Drug Substance Attributes	Drug Product CQA				
	Assay	**Related Substance**	**pH**	**Delivery Rate**	**Ethanol Content**
Description	Low	Low	Low	Low	Low
Solubility	Medium	Low	Low	Low	Low
Identification	Low	Low	Low	Low	Low
Melting Range	Low	Low	Low	Low	Low
Optical Rotation	Low	Low	Low	Low	Low
Loss on drying	Low	Low	Low	Low	Low
Residual solvents	Low	Low	Low	Low	Low
Assay	Medium	Low	Low	Low	Low
Drug substance PSD	Low	Low	Low	Low	Low
Hygroscopicity	Low	Low	Low	Low	Low
Related substances	Low	Medium	Low	Low	Low
Chemical stability	Low	Low	Low	Low	Low

Table 12 Justification for Initial risk assessment of drug substance attributes

Drug Substance Attributes	Drug Products CQAs	Justification
Description	Assay	API description will not affect drug product assay, related substance, pH, delivery rate and ethanol content. The risk is low.
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
Solubility	Assay	Sufficient solvent is necessary to fully dissolve the drug substance. The formulation and manufacturing process will be designed to mitigate this risk. The risk is medium
	Related Substance	Solubility does not affect related substance, pH, delivery rate and ethanol content of the product. Thus, the risk is low.
	pH	
	Delivery Rate	
	Ethanol Content	
Identification	Assay	
	Related Substance	

	pH	Drug substance identification will be controlled by IR. The drug substance ID does not affect drug product assay, related substance, pH, delivery rate and ethanol content. The risk is low.
	Delivery Rate	
	Ethanol Content	
Melting Range	Assay	Melting range is controlled in drug substance specification (between 194°C - 200°C). Melting range will not affect drug product assay, related substance, pH, delivery rate and ethanol content. The risk is low.
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
Optical Rotation	Assay	Optical rotation is controlled in drug substance specification (between +98° and +104°). Optical rotation will not affect drug product assay, related substance, pH, delivery rate and ethanol content. The risk is low.
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
Loss on drying	Assay	Loss on drying is controlled in the drug substance specification (NMT 2.0%w/w) and the drug substance is not hygroscopic. Thus, it is unlikely to impact assay, related substance, pH, delivery rate and ethanol content. The risk is low.
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
Assay	Assay	The drug substance assay is closely related to drug product assay. The API assay is controlled in drug substance specification (97.0%-102.0%). The risk is medium.
	Related Substance	The drug substance assay will not affect drug product related substance, pH, delivery rate and ethanol content. The risk is low.
	pH	
	Delivery Rate	
	Ethanol Content	
Drug substance PSD	Assay	The drug substance is easily dissolved in Alcohol phase. Therefore, the API PSD will not affect drug product assay, related substance, pH, delivery rate and ethanol content. The risk is low
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
Hygroscopicity	Assay	Clobetasol Propionate is not hygroscopic. The risk is low.
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
	Assay	Total degradation products are controlled in the drug substance specification. API impurity limits comply with compendial

Related Substance		recommendations. Within this range, related substance is unlikely to impact assay.
	Related Substance	The API related substance is controlled in drug substance specification. The drug substance related substance level can affect drug product related substance level. The risk is medium
	pH	Total degradation products are controlled in the drug substance specification. API impurity limits comply with compendial recommendations. Within this range, related substance is unlikely to impact pH, delivery rate and ethanol content. The risk is low.
	Delivery Rate	
	Ethanol Content	
Residual solvents	Assay	Residual solvents are controlled in the drug substance specification and comply with USP <467>. At ppm level, residual solvents are unlikely to impact assay, related substance, pH, delivery rate and ethanol content. The risk is low.
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	
Chemical stability	Assay	Since drug substance is stable in the solid state based on the drug substance stability data, the chemical stability is unlikely to impact drug product assay, related substance, pH, Delivery Rate and Ethanol content. Thus, the risk is low. .
	Related Substance	
	pH	
	Delivery Rate	
	Ethanol Content	

2.1.2 Excipients

The excipients used in clobetasol foam were selected based on the excipients used in the RLD and excipient compatibility studies. A summary of the excipient-drug substance compatibility studies and the selection of each excipient grade are provided in the following section.

2.1.2.1 Excipient selection by compatibility studies

Based on the reversed engineering and RLD label, the RLD contains 0.5 mg clobetasol propionate, USP in every gram of OLUX (clobetasol propionate) Foam, 0.05%. The foam also contains cetyl alcohol, citric acid, ethanol, polysorbate 60, potassium citrate, propylene glycol, purified water, and stearyl alcohol pressurized with a hydrocarbon (propane/butane) propellant. Different source of properly glycol were evaluated in Section 2.2.1.4 Formulation Development Study #1 Effect of Propylene glycol on impurities and related substances.

Excipient-drug substance compatibility was assessed through HPLC analysis of binary mixtures of excipient and drug substance at the proposed formulation ratio, except for water and alcohol. Due to high percentage of alcohol in the purposed formulation, a 1 to 1 ratio between alcohol and drug substance was evaluated. The drug substance compatibility in water was demonstrated in 2.1.1.2 drug substance chemical stability section. Samples were stored at 40 °C/75 % RH in closed containers for up to 1 month. **Table 13** summarizes the results of the study.

Table 13 Excipient compatibility (binary mixtures, Excipient to API ratio based on formulation)

Mixture	Total Impurities (%) Initial	Total Impurities (%) 40 ºC/ RH 75%, 14 days (%w/w)	Total Impurities (%) 40 ºC/ RH 75%, 30 days (%w/w)
Clobetasol Propionate/DS (1:1)	1.66	1.92	2.12
Cetyl Alcohol/ DS (1:22.8)	1.50	1.51	1.69
Stearyl Alcohol/ DS (1:10.2)	1.81	1.46	1.33
Polysorbate 60/ DS (1:8.2)	1.95	1.78	1.84
Dehydrate Alcohol/ DS (1:1)	2.26	1.86	1.94
Propylene Glycol/ DS (1:41.8)	3.34	2.31	2.26
Citric Acid Anhydrous/ DS (1:1.6)	1.89	0.74	1.61
Potassium Citrate/ DS (1:2.6)	2.65	2.24	1.67

Significant growth of impurities was not observed in the compatibility study, indicating that an incompatibility was not observed for the selected excipients. Subsequent assurance of compatibility was provided by registration batch stability studies using the formulation proposed for commercialization.

2.1.2.2 Excipient Grade Selection

Based on the results of excipient compatibility studies, identical excipient types to the RLD formulation were selected for the generic product development. The selection of excipient grade and supplier was based on previous formulation experience of topical dosage forms as given in **Table 14**. All excipients are of USP/NF grade if available. The level of excipients used in the formulation were studied in subsequent formulation development studies.

Table 14 Initial selection of excipient type, grade, and supplier

Excipient	Grade	Other Name	Supplier
Cetyl Alcohol	NF	Kolliwax® CA	BASF
Stearyl Alcohol	NF	Kolliwax® SA	BASF
Polysorbate 60	NF	Kolliphor® PS 60	BASF
Dehydrate Alcohol	USP	Ethyl Alcohol 200 Proof, Absolute	PHARMACO-AAPER
Propylene Glycol	USP	Kollisolv® PG	BASF
Purified Water	USP	None	Pharmasol DI Water System
Citric Acid Anhydrous	USP	None	Jungbunzlauer Inc.
Potassium Citrate monohydrate, Granular	USP	None	Penta Manufacturing Company

Propellant AP-70	Released using Specification # RM-43070	Blend of *iso*-butane, propane, and *n*-butane	Aeropres Corporation

Cetyl Alcohol: Cetyl alcohol is commonly used as an emulsifier in topical dosage forms, and act as a foam stabilizer in foam formulation. It is able to dissolve in alcohol under room temperature. Increasing alcohol temperature could expedite the dissolving process. Cetyl alcohol USP from BASF was selected since it is compatible with clobetasol drug substance.

Stearyl Alcohol: Stearyl Alcohol is also commonly used as an emulsifier and foam stabilizer for aerosol foam dosage form. It is able to dissolve in alcohol under room temperature. Increasing alcohol temperature could expedite the dissolving process. Stearyl alcohol NF from BASF was selected since it is compatible with clobetasol drug substance.

Polysorbate 60: Polysorbate 60 is a common emulsifier in topical dosage forms. Polysorbate 60 NF from BASF was selected based on previous excipient compatibility study results.

Dehydrate Alcohol: Dehydrate alcohol is one of the most commonly used solvent. It is also used with purified water as the vehicle for the foam formulation. Alcohol and water vehicle comprise about 95% of the total product composition, providing good API solubility. Dehydrate alcohol with USP grade from Pharmaco-Aaper was selected based on compatible results with the drug substance.

Propylene Glycol: Propylene glycol is a commonly used solvent, and it could also be used as a humectant. Propylene glycol from different source was evaluated in the formulation development studies. Propylene glycol with USP grade from BASF was selected due to least impurity growth in formulations.

Purified Water: Purified water is commonly used as a solvent. It is also often to be used with alcohol as vehicle for topical dosage form. The purified water is supplied in house by the manufacture (Pharmasol)'s DI water system. The purified water is controlled by Pharmasol, and it is USP grade.

Citric Acid Anhydrous: Citric acid is a common buffering agent. It is combined with citric acid to form a buffer system and stabilize drug product pH. The Citric acid anhydrous with USP grade supplied by Jungbunzlauer Inc. was selected.

Potassium Citrate Monohydrate: Potassium Citrate Monohydrate is used as a buffering agent in foam formulation. It is combined with citric acid to form a buffer system, and stabilize drug product pH. The USP grade of potassium citrate monohydrate from supplier Penta Manufacturing Company was selected.

Propellant AP-70: Propellant AP-70 is used to pressurize the cannister and assist aerosolization of the foam solution. The propellant AP-70 is a blend of iso-butane, propane, and n-butane. The AP-70 was controlled by Manufacturer's specification number RM-43070. Aeropres Corporation is the supplier for propellant AP-70.

2.1.2.3 Composition of Aucta's Clobetasol Foam, 0.05%

The composition of Aucta's Clobetasol Foam is listed in

Table 15 for both 50 gram and 100 gram packaging configurations.

Table 15 Composition of Aucta's Generic Clobetasol Propionate Foam, 0.05% with 50g and 100g configuration

Ingredient	Function	Bulk Composition (%w/w)	50 g can composition (g)	100g can composition (g)	IID Limit (%w/w)	Complies (Yes/No)
Clobetasol Propionate, USP	Active	0.05	0.025	0.05		
Cetyl Alcohol, NF	Emulsifier, Foam Stabilizer	1.14	0.57	1.14	3.23	Yes
Stearyl Alcohol, NF	Emulsifier, Foam Stabilizer	0.51	0.255	0.51	1	Yes
Polysorbate 60, NF	Emulsifier	0.41	0.205	0.41	0.43	Yes
Dehydrate Alcohol, USP	Solvent	60.71	30.355	60.71	68.5	Yes
Purified Water, USP	Solvent	34.88	17.44	34.88		
Propylene Glycol, USP	Solvent, Humectant	2.09	1.045	2.09	21.05	Yes
Citric Acid Anhydrous Powder, USP	Buffering Agent	0.08	0.04	0.08	0.11	Yes
Potassium Citrate Monohydrate Granular, USP	Buffering Agent	0.13	0.065	0.13	0.17	Yes
Total		100.0	50.0	100.0		
Propellant AP-70	Propellant	5.29*	2.66*	5.29*		

* The propellant is listed as an inactive ingredient; however, it does not have to be calculated in the composition of the formulation since it evaporates immediately upon dispense. Nonetheless, the MDE is calculated under the worst-case scenario to demonstrate that Aucta's generic product is safe. The components of the propellant are listed in the GRAS list, the composition specification sheet and the manufacturer document for GRAS and Residual Solvents statements are provided in 3.2.P.4.4 Propellant AP-70.

2.2 Drug Product

2.2.1 Formulation Development

The proposed generic formulation for OLUX foam 0.05%, was developed based upon the clinical, pharmacokinetic, and physicochemical characterization of the RLD product (Refer to Section 1.2), and the initial formulation strategy was defined and justified as follows:

- Perform initial risk assessment on all formulation variables and identify formulation variables with medium or high risks.
- Reduce the risk of propylene glycol introduced drug product impurities by testing

formulation chemical stabilities using propylene glycol from different suppliers.
- Reduce the risk of drug product initial pH by reverse engineering and verify the pH stability over time by monitoring product pH overtime.
- Update the initial risk assessment based on study results.

2.2.1.1 Initial Risk Assessment of Formulation Variables

Based upon the physicochemical and biological properties of the drug substance, the results of the initial risk assessment of the formulation variables are presented in **Table 16** and the justification for the risk assignment is presented in **Table 17**.

Table 16 Initial risk assessment of the formulation variables

Formulation Variables	Drug Product CQA				
	Assay	Related Substance	pH	Delivery Rate	Ethanol Content
Cetyl Alcohol	Low	Low	Low	Low	Low
Stearyl Alcohol	Low	Low	Low	Low	Low
Polysorbate 60	Low	Low	Low	Low	Low
Dehydrate Alcohol	Medium	Low	Low	Low	Low
Propylene Glycol	Low	Medium	Low	Low	Low
Purified Water	Low	Low	Low	Low	Low
Citric Acid	Low	Low	Medium	Low	Low
Potassium Citrate	Low	Low	Medium	Low	Low

Table 17 Justification for the initial risk assessment of the formulation variables

Drug Substance Attributes	Drug Products CQAs	Justification
Cetyl Alcohol	Assay	Cetyl alcohol is a commonly used emulsifier in topical products. The drug substance is compactable with cetyl alcohol. The level of cetyl alcohol is unlikely to impact assay, related substance, pH, delivery rate and ethanol content of the drug product. The risk is low.
	Related Substances	
	pH	
	Delivery Rate	
	Ethanol Content	
Stearyl Alcohol	Assay	Stearyl alcohol is a commonly used emulsifier in topical products. The drug substance is compactable with stearyl alcohol. The level of stearyl alcohol is unlikely to impact assay, related substance, pH, delivery rate and ethanol content of the drug product. The risk is low.
	Related Substances	
	pH	
	Delivery Rate	
	Ethanol Content	
Polysorbate 60	Assay	Polysorbate 60 is a commonly used surfactant in topical products. The drug substance is compactable with Polysorbate 60. The level of polysorbate 60 is unlikely to impact assay, related substance, pH,
	Related Substances	
	pH	

	Delivery Rate	delivery rate and ethanol content of the drug product. The risk is low.
	Ethanol Content	
Dehydrate Alcohol	Assay	Alcohol level needs to be sufficient to dissolve ingredients such as drug substance and form a clear solution. Thus, the risk is medium
	Related Substances	The level of dehydrate alcohol is unlikely to impact related substance, pH and delivery rate of the drug product. The risk is low.
	pH	
	Delivery Rate	
	Ethanol Content	The ethanol content will monitor the dehydrate alcohol level. The risk is low.
Propylene Glycol	Assay	The drug substance is compactable with propylene glycol. The propylene glycol level is unlikely to impact drug product assay. The risk is low.
	Related Substances	Impurities in Propylene glycol can potentially introduce drug product impurity growth. Propylene glycol USP from different source may contain distinct impurities, and consequently introduce drug product related substance. The risk is medium
	pH	The propylene glycol level is unlikely to impact pH and delivery rate of the drug product. The risk is low.
	Delivery Rate	
	Ethanol Content	The propylene glycol level is unlikely to impact the ethanol content of the drug product. The risk is low.
Citric Acid	Assay	The drug substance is compactable with citric acid, so the level of citrate acid is unlikely to impact assay of the drug product. The risk is low.
	Related Substances	
	pH	As a buffering agent, the level of citric acid can impact product pH and buffer capacity. Thus, the risk is medium.
	Delivery Rate	The level of citric acid is unlikely to impact delivery rate and ethanol content of the drug product. The risk is low.
	Ethanol Content	
Potassium Citrate	Assay	The drug substance is compactable with potassium citrate, so the level of potassium citrate is unlikely to impact assay of the drug product. The risk is low.
	Related Substances	
	pH	As a buffering agent, the level of potassium citrate can impact product pH and buffer capacity. Thus, the risk is medium.
	Delivery Rate	The level of potassium citric is unlikely to impact delivery rate and ethanol content of the drug product. The risk is low.
	Ethanol Content	

2.2.1.2 Drug Substance solubility and Particle Size Selection for Product Development

Clobetasol Propionate drug substance solubility in alcohol was evaluated by adding drug substance in dehydrate alcohol. More than 0.5 grams of API was added into 60.71 grams of dehydrate alcohol with 150 rpm stir bar mixing under room temperature, and the API dissolved into alcohol immediately. Thus, the API solubility in alcohol is at least 0.6%, which is much

larger than target API strength (0.05%). The API should have sufficient solubility in drug product.

Below lots in **Table 18** were used in the formulation and process development. Due to enough solubility of API in drug product, the particle size distribution (PSD) of drug substance is not critical to the quality of the drug product. Based on supplier's availability and to potentially minimize process time, micronized drug substance was used throughout the study.

Table 18 PSD for API lots used in development

API Lot #	D90 (μm)	D99.5 (μm)
CBPy17001	8.99	14.5
CBPy17002	6.05	11.92
CBPy17003	9.19	14.31
CBPy17007	9.32	14.73
CBPy17008	8.92	14.25

2.2.1.3 Process selection

Formulation components are incorporated in the finished product in the solubilized state. Based on the lipophilicity and hydrophilicity of the excipients, alcohol and water are used as solvents to dissolve lipophilic and hydrophilic components, respectively. Raw materials such as the drug substance, cetyl alcohol, stearyl alcohol, polysorbate 60 and propylene glycol can be easily dissolved in alcohol, while citric acid and potassium citrate can be easily dissolved in water, therefore, a two-phase process was designed.

During the compounding of the alcohol phase, cetyl alcohol, stearyl alcohol, propylene glycol, and polysorbate 60 were added into the dehydrate alcohol in sequence. Then heat the alcohol phase up to 45℃, and mix using mechanical stirrer in order to shorten the dissolving time of fatty alcohols. Once all ingredients were dissolved, the clobetasol propionate drug substance was added into the alcohol phase under 45℃. Sufficient mechanical mixing was provided to dissolve the API.

The aqueous phase was separately prepared. The water was heated up to 45℃, and then add citric acid anhydrous and potassium monohydrate. Keep mechanical mixing and 45℃ until the buffer agents were dissolved.

Once both phases were prepared, the aqueous phase was transferred into the alcohol phase, and continued mixing under 45℃ until a clear solution was formed. The resulting foam solution was filled into both 50g and 100g cans, and the propellant AP-70 was filled once the can was crimped using an aluminum valve. The HDPE spout and PP cap was manually placed onto the valve once crimped.

2.2.1.4 Formulation Development Study #1 Effect of Propylene glycol on impurities and related substances

Formulation development focused on evaluation of the high and medium risk formulation variables as identified in **Table 16**. The first formulation study evaluated the impact of the propylene glycol source on drug product related substance. It is well understood that certain impurities in propylene glycol may impact the stability of drug substance in liquid product, therefore, propylene glycol from three different suppliers (BASF, CRODA, and Dow) were evaluated for the impact on drug product related substance. The formulations used to evaluate the propylene glycol supplier were listed in **Table 19**. Same process as described in section 2.2.1.3 was used to make the foam solution, except the foam was not pressurized using propellant due to limitation of process feasibility at lab scale. The API was easily dissolved in alcohol phase within minutes. The foam solutions with different propylene glycol source were stored under same condition at 40 ºC, 65% RH for up to 14 days. Related substance levels were evaluated using HPLC, and the results is listed in **Table 20**.

Table 19 Formulation compositions of batches for propylene glycol supplier selection

Formulation	**20170831-1**	**20171113-1**	**20171113-2**
Ingredients	w/w%	w/w%	w/w%
Clobetasol	0.05	0.05	0.05
Cetyl Alcohol	1.14	1.14	1.14
Stearyl Alcohol	0.51	0.51	0.51
Polysorbate 60	0.41	0.41	0.41
Dehydrate Alcohol	60.71	60.71	60.71
Propylene Glycol	2.09 (BASF)	2.09 (CRODA)	2.09 (DOW)
Purified Water	34.88	34.93	34.93
Citric Acid Anhydrous	0.08	0.08	0.08
Potassium Citrate	0.13	0.13	0.13
Batch Size	200 g	200 g	150 g
Propellant AP-70	0.00	0.00	0.00

Table 20 Related substance results for formulations with different propylene glycol suppliers after 14 days under 40 ºC, 65% RH

Formulation		API	20170831-1	20171113-1	20171113-2	20170831-1	20171113-1	20171113-2
Condition	RRT	Initial	Croda 0day	Dow 0day	BASF 0day	Croda 14days	Dow 14days	BASF 14day
Unknown Impurity 1	0.32	0.02	N/A	N/A	0.02	0.17	0.17	0.14
Impurity A	0.4	0.06	0.05	0.05	0.06	0.05	0.05	0.05
Impurity B	0.58	0.07	0.11	0.09	0.08	0.10	0.09	0.12
Clobetasol	1	99.70	99.72	99.75		99.36	99.37	
Impurity D	1.21	0.14	0.12	0.11	0.12	0.12	0.11	0.11
Unknown Impurity 2	1.34	N/A	N/A	N/A	N/A	0.13	0.13	0.08
Total	-	0.3	0.28	0.25	0.28	0.64	0.63	0.50

The 14-day accelerated condition results showed no significant difference on product related substance between three propylene glycol suppliers. Due to lowest total impurities and least

related substance growth, propylene glycol from BASF was selected for final formulation and future studies.

2.2.1.5 Formulation Development Study #2: Selection of buffering agent concentrations

The second formulation study is focused on obtain the appropriate level for the buffer agents: citric acid and potassium citrate. The buffering agent amount and concentration would affect the pH of the drug product along shelf life. The buffer system consists of Citric Acid (H_3Cit) and Potassium Citrate (K_3Cit). Aqueous solutions were prepared with citric acid and potassium citrate at various molar ratios, and the corresponding pH values of the solutions were determined. A citric acid and potassium citrate ratio vs pH trend line study was performed as shown in

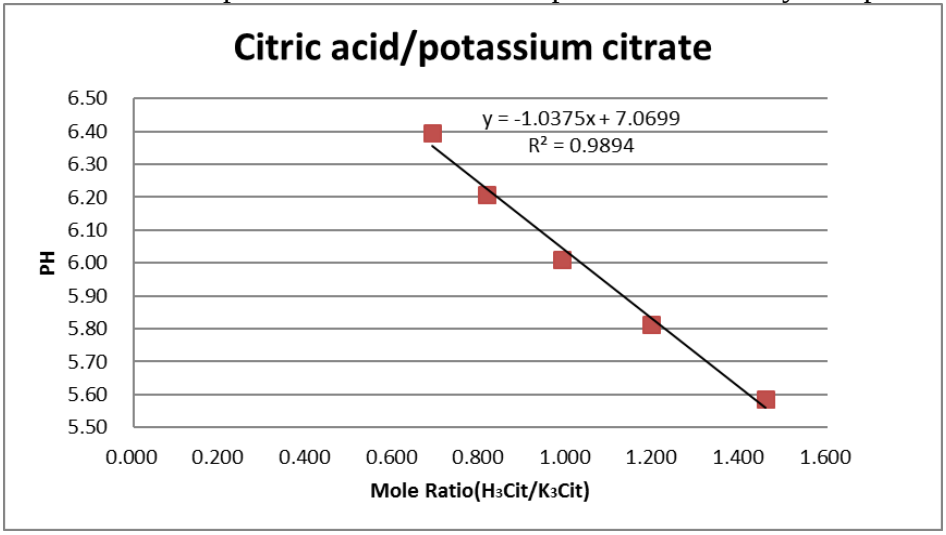

Figure 4, using the study results obtained from data in **Table 21**. Since the pH value of RLD is around 6.13, based on the linear equation of the trend line analysis, the corresponding citric acid to potassium citrate molar ratio is 0.906.

Table 21 pH values of Buffer Systems with varying Citric Acid to Potassium Citrate molar ratio

Name	weight (mg)	Mole (mM)	Molar Ratio (H3Cit/K3Cit)		pH
Citric Acid	6.67	0.035	0.8:1.2	0.689	6.40
Potassium Citrate	15.44	0.05			
Citric Acid	7.16	0.037	0.9:1.1	0.814	6.21
Potassium Citrate	14.02	0.046			
Citric Acid	8.08	0.0421	1.0:1.0	0.987	6.01
Potassium Citrate	13.05	0.0426			
Citric Acid	8.71	0.0453	1.1:0.9	1.193	5.82
Potassium Citrate	11.64	0.038			
Citric Acid	9.58	0.0499	1.2:0.8	1.456	5.59
Potassium Citrate	10.49	0.0342			

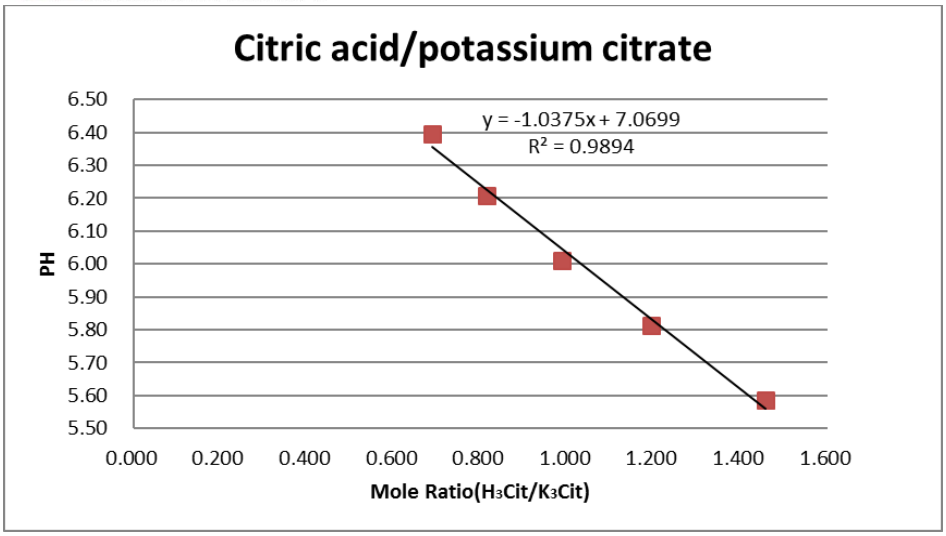

Figure 4 Trend study for Citric Acid and Potassium Citrate Molar Ratio vs pH values in aqueous solutions

In addition, as shown in Error! Not a valid bookmark self-reference., reverse engineering of total citrate amount using HPLC was performed. Since the ratio between citric acid and potassium citrate is known, an estimated level of citric acid anhydrous and potassium citrate was calculated to be around 0.06% and 0.10% w/w respectively. Based on publicly available information such as patent search and the results obtained from reverse engineering, 0.08% w/w Citric Acid and 0.13% w/w Potassium Citrate is determined to be used in the product formulation of Aucta's generic Clobetasol Propionate Foam, 0.05%.

Table 22 Reverse Engineering for Citric Acid and Potassium Citrate w/w% based on HPLC results and product pH values

Analyte	Weight (mg)	peak Area	AVE	Conc. mol/L	Name	Mole Ratio (H3Cit/K3Cit)	Conc. mol/L	Actual (mg)	w/w%	AVE% (H3Cit)	AVE% (K3Cit)
RLD	348.7	87.69	88.08	0.092	H3Cit	0.906	0.044	0.209	0.06	**0.06**	**0.10**
		88.47			K3Cit		0.048	0.368	0.11		
	298.7	72.53	72.28	0.075	H3Cit		0.036	0.172	0.06		
		72.03			K3Cit		0.039	0.302	0.10		
	310.0	74.05	74.06	0.077	H3Cit		0.037	0.176	0.06		
		74.07			K3Cit		0.040	0.310	0.10		

Besides the initial pH, pH variation overtime was also measured in order to evaluate the buffer capacity. Three lab and scale up batches listed in **Table 23** were formulated using same formulation and similar process, and the pH was monitored under accelerated, intermediate and long-term storage conditions. **Table 24** shows the results for the pH study. With the citric acid and potassium citrate amount indicated in **Table 23**, the pH showed no significant change, and the buffer system was able to maintain target pH. The pH value was stable at least 6 months under accelerated condition, 11 months under intermediate condition, and 19 months under long term condition. Therefore, current level for the buffer agents is acceptable, and should be able to maintain the pH values of the product throughout the shelf life.

Table 23 Formulations for lab and scale up batches monitored for pH study

Formulation	31878	732112	31982
Ingredients	%w/w	%w/w	%w/w
Clobetasol	0.05	0.05	0.05
Cetyl Alcohol	1.14	1.14	1.14
Stearyl Alcohol	0.51	0.51	0.51
Polysorbate 60	0.41	0.41	0.41
Dehydrate Alcohol	60.71	60.71	60.71
Propylene Glycol	2.09	2.09	2.09
Purified Water	34.88	34.88	34.88
Citric Acid Anhydrous	0.08	0.08	0.08
Potassium Citrate	0.13	0.13	0.13
Batch Size	150 kg	3 kg	150 kg
Propellant AP-70	5.00	5.00	5.00

Table 24 Results for pH values of Aucta's clobetasol foam 0.05% under accelerated, intermediate, and long-term condition

Lot Number	Condition	pH
31878	Initial	6.09
31878	6 M 40°C/RH 75%	6.22
31878	10 M 30°C/RH 65%	6.31
732112	Initial	6.07
732112	19 M 25°C/RH 60%	6.31
31982	Initial	6.10
31982	11M 30°C/RH 65%	6.20

2.2.1.6 Formulation Development Conclusions

The formulation composition was finalized based on the aforementioned formulation development studies and reverse engineering study. The finalized formulation for Generic Clobetasol Propionate Foam, 0.05% is presented in **Table 25**. The composition was submitted to FDA Office of Generic Drugs (OGD) for Q1/Q2 assessment (Control Correspondence # 15457592), and OGD recommended option I: *Waiver option described in the draft guidance on Clobetasol Propionate* on formulation listed in **Table 25**. All the excipients in the final formulation are present in the RLD.

Table 25 Formulation selected for Generic Clobetasol Propionate Foam, 0.05%

Ingredient	Function	Composition (%w/w)
Clobetasol Propionate	Active	0.05
Cetyl Alcohol NF	Emulsifier, Foam Stabilizer	1.14
Octadecan-1-ol (Stearyl Alcohol) NF	Emulsifier, Foam Stabilizer	0.51
Polysorbate 60 NF	Emulsifier	0.41

Ethanol (Dehydrate Alcohol USP)	Solvent	60.71
Purified Water USP	Solvent	34.88
Propylene Glycol USP	Solvent, Humectant	2.09
Citric Acid Anhydrous USP	Buffering Agent	0.08
Potassium Citrate USP	Buffering Agent	0.13
Butane/Propane (propellant AP-70)	Propellant	5.00*
Total		100.0

* The propellant is listed as an inactive ingredient; however, it does not have to be calculated in the composition of the formulation since it evaporates immediately upon dispense. For Aucta's generic foam, the container is pressurized with 5% (w/w) of propellent for both packaging configurations.

2.2.3 Updated risk assessment of formulation variable

The potential high and medium risk formulation variables have been evaluated. Based on the results of the initial formulation and process development, the updated risk assessment of the formulation variables is given in **Table 26**. The justifications are provided in **Table 27**.

Table 26. Updated risk assessment of the formulation variables

Formulation Variables	Drug Product CQA				
	Assay	Related Substance	pH	Delivery Rate	Ethanol Content
Cetyl Alcohol	Low	Low	Low	Low	Low
Stearyl Alcohol	Low	Low	Low	Low	Low
Polysorbate 60	Low	Low	Low	Low	Low
Dehydrate Alcohol	Low*	Low	Low	Low	Low
Propylene Glycol	Low	Low*	Low	Low	Low
Purified Water	Low	Low	Low	Low	Low
Citric Acid	Low	Low	Low*	Low	Low
Potassium Citrate	Low	Low	Low*	Low	Low

*The level of risk was reduced from the initial risk assessment.

Table 27 Justification for the reduced risks of the formulation variables

Drug Substance Attributes	Drug Products CQAs	Justification
Dehydrate Alcohol Level	Assay	This risk was reduced from medium to low since the API could be easily dissolved in current alcohol phase.
Propylene Glycol Source	Related Substances	The risk was reduced from medium to low after BASF has been selected as the supplier for propylene glycol. Propylene glycol from BASF is not likely to introduce more related substances.

Citric Acid Level	pH	The risk was reduced from medium to low, since the tested buffer system could reach and maintain target pH of the drug product
Potassium Citrate Level	pH	The risk was reduced from medium to low, since the tested buffer system could reach and maintain target pH of the drug product

2.2.4 Overages

No overage is used in the manufacturing of Aucta's Clobetasol Propionate foam 0.05%

2.2.5 Physicochemical and Biological Properties

Refer to Section 1.4 for a discussion of the waiver option of the in vivo bioequivalence (BE) study, and the comparative in vitro foam performance studies.

2.3 Manufacturing Process Development

As discussed in Section 2.2.1.3 Process Selection, a two-phase process was designed to manufacture generic clobetasol foam. **Figure 5** presents the process flow diagram for compounding the finalized formulation of Genetic Clobetasol Propionate, 0.05%, while **Figure 6** presents the flow diagram for filling the finalized formulation of Genetic Clobetasol Propionate. Each process step in the manufacturing process is listed in the sequence of occurrence. This flow chart was used to guide the risk assessments performed during process development.

Manufacturing process development studies were conducted at 0.1-12.0 kg lab scale, filling in both packaging configurations. A process development study overview was summarized in **Table 28** below.

Table 28 Process development studies of generic Clobetasol Propionate Foam, 0.05%

Study	Lot number	Scale	Section
Dissolve API in alcohol or water phase	N/A	N/A	2.3.2
40℃ Process temperature	20191115-2	100 g	2.3.2
50℃ Process temperature	20191115-1	100 g	2.3.2
Alcohol and aqueous phase addition order	N/A	N/A	2.3.4
Bulk hold	32598	12 kg	2.3.5
Propellant level evaluation	732112	3 kg	2.3.6.1
Vacuum crimp	732112	3 kg	3.2.6.2
Engineering Batch	31878	150 kg	2.3.7
Registration Batch	31982	150 kg	3.2.8
Registration Batch	32595	150 kg	3.2.8
Registration Batch	32598	150 kg	3.2.8

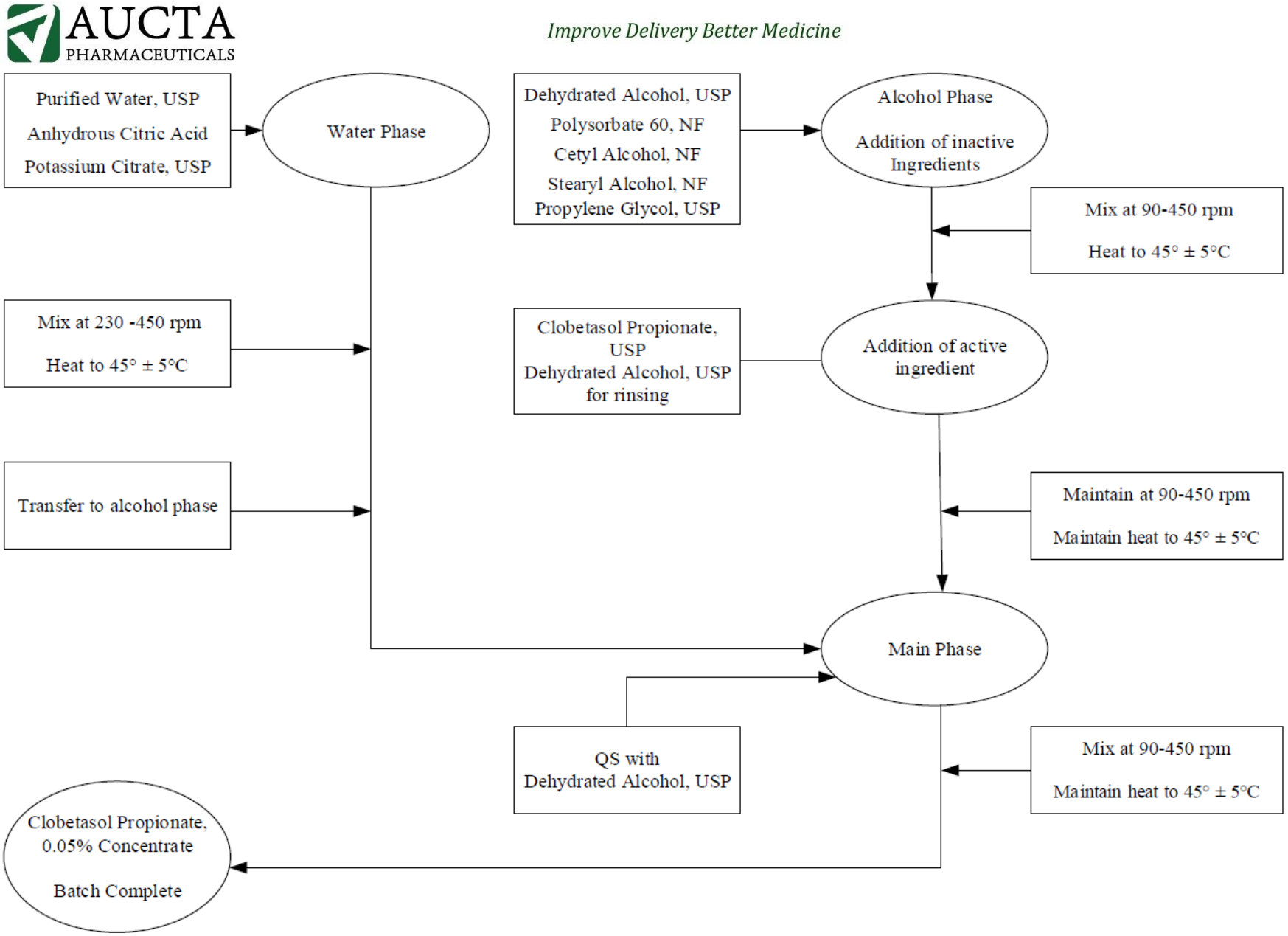

Figure 5 Generic Clobetasol Propionate, 0.05% Manufacturing Process Flow

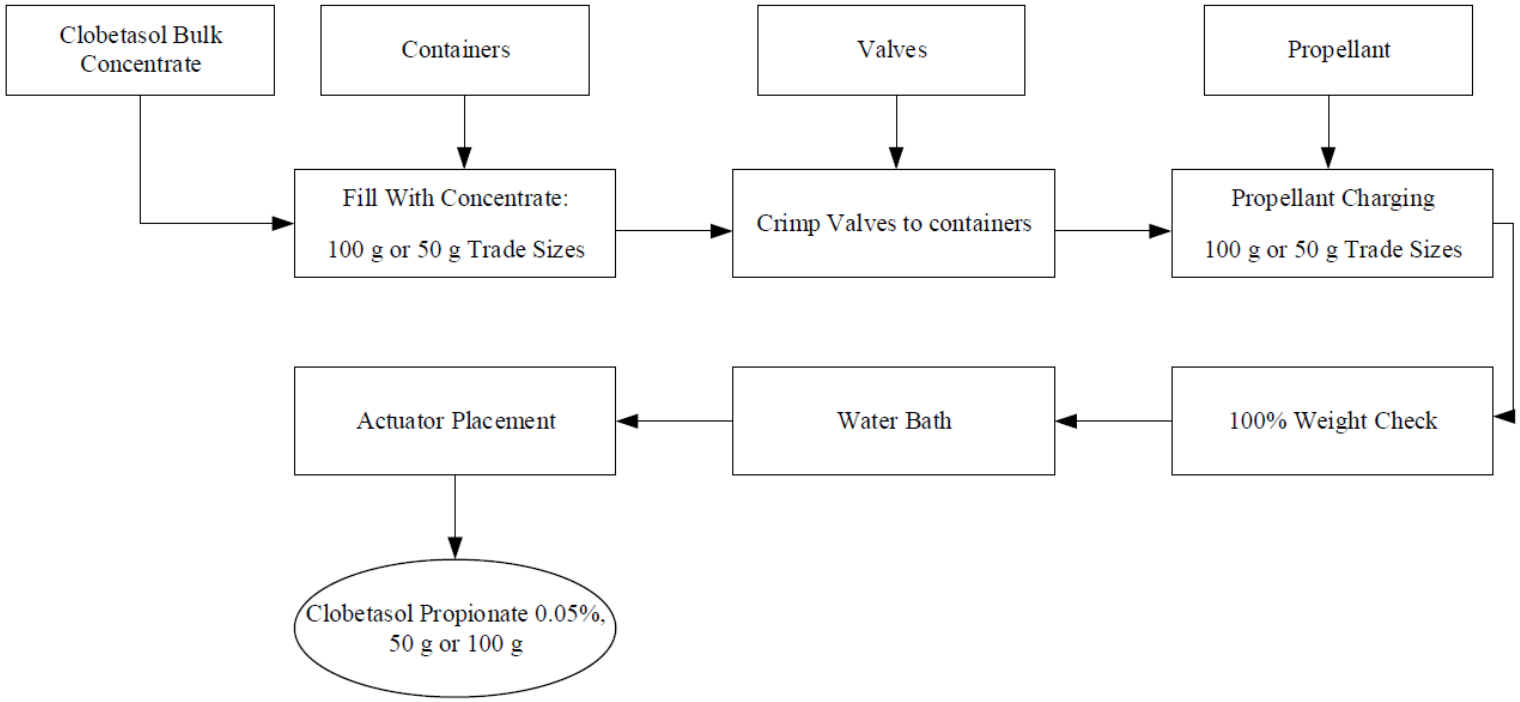

Figure 6 Generic Clobetasol Propionate 0.05% filling process flow chart

2.3.1 Initial risk assessment of drug product process variables

A risk assessment of the overall drug product manufacturing process was performed to identify the medium or high-risk steps that may affect the CQAs of the final drug product. For each process step, a risk assessment was conducted to identify potentially high-risk process variables which could impact the drug product CQAs. These variables were then investigated in order to better understand the manufacturing process and to develop a control strategy to reduce the risk of a failed batch. This method of identifying process variables for further study is applied in each process step risk assessment.

Based on common scientific knowledge on drug product ingredients, the manufacturing process would consist compounding of two phases: alcohol phase and aqueous phase. Dehydrate alcohol, polysorbate 60, cetyl alcohol, stearyl alcohol, propylene glycol and the drug substance would mix until clear to form the alcohol phase. Purified water, citric acid and potassium citrate would mix until clear to form the water phase. Due to the characteristic of the excipients, and in order to prevent formulation gelation, both phases need to be heated to around 45 ℃ prior than combining. After combining two phases, the final product will be filled into aluminum cans, and crimp with aluminum valves. The actuator with cap will be caped onto the can.

The initial risk assessment of the overall manufacturing process is shown in **Table 29** and justifications are provided in **Table 30**. Previous experience with these process steps was used to determine the degree of risk associated with each process step and its potential to impact the CQAs of the finished drug product.

Table 29 Initial risk assessment of the process variables

Drug Product CQA	**Process Variables**						
	Alcohol Phase Phase A		Aqueous Phase Phase B	Main Phase	Bulk Solution Homogeneity	Primary Packaging	
	API Solubility	Mixing Temperature	Mixing Temperature	Order of Addition	Hold Time	Propellant Amount	Vacuum Crimp
Delivery Rate	Low	Low	Low	Low	Low	Medium	Medium
Leakage Test	Low	Low	Low	Low	Low	Low	Low
pH	Low	Low	Low	Low	Low	Low	Low
Assay	Medium	Medium	Low	Medium	Medium	Low	Low
Related Substances	Low	Medium	Low	Low	Low	Low	Medium
Ethanol Content	Low	Low	Low	Low	Medium	Low	Low

Table 30 Justification for the initial risk assessment of the process variables

Process Step	**Process Variables**	**Drug Products CQAs**	**Justification**
Alcohol Phase	API	Delivery Rate	The API solubility is unrelated to delivery rate and

(Phase A)	Solubility	Leakage Test	leakage test. The risk is low.
		pH	Drug product pH has been determined in formulation development. API solubility will not affect product pH. The risk is low.
		Assay	API solubility will affect drug product assay. The risk is medium.
		Related Substances	API Solubility is unrelated to related substance and ethanol content. Thus, the risk is low.
		Ethanol Content	
	Mixing Temperature	Delivery Rate	The mixing temperature of alcohol phase is unrelated to delivery rate, leakage test and pH. The risk is low.
		Leakage Test	
		pH	
		Assay	Low mixing temperature of the alcohol phase could cause API solubility issue, while high mixing temperature could cause API degradation. The risk is medium.
		Related Substances	Mixing under high temperature could potentially accelerate the generation of API related substance. The risk is medium.
		Ethanol Content	Sealed containers will be used to prevent alcohol from evaporation. The alcohol will be QS to 100% to compensate the evaporation caused by heating during the process. The risk is low.
Aqueous Phase (Phase B)	Mixing Temperature	Delivery Rate	The mixing temperature of Aqueous phase is unrelated to delivery rate, leakage test, pH, assay, related substance and Ethanol content. The mixing temperature of aqueous phase will be set as the same with alcohol phase to prevent temperature shift once two phases are mixed in next step. The risk is low.
		Leakage Test	
		pH	
		Assay	
		Related Substances	
		Ethanol Content	
Main Phase	Order of Addition	Delivery Rate	The order of addition for the main phase will not affect the delivery rate, leakage test and pH. The risk is low.
		Leakage Test	
		pH	
		Assay	The miscibility of the two phases need to be tested, and the order of addition could potentially affect the necessary mixing time. Drug product assay will vary if the two phases are not fully miscible. Thus, the risk is medium.
		Related Substances	The order of addition for the main phase will not affect related substances and ethanol content. The risk is low.
		Ethanol Content	

Bulk Solution Homogeneity	Hold Time	Delivery Rate	The hold time will not affect drug product delivery rate, leakage and pH. The risk is low.
		Leakage Test	
		pH	
		Assay	During the hold time period, the assay will be affected if evaporation occurs. The homogeneity of the bulk solution needs to be confirmed once foam solution congealed at room temperature. The risk is medium.
		Related Substances	The hold time of the bulk solution will not affect related substances. The risk is low.
		Ethanol Content	During the hold time period, the ethanol content will decrease if evaporation occurs. The risk is medium.
Primary Packaging	Propellant Amount	Delivery Rate	The propellant amount will affect drug product pressure. Different product pressure could cause varying foam appearance and foam density. Therefore, the delivery rate can be affected by drug product propellant amount. The risk is medium.
		Leakage Test	The propellant amount is unrelated to leakage test, pH, assay, related substances and ethanol content. The risk is low.
		pH	
		Assay	
		Related Substances	
		Ethanol Content	
	Vacuum Crimp	Delivery Rate	Vacuum crimping will reduce drug product pressure and cause variations in delivery rate. The risk is medium.
		Leakage Test	The vacuum crimp is unrelated to leakage test, pH, and assay. The risk is low.
		pH	
		Assay	
		Related Substances	With vacuum crimping process, the related substance should be reduced due to less air in the drug product. The risk is medium.
		Ethanol Content	Vacuum crimping is unlikely to affect ethanol content. The risk is low.

2.3.2. Alcohol Phase (Phase A)

The solubility of drug substance in alcohol has already been tested in formulation development section. In this section, the API solubility was confirmed with target strength, as listed in **Table 31**. API could easily dissolve in both alcohol water solution, and alcohol plus propylene glycol solution. However, the API will not fully dissolve in water, even with the presents of propylene

glycol. Therefore, API will be added in alcohol phase, instead of aqueous phase. In addition, water added to alcohol phase will not cause API precipitation or affect the soluble status of the API.

Table 31 API solubility in various cosolvent systems consisting of water, alcohol and propylene glycol

Formulation	**1**	**2**	**3**
Ingredients	w/w%	w/w%	w/w%
Clobetasol	0.05	0.05	0.05
Dehydrate Alcohol	63.47	92.62	
Propylene Glycol		3.33	5.65
Purified Water	36.48		94.30
Dissolve Time	Immediately	Immediately	Cannot fully Dissolve

Experiment has been performed that fatty alcohols (i.e. cetyl alcohol and stearyl alcohol) with the formulation concentration was able to dissolve in formulation amount of dehydrate alcohol under room temperature. However, the time that is needed to dissolve cetyl alcohol and stearyl alcohol is longer at room temperature in comparison to higher mixing temperature. At the meantime, increasing process temperature could also cause API degradation, and generate more impurities. Therefore, a study has been done to evaluate a suitable temperature range for alcohol phase mixing.

With the final formulation design listed in section 2.2.1.7, the bulk formulation will start to congeal at temperature lower than 40**℃** and change from solution state into solid state without under pressurization with propellant. In order to prevent bulk solution from congealing, the lowest alcohol phase mixing temperature of 40**℃** was tested. Since alcohol is potentially explosive and flammable, the higher end of alcohol phase mixing temperature proposed would be set as 50**℃**.

During the process of alcohol phase manufacturing at 40**℃**, all excipients were able to dissolve freely without any issues. A clear solution was observed quickly after each ingredient were added. Thus, 40°C is an acceptable temperature for alcohol phase mixing. Due to feasibility of the manufacturing, a range need to be set for the alcohol phase mixing. A batch with 50°C process temperature was also manufactured. All excipients were easily dissolved at 50°C as well.

Samples from batches using both 40**℃** and 50**℃** were tested for assay and impurity levels in order to evaluate the chemical stability of the drug product under 40**℃** and 50**℃** mixing temperatures. The results for the assay and impurity test were listed in **Table 32**. No significant differences regard to assay and impurity levels were observed between 40°C and 50°C mixing temperatures, and none of the impurities exceeded product specification. Since 40°C and 50°C are both acceptable mixing temperatures of the alcohol phase, the target mixing temperature will be set at 45°C, with range from 40°C to 50°C.

Table 32 Assay and related substance results for final formulation with 40°C and 50°C process temperature

Sample	% Assay	RRT_ 0.27	RRT_ 0.37	RRT_ 0.42	EP Impurity A	EP Impurity B	EP Impurity D	Total -Unk. Imp.
50°C mixing	100.45	ND	ND	0.03	0.05	0.05	0.11	0.29
40°C mixing	102.65	ND	ND	0.03	0.05	0.05	0.12	0.43

2.3.3. Aqueous Phase (Phase B)

The aqueous phase was manufactured by dissolving citric acid and potassium citrate in water. Both buffer agents are very soluble in water, with solubility larger than 383mg/ml at 25ºC for both citric acid and potassium citrate. The solubility for both buffer agents is much higher than the final formulation amount. Therefore, the risk for this step is low. The mixing temperature of aqueous phase is set as 45 ºC with range from 40ºC to 50ºC. This target aqueous phase mixing temperature is set to match with the alcohol phase, in order to maintain the temperature of main phase to be around 45ºC, once two phases were mixed and combined together**.**

2.3.4. Main Phase

Since the product contains both alcohol and aqueous phase, the order of addition was evaluated in a trial study to rule out API precipitation, or immiscible situation. Both alcohol phase and aqueous phase were prepared separately and added together based on formulation amount. One batch was made by adding alcohol phase into the aqueous phase. The other batch was made by adding aqueous phase into the alcohol phase.

The observations for the main phase immediately after the second phase addition were captured in **Table 33**. For both addition orders, a portion of the solution became white and cloudy immediately after two phases were mixed together. A larger white cloudy portion was observed in the vial made by adding alcohol phase into water phase. However, within seconds and with gentle mixing, the white cloud disappeared, and clear solutions were obtained for both addition orders. Therefore, the alcohol phase and the aqueous phase is miscible, and the order of addition would not affect clear solution formation. Based on the formulation, alcohol phase contains bigger volume. Therefore, in order to facilitate the ease of manufacturing process, aqueous phase will be transferred into the alcohol phase.

Table 33 Observations for alcohol and aqueous phase with different addition orders.

Immediately add Alcohol phase into the water phase	Immediately add Water phase into Alcohol phase	Both vials after gentle shaking
The bottom haft of the solution became white and cloud, while the top half of the solution is clear	The bottom 1/3 of the solution became white and cloudy, while the top half of the solution is clear	Clear solution was obtained immediately after gentle shaking

2.3.5. Bulk Hold and Solution Homogeneity

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. Information related to the containers are listed in **Table 34**. Samples were collected at completion of the compounding operation and at 71 days and tested appearance and related CQAs (pH, assay, and ethanol content).

The results obtained from this study support the manufacturing hold period of up to 71 days of the bulk solution of Clobetasol Propionate Foam 0.05%. The assay results showed the drug product is chemically stable, and the ethanol content test confirmed no evaporation of alcohol during 71 days of holding period. Test results are summarized in the **Table 35** below.

Table 34 Details of the holding container

Details	Holding Container Hold Study	Exhibit Batch Holding Container	Proposed Commercial Holding Container
Holding Container	Stainless Steel Tank	Stainless Steel Tank	Stainless Steel Tank
Material of Construction	SS316	SS316	SS316
Tank ID	N/A	Tank 604	Tank 250J
Tank Capacity	5 Gallon	60 Gallon	250 Gallon

Table 35 Bulk hold study testing results

Test	Method	Test Specification	Results
Appearance (at 45ºC)	Visual	Clear solution with no visible particles	Top: Confirm Middle: Confirm Bottom: Confirm
pH	Current USP <791>	5.0-7.0	Top: 6.0 Middle: 6.0 Bottom: 6.0 Average: 6.0
Assay by HPLC	100-3-142	NTL 90.0% and NMT 110.0% of the labeled amount of Clobetasol Propionate	Top: 101.7 Middle: 101.4 Bottom: 101.2 Average: 101.4
Ethanol Content	100-3-143	90.0% - 110.0%	Top: 99.5 Middle: 99.4 Bottom: 99.6 Average: 99.5

2.3.6. Primary Packaging Process

3.2.6.1 Determination of Propellant Amount

The propellant amount in drug product could affect multiple characteristics of the drug product, such as foam appearance, pressure, and delivery rate. Based on public information and general knowledge of the aerosol product, the range of Propellant AP-70 (Propellant) in drug product could go from 3.5% to 6.0%. Thus, finished product using final formulation with different amount of propellant filled were made, as indicated in **Table 36**. The results of appearance, pressure, and delivery rate were characterized.

Table 36 Finished Product with different amount of Propellant AP-70

Theoretical Percentage of Propellant AP-70 (%)	Bulk Solution Weight (g)	Propellant AP-70 Fill Weight (g)*	Actual Percentage of Propellant AP-70 (%)
3.5	50	1.81	3.41
4.0	50	2.09	3.92
4.5	50	2.36	4.43
5.0	50	2.63	4.94
5.5	50	2.91	5.47
6.0	50	3.19	6.00

*Propellant AP70 (grams) $= \frac{\text{50g * \% of propellant}}{\text{1-\% of propellant}}$

The foam appearance for the drug product with different amount of propellant charged is shown in

Table 37. When percentage of propellant is below 4.5%, the foam could not be shaped and quickly collapsed, and the appearance is not satisfactory. The drug product with 5% and 5.5% of propellant showed similar appearance with the RLD. When the percent of propellant reached 6%, the foam texture looked denser and less fluffy when comparing with RLD. Thus, drug product with 5% and 5.5% propellant fill provided best appearance and foam quality, while drug product with 4.5% and 6.0% showed acceptable foam appearance. The drug product with less or equal to 4.0% could not form acceptable foam appearance, so it will not be tested further.

Table 37 Foam appearance of drug products with different amount of propellant AP-70

Percent of Propellant Filled	Appearance
RLD	

3.5% Propellant	
4.0% Propellant	
4.5% Propellant	

5.0% Propellant	
5.5% Propellant	
6.0% Propellant	

Pressure and delivery rate of drug products with propellant percentage of 4.5% to 6.0% that have good or acceptable foam appearance, and the RLD were evaluated. The pressure was measured from the valve directly using a pressure gauge, and the delivery rate was measured by amount of foam dispensed from the can in 5 seconds. The results were listed in **Table 38**. The pressure of the RLD product is 64 psi, which is in between drug product with 4.5% propellant filled and drug product with 5.0% propellant filled. The delivery rate of tested products was comparable even though slightly lower than RLD. Based on the foam appearance, pressure, and delivery rate, 5.0% propellant was selected to be used in the final optimized process.

Table 38 Pressure and Delivery Rate results for drug product with different propellant percentage

% Propellant	Pressure (psi)	Delivery Rate (g/sec)
4.5%	58	3.75
5.0%	70	3.69
5.5%	72	3.49
6.0%	76	3.62
OLUX RLD	64	3.82

3.2.6.2 Application of Vacuum During Crimping

Since vacuum crimping is a common technique used during pharmaceutical aerosol primary packaging, and the air pressure in drug product can is around 7 psi, vacuum crimping versus direct crimping on drug product with 5.0% propellant fill were compared for pressure, delivery rate and chemical stability. The results for delivery rate and pressure were listed in **Table 39**, while the results for chemical stability comparison was demonstrated in **Table 40**. Vacuum crimped drug product with 5.0% propellant fill showed very similar pressure and delivery rate with the RLD. Furthermore, vacuum crimped product showed similar chemical stability results with directly crimped product after 1 mouth under accelerated condition. Therefore, 5% of the propellant filling with vacuum crimping was selected for the final process.

Table 39 Pressure and delivery rate results for drug product with or without vacuum crimp

% Propellant	Pressure (psi)	Delivery Rate (g/sec)
5% Non-Vacuum Crimp	70	3.6897
5% Vacuum Crimp	65	3.80
RLD*	64	3.8175

Table 40 Chemical stability results for drug product with or without vacuum crimp

Related substances (%)	RRT0.31	Imp 1	RRT0.42	RRT0.44	RRT0.47	A	G	K	B	I	J	D	Imp 2	RRT1.37	Total Imp (%)
RRT	0.31	0.34	0.42	0.44	0.47	0.58	0.61	0.66	0.71	0.84	1.07	1.14	1.23	1.37	-
5.0% propellant fill initial	N/A	0.01	N/A	N/A	N/A	0.03	N/A	N/A	0.06	99.65	0.08	0.17	N/A	N/A	0.35

5.0% vacuum crimp under 40/75 1Month	0.02	0.27	0.01	0.01	0.01	0.03	0.04	0.03	0.1	0.02	0.02	0.18	0.22	0.02	0.96
5.0% non-vacuum crimp under 40/75 1 month	0.02	0.27	0.01	0.02	0.01	0.03	0.04	0.03	0.1	0.01	0.01	0.17	0.23	0.02	0.94

Based on the recommendation of the manufacturer of the primary packaging material, the crimp depth was set as 0.190 inch to 0.200 inch for both 50 g and 100 g packaging configurations. The crimp radial was set as 1.065 inch to 1.075 inch for both 50 g and 100 g packaging configurations. The 50 g and 100 g aluminum can have same crimping neck, so same valve could be applied to both cans. Once crimped, the cans were submerged in warm water to test for leakage. If there is leakage of the can, continuous bubbles generated by the can could be observed in the water bath. With the pre-set crimping parameters, no leak cans were observed for all the manufactured products. Therefore, the crimping depth of 0.190 inch to 0.200 inch, and crimping diameter of 1.065 inch to 1.075 inch will be used for the final process.

2.3.7. Scale-Up from Lab to Pilot Scale and Commercial Scale

Process development was initially performed on the lab scale (0.1kg -12.0 kg). This section describes the principles used to scale-up the process to the pilot scale (150.0 kg) in order to manufacture the engineering and exhibit batch. The same principles will be employed to scale-up the process to the commercial scale upon product approval. **Table 41** summarizes the different process scales.

Table 41 Process Scale Summary

Scale	Batch Size (kg)
Lab (Process Development)	0.1-12.0
Pilot (Engineering & Exhibit)	150.0
Commercial (Proposed)	500.0

2.3.7.1 Scale-Up of the Alcohol Phase

In the alcohol phase manufacturing, there are two parameters that need to be considered during scale up: temperature and mixing speed. Based on the process development work, the temperature for alcohol phase is consider critical process parameter. The alcohol phase scale up manufacturing need to target 45℃, with 5℃ variation allowed. The manufacturing temperature at the pilot scale is the same as lab scale productions.

The mixing speed was evaluated and not found to be critical to product quality attributes during development phase. The scale up strategy for mixing speed is achieved by forming an adequate vortex to provide sufficient mixing. Since the viscosity for alcohol phase around 45℃ is low, based on previous experience with tank 604 (60-gallon tank for pilot scale) with 40% - 60% fill volume, as confirmed during manufacturing of engineering batch 31878, a good vortex was formed with propeller speed of 100 ± 10 rpm. Due to high solubility of the ingredients added in

alcohol phase, a clear alcohol phase was obtained in a short amount of time. In engineering batch (lot 31878) and registration batches, once temperature reached 45°C, all ingredient was dissolved in 30 minutes. For manufacturing at commercial scale, the mixing speed will be adjusted under same principle to generate adequate mixing.

2.3.7.2 Scale-Up of the Aqueous Phase

The scale up of aqueous phase manufacturing will use same mixing temperature as used in lab scale process development phase, which is 45°C ± 5°C. Even though the mixing temperature is not as critical in aqueous phase manufacturing, by maintaining the same temperature as the alcohol phase, the main phase could remain 45°C ± 5°C once alcohol phase and aqueous phase are combined.

Due to good solubility of the buffer agents in water, the mixing speed for aqueous phase was found to be not critical to drug product quality attributes. Same strategy was used as the alcohol phase scale up regard to the selection of scale up mixing speed. In order to achieve adequate mixing of the aqueous phase, based on experience with tank 13J (13-gallon tank for pilot scale) with around 90% solution fill capacity, propeller speed of 250 ± 30 rpm was able to provide sufficient mixing, and the buffer agents will fully dissolve in short amount of time. For commercial scale up, the mixing speed will be adjusted under same principle to generate adequate mixing.

2.3.7.3 Scale-Up of the Main Phase

The same order of addition used in lab scale process development is applied to manufacture at pilot and commercial scale, which is transferring aqueous phase into the alcohol phase. In order to assure well mixing of the scale up batches, recirculation need to be applied to avoid insufficient mixing at the bottom of the tank due to tank structure design. At pilot scale, liquid was collected from the bottom of the tank, and added back to the tank from the top 2 to 3 times. For commercial batches, Tank 250J (250-gallon tank) has smooth bottom structure and is not likely to withhold any material at the bottom of the tank. Recirculation will also be applied on Tank 250J for commercial batches to ensure sufficient mixing.

2.3.7.4 Scale-Up of the Bulk Solution Homogeneity

Lab scale manufacturing do not require to hold the bulk solution during filling, since the duration of lab scale filling process was relatively short. Immediate filling after compounding is preferred for pilot and commercial manufacturing. However, unlike lab scale, the filling will take relatively longer time for pilot and commercial batches, and the bulk solution will be hold in the tank for a certain period until the whole batch is filled. A bulk hold study was performed during process development. For pilot scale, the bulk solution was remained slow mixing (90 ± 10 rpm) at 45°C ± 5°C during filling operation. For commercial manufacturing, the bulk solution during filling process will remain at 45°C ± 5°C and sufficient slow mixing condition to maintain homogeneous and prevent congealing.

2.3.7.5 Scale-Up of the Primary Packaging Process

The same primary packaging parameters utilized during primary packaging process development were used in exhibit batches and will be used for commercial scale production. Detailed parameters that affect the primary packaging process were already explored and discussed in section 2.3.5. The drug product weight check after propellant fill and crimping leakage check under warm water bath were measured on 100% of the drug product during exhibit batches. These measurements will be tested 100% during commercial batches as well. The crimping depth (0.190 inch to 0.200 inch) and crimping radial (1.065 inch to 1.075 inch) were tested every hour, while bulk solution fill weight and propellant fill weight were verified during the primary packaging process of the exhibit batches. These parameters will be kept the same and will be monitored at similar frequency for future commercial batches.

2.3.8. Exhibit Batch

Based on the scale-up principles detailed in Section 2.3.7, three 150.0 kg cGMP exhibit batches were manufactured with drug substance Lot CBPy17007 and CBPy17008 at the pilot scale and the batches were used for the performance studies (birefringence, time to break, weight per volume ratio) indicated in the drug product specific guidance. The registration batches and performance studies were performed at Pharmasol corporation in South Easton, MA. **Table 42** summarizes the equipment and process parameters used for the exhibit batch at pilot scale.

Table 42 Equipment and process parameters used for the exhibit batch

Process Steps		**Equipment and Process Parameters**
Alcohol Phase		60-gallon stainless steel tank Mixing: 100 ± 10 rpm Temperature: 45° ± 5°C.
Aqueous Phase		13-gallon stainless steel tank Mixing: 250 ± 30 rpm Temperature: 45° ± 5°C.
Main Phase		60-gallon stainless steel tank Mixing: 100 ± 10 rpm Temperature: 45° ± 5°C.
Bulk Solution homogeneity		60-gallon stainless steel tank Mixing: 100 ± 10 rpm Temperature: 45° ± 5°C.
Primary Packaging	Concentrate Filling	Volumetric fillers <u>100g cans:</u> Concentrate: 100.5 ± 0.5 g <u>50g cans:</u> Concentrate: 50.5 ± 0.5 g
	Crimping	Vacuum crimpers <u>100g cans and 50g cans:</u> Crimp Depth: 0.190” – 0.200”

		Crimp Diameter: 1.065" – 1.075" Vacuum: NLT 15 inHg
	Gassing	Trough the valve gassing injectors 100g cans: Propellant: 5.29 ± 0.2g 50g cans: Propellant: 2.66 ± 0.2g
	Checkweigher	Manual scales
	Actuator assembly	Manual actuator placer

The bulk solution (concentrate) release testing results and in-process control results for exhibit batches are summarized in **Table 43** and **Table 44**. For drug product final release results, please refer to Section 32p54 Drug Product CoA. All results are within specification.

Table 43. Bulk Solution (Concentrate) Release Testing Results for Exhibit Batches

Test	In Process Control	Results					
		31982 50g	31982 100g	32595 50g	32595 100g	32598 50g	32598 100g
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%	

Table 44 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	50.0g-51.0g for 50g can 100.0g – 101.0g for 100g can	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	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”	1.070	1.070	1.070	1.070	1.070	1.070
Vacuum (inHg)	NLT 15 inHg	16	16	16	16	16	16

2.3.9. Updated Risk Assessment of the Drug Product Manufacturing Process

The potential high or medium risk process variables have been evaluated. Based on the results of the process development and manufacturing experience and with proper control strategy in place the updated risk assessment of the process variables is given in **Table 45**. The justifications are provided in **Table 46**.

Table 45 Updated risk assessment of the manufacturing process for Generic Clobetasol Propionate Foam 0.05%

Drug Product CQA	**Process Variables**						
	Alcohol Phase Phase A		Aqueous Phase Phase B	Main Phase	Bulk Solution Homogeneity	Primary Packaging	
	API Solubility	Mixing Temperature	Mixing Temperature	Order of Addition	Hold Time	Propellant Amount	Vacuum Crimp
Delivery Rate	Low	Low	Low	Low	Low	Low*	Low*
Leakage Test	Low	Low	Low	Low	Low	Low	Low
pH	Low	Low	Low	Low	Low	Low	Low
Assay	Low*	Low*	Low	Low*	Low*	Low	Low

Related Substances	Low	Low*	Low	Low	Low	Low	Low*
Ethanol Content	Low	Low	Low	Low	Low*	Low	Low

*The level of risk was reduced from the initial risk assessment

Table 46 Justification for the updated risk assessment of the manufacturing process for Generic Clobetasol Propionate Foam, 0.05%

Process Variables		Drug Product CQAs	Justification
Alcohol Phase	API Solubility	Assay	The solubility of alcohol phase is sufficient. Drug substance can be easily dissolved in alcohol phase. The risk is reduced from medium to low
	Mixing Temperature	Assay	The mixing temperature is controlled at 40℃ to 50℃, target 45℃. The controlled temperature range will not cause assay loss, and the product will not congeal at proposed temperature range. The risk is reduced from medium to low.
		Related Substance	Alcohol phase with mixing temperature of 40℃ to 50℃, target 45℃ will not significantly increase degradation products. The risk is reduced from medium to low.
Main Phase	Order of Addition	Assay	Aqueous phase and alcohol phase are miscible. Adding aqueous phase into alcohol phase did not increase necessary mixing time. The risk is reduced from medium to low.
Bulk Solution Homogeneity	Hold Time	Assay	The hold time will not cause non-homogeneous product, and the product assay was not affected due to the hold time. The risk is reduced from medium to low.
		Ethanol Content	Ethanol evaporation was not observed since the ethanol content did not change significantly during holding in a sealed container. The risk is reduced from medium to low.
Primary Packaging	Propellant Amount	Delivery Rate	When 5% propellant was filled into vacuum crimped drug product, the foam delivery rate is similar to RLD. The foam appearance and pressure also showed acceptable results. Thus, by using 5.0% propellant fill, the risk reduced from medium to low.
	Vacuum Crimp	Delivery Rate	The delivery rate and pressure were similar to RLD when the can is vacuum crimped with 5.0% propellant filled. The foam appearance was also acceptable. The risk reduced from medium to low.
		Related Substance	Vacuum crimping would not cause any significant changes in drug product impurity level, in comparison to non-vacuum crimped product. The impurity levels for vacuum crimped drug product were low. The risk reduced from medium to low.

2.4 Container Closure System

2.4.1. Aluminum can- Primary Packaging

To be consistent with the RLD, the proposed generic drug product is intended to be labeled for storage at 25 °C (77 °F) with excursions permitted to 15-30 °C (59-86 °F). The innovator has chosen 50g and 100g aluminum can with metal valve, plastic spout and cap assembly. Generic Clobetasol Propionate Foam 0.05% are packaged in container close system with similar quality attributes, and the packaging details are summarized in **Table 47**. For detailed information regard to primary packaging materials, please refer to 3.2.P.7 Container Closure System Summary.

Table 47 Proposed commercial packaging for Generic Clobetasol Propionate Foam 0.05%

Packaging Component		**Description**	**Supplier**	**DMF**
50g Cans		Aluminum. Round shoulder, non-machined curl, white, unprinted, 35mm* 125mm, Pam internal lining	Montebello Packaging	009025
100g Cans		Aluminum. Oval shoulder, non-machined curl, white, unprinted, 45mm* 120mm, Pam internal lining		
S-90 Valve	Stem	Super 90 with Double Orifice, with Nylon material	Precision Valve Corporation	
	Stem Gasket	S90 DB-227, with Buna material		005004
	Spring	0.020 wire, with Stainless steel material		
	Body	Super 90, inverted, with Nylon material		
	Mounting Cup	Spherical cup, Epon coated, with aluminum material		028605 001627
Actuator		Actuator White, HDPE Mars Spout Inverted, Natural PP Caps	Precision Valve Corporation	

The proposed container closure system complies with requirements for use in the pharmaceutical packaging of topical aerosol foam (liquid) dosage form. The packaging components were received, sampled, and tested according to material specifications. All test specifications were met. The extractable assessment was conducted for the container closure system used in the packaging of the finished product, Clobetasol Propionate Foam, 0.05% and the organic volatiles and extractables were further evaluated in a screening exercise. For full details, refer to Module 3.2. P.7. The suitability and compatibility of the drug product with the primary packages have been demonstrated through accelerated (40ºC/75%RH) and long-term (25ºC/60%RH) stability studies presented in 3.2.P.8.3 Stability Data.

2.4.2. Carton - Secondary Packaging

Carton is the secondary packaging material. It has no direct product contact and does not provide additional protection in product stability. Only one bottle and the full prescription information leaflet are packaged into a printed carton as the marketing unit.

2.5 Microbiological Attributes

The product is manufactured under GMP environment as a non-sterile product. An accelerated stability study of three exhibit batch demonstrated that the drug product is not capable of supporting microbial growth due to high alcohol content and controls on incoming raw materials. The finished product is tested upon release and throughout its shelf-life for microbial testing including total aerobic microbial, total yeasts and molds count, Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli and Salmonella species as required for topical dosage forms.

2.6 Compatibility

This section is not applicable because the drug product is stored as finished dosage form in aluminum aerosol can. Aluminum cans are compatible with the product. Please refer Module 3, section 3.2.P.8.3 for clobetasol foam stability data. There are no reconstitution diluents. Therefore, this section is not applicable.

2.7 Control strategy

The control strategy for the commercial manufacture of Generic Clobetasol Propionate Foam, 0.05%, is proposed and presented in **Table 48**. The control strategy includes Clobetasol drug substance and excipients attributes controls, in process controls, high risk process parameter ranges studied during development and the proposed operating ranges for commercial manufacture. The purpose of the controls is also briefly discussed. The release specification for the final product is provided in **Table 49**.

Table 48 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 (micronized)	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 – 15L)	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				
Main Phase Process Parameters					
Mixing Tank 1	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	Propellant 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	
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,			
Extrusion	100% of the units		No visible dent			
Concentrate fill weight	1 can per station every 60 min	50g	50.5 ± 0.5 g			
		100g	100.5 ± 0.5 g			
Propellant 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

Table 49 Generic Clobetasol Foam, 0.05% release specification

Test	Acceptance Criteria
Appearance	A white to off white colored foam when dispensed from the can.
Packaging Inspection	A white aluminum can, white actuator attached to can with a transparent cap and no visible traces of the product (leakage) on the outside of either actuator or can.
Product/Packaging Interaction	No visual evidence of corrosion shall be observed at the valve/can.
Minimum Fill	The net weight of the contents of each of the 10 containers shall be Not Less Than the labeled amount.
Delivery Rate (g per second)	NLT 3.5 g/sec
Delivered Amount	NLT the labeled amount
Pressure Test	50-75 psi
Leakage Test	***Criteria 1***: 1. Average leakage rate per year for 12 containers shall be not more than 3.5% of the net fill weight per year

	2. None of the containers shall leak more than 5.0% of the net fill weight per year. If 1 container leaks more than 5.0% per year, and, if none of the containers leaks more than 7.0% per year, test an additional 24 containers. ***Criteria 2***: 1. Not More Than 2 of the 36 containers shall leak more than 5.0% of the net fill weight per year 2. None of the 36 containers shall leak more than 7.0% of the net fill weight per year.
pH	5.0 to 7.0
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 solution for the assay chromatogram.
Identification by UV	UV spectrum matches that of standard.
Assay by HPLC	90.0-110.0% of the labeled amount of Clobetasol Propionate
Related Substances by HPLC EP Impurity A (RRT 0.63) EP Impurity B (RRT 0.74) EP Impurity D (RRT 1.12) EP Impurity J (RRT 1.05) Unknown Impurity 1 (RRT 0.27) Unknown Impurity 2 (RRT 0.37) Unknown Impurity 3 (RRT 1.19) Any Unspecified Impurity Total Impurities	 NMT 0.5% NMT 0.5% NMT 0.5% NMT 0.5% NMT 0.5% NMT 0.5% NMT 0.5% NMT 0.5% NMT 3.0%
Ethanol Content	90.0-110.0%
Microbial Enumeration and Test for Specified Microorganisms Total Aerobic Microbial Count (TAMC)	Not More Than 200 CFU/g
Total Combined Yeast/Molds Count (TYMC)	Not More Than 20 CFU/g
Pseudomonas aeruginosa	Absent/1g
Staphylococcus aureus	Absent/1g
Escherichia coli	Absent /1g
Salmonella species	Absent 10/g
Residual Solvents	Complies with USP<467>, Option 2 requirements
Elemental Impurities	Complies with USP<232> and ICH Q3D

2.7.1 Control Strategy for Raw Material Attributes

The drug substance particle size is not critical due to sufficient solubility in alcohol and alcohol phase. However, in order to facilitate the mixing and dissolving process, the particle size of Clobetasol Propionate drug substance is controlled by d_{90} less than 10 µm. The drug substance with d90 less than 10 µm is fully dissolved within a short period of time (i.e. less than 30 minutes).

2.7.2 Control Strategy for Alcohol Phase (Phase A)

The control strategy for alcohol phase is to maintain mixing temperature as 45° ± 5°C while providing sufficient mixing. Sufficient mixing can be controlled by forming a good vortex in the mixing tank. The appearance of the alcohol phase is controlled by visual check that a clear solution is obtained.

2.7.3 Control Strategy for Aqueous Phase (Phase B)

The control strategy for aqueous phase to maintain mixing temperature as 45° ± 5°C while providing sufficient mixing. Sufficient mixing can be controlled by adjusting propeller speed and forming a good vortex in the mixing tank. The appearance of the aqueous phase is controlled by visual check that a clear solution is obtained.

2.7.4 Control Strategy for Bulk Solution

The control strategy for bulk solution is to maintain tank temperature as 45° ± 5°C while providing gentle mixing. Gentle mixing can be controlled by reducing the propeller speed so that no splashing or strong vortex will be observed. The bulk solution appearance is controlled by visual verification of the solution that it is **clear**. Besides appearance, ID, pH, Assay and ethanol content is controlled to ensure CQAs are met.

2.7.5 Control Strategy for Primary Packaging

The primary packaging contains multiple steps such as concentrate filling, vacuum crimping, gassing, checkweigher and actuator assembly. Control strategy for each step will be discussed as follow.

The control strategy for concentrate filling line set us is by adjusting the peristatic pump setting to achieve target fill weight of 100.5 ± 0.5 g for 100g packaging configuration, and 50.5 ± 0.5 g for 50g packaging configuration. The concentrate filling weight is verified by weighting one can per station every hour during the concentrate filling operation.

The control strategy for crimping is to set crimping depth and crimping diameter to 0.190” – 0.200” and 1.065” – 1.075” respectively to ensure packaging integrity. The crimp depth and radius are verified by measuring one can every 30 minutes during the crimping operation. The vacuum crimping is controlled by vacuum pressure. The vacuum pressure is set up as no less than 15 inHg, and it will be verified by testing one can every hour.

The control strategy for propellant fill is by setting up the gasser to fill 5.29 ± 0.2g propellant into 100g cans, and to fill 2.66 ± 0.2g propellant into 50g cans. The propellant fill weight is verified by weighting one can per station every hour during the propellant filling operation.

The total product weight is controlled by passing every single unit through weight check station and reject all the unit with weight outside of the controlled range. The lower edge of the controlled drug product weight is calculated by adding lower edge of the allowed concentrate fill weight, lower edge of the allowed propellant fill weigh and packaging material weight. The higher edge of the controlled drug product weight is calculated by adding higher edge of the

allowed concentrate fill weight, higher edge of the allowed propellant fill weigh and packaging material weight.

The packaging integrity is controlled by submerge all units in the heat water tank and observe that no stream of bubble coming from the crimped area of the container or around the stem of the valve. The appearance of the unit from outside is controlled by visual checking all units once the actuator is placed onto the can. The visual check includes no dents on the can, no visual defaults, and clear lot number printed at the bottom of the can.

2.7.6 Product Lifecycle Management and Continual Improvement

The manufacturing process for Aucta's generic Clobetasol Propionate Foam 0.05%, will be validated using the lifecycle approach that employs risk-based decision making throughout the drug product lifecycle as defined in the FDA process validation guidance.

The QbD approach taken during pharmaceutical development of Aucta's Clobetasol Propionate Foam 0.05% facilitated product and process understanding relevant to Stage 1 (Process Design) of process validation. During Stage 1, the commercial manufacturing process was defined based on knowledge gained through development and scale up activities and a strategy for process control was developed. The goal of Stage 2 (Process Qualification) is to evaluate if the process is capable of reproducible commercial manufacturing. The manufacturing facility will be designed according to cGMP regulations on Building and Facilities. Activities will be taken to demonstrate that utilities and equipment are suitable for their intended use and perform properly. The protocol for process performance qualification will be written, reviewed, approved, and then executed to demonstrate that the commercial manufacturing process performs as expected. The goal of Stage 3 (Continued Process Verification) is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture.

Throughout the product lifecycle, the manufacturing process performance will be monitored to ensure that it is working as anticipated to deliver the product with desired quality attributes. Process stability and process capability will be measured and evaluated. If any unexpected process variability is detected, appropriate actions will be taken to correct, anticipate, and prevent future problems so that the process remains in control. The additional knowledge gained during routine manufacturing will be utilized for adjustment of process parameters as part of the continual improvement of the drug product. As a commitment, the regulatory agency will be notified in accordance with CFR 314.70 regarding each change in each condition beyond the variability already provided in this application