CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218158Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number	NDA 218158		
Applicant Name	Formosa Pharmaceuticals, Inc.		
Drug Product Name	Clobetasol Propionate Ophthalmic Suspension		
Dosage Form	Suspension		
Proposed Strength(s)	0.05%		
NDA Classification	Type 5 – New Formulation or New Manufacturer		
Route of Administration	Ophthalmic		
Maximum Daily Dose	0.05 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	Treatment of post-operative inflammation and pain in patients following ocular surgery		
Drug Product Description	Clobetasol Propionate Ophthalmic Suspension 0.05%, is a sterile, preserved, multi-dose ophthalmic suspension packaged in a 5 mL LDPE white eyedropper with 3.5 mL fill volume.		
Co-packaged product information	NA		
Device information	A multi-dose LDPE eyedropper		
Storage Temperature/ Conditions	Store at 15°C to 25°C		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Stephanie Springer	Sithamalli Chandramouli
	Drug Product/ Labeling	Elise Luong	Chunchun Zhang
	Manufacturing	Sureshbabu Dadiboyena	Sudipan Karmakar

	Biopharmaceutics	Rajesh Savkur	Kevin Wei
	Microbiology	David Bateman	Laura Wasil
	Other (specify)	NA	
	RBPM	Shazma Aftab	
	ATL	Chunchun Zhang	
Consults			

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The proposed shelf life of 24 months is granted when store at 15°C to 25°C (59°F to 77°F).

b. Additional Comments for Action: NA

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

Satisfactory information and responses have been submitted to support the drug substance, drug product, manufacturing process, biopharmaceutics and quality microbiology aspects.

The product is regulated as a drug and device combination product per the Genus decision. However multi-dose eyedroppers are considered low risk; and CDRH confirmed that a CDRH consult review is not necessary on 5/12/2023.

All the manufacturing facilities are acceptable based on the profile review and inspectional history. OPMA issued an overall recommendation of "approval" on Jul 21, 2023. Therefore, NDA 218158 is recommended Approval from Product Quality perspective.

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate

Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: NA

Application Technical Lead Name and Date: Chunchun Zhang, Ph.D.; 12/21/2023

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CHAPTER III: ENVIRONMENTAL

R REGIONAL INFORMATION

Environmental Analysis (EA)

In accordance with 21 CFR 25.31(a), Formosa Pharmaceuticals, Inc. hereby claims a categorical exclusion from the requirement to prepare an Environmental Assessment since the estimated introduction concentration (EIC) of Clobetasol Propionate at the point of entry into aquatic system will be less than 1 part per billion, equivalent to 1 microgram per liter. To the applicant's knowledge, no extraordinary circumstances exist that would suggest a potential for serious harm to the environment or adverse effects on protected species at the expected level of exposure.

Assessment: ***Adequate from a CMC perspective.***

To the best knowledge of the applicant, no extraordinary circumstances exist associated with the proposed actions. The EA review team will document its review under the OND's Integrated Review Process (if applicable).

Primary Environmental Assessor Name and Date: Elise Luong, Ph.D.; 12/18/2023.

Secondary Assessor Name and Date (and Secondary Summary, as needed): ChunChun Zhang, Ph.D.; 12/18/2023 I concur with the reviewer's assessment.

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	Pending review by DMEPA
Established name(s)	Clobetasol propionate	Adequate
Route(s) of administration	Topical ophthalmic (b) (4)	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Ophthalmic suspension (b) (4) (b) (4) (b) (4) containing (b) (4) clobetasol propionate (b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

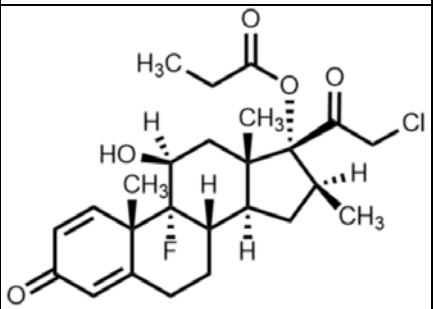
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	[redacted] (b) (4) wash hands well before each use. Instill one drop of [redacted] (b) (4) into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.	Adequate

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	(b) (4) suspension containing (b) (4) clobetasol propionate at 0.5 mg/mL	Adequate
Strength(s) in metric system	0.5 mg/mL (0.05% (b) (4)	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary Name Established name(s)	(b) (4) Clobetasol propionate	Pending review by DMEPA
Dosage form(s) and route(s) of administration	Topical Ophthalmic (b) (4) suspension	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	N/A
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Sodium Chloride, Hydrogenated Soybean Lecithin, Citric Acid, Glycerin, Poloxamer 407, Polyvinyl alcohol, Boric Acid, Edetate Disodium Dihydrate, Methylcellulose, Trisodium Citrate, Water for Injection Preservative: Benzalkonium Chloride	Adequate
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	N/A

If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The drug product does not contain alcohol	N/A
Statement of being sterile (if applicable)	This product is sterile	Adequate
Pharmacological/ therapeutic class	Corticosteroid	Adequate
Chemical name, structural formula, molecular weight	 Molecular weight: 467 (b) (4) $C_{25}H_{32}ClFO_5$	Adequate
If radioactive, statement of important nuclear characteristics	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	Section 3.2.S.1.2	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	N/A

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	There is no misleading statement on the labels.	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	(b) (4) suspension	Adequate
Strength(s) in metric system	0.5 mg/mL (0.05% (b) (4)	See comment(s) to labeling team
Available units (e.g., bottles of 100 tablets)	(b) (4) is supplied (b) (4) sterile (b) (4) in low-density polyethylene (LDPE) eye-dropper bottle (5 mL) with LDPE (b) (4) tip and high-density polyethylene (HDPE) pink cap. 3.5 mL in a 5-mL bottle	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	(b) (4)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.)	Store upright at 15 °C to 25 °C (59 °F to 77 °F). Do not freeze. Do not use if tamper-evident ring seal is broken. Keep the bottle tightly closed with the pink cap (b) (4) not in use.	Adequate.
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	N/A	N/A
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 15 °C to 25 °C (59 °F to 77 °F). Do not freeze	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid	N/A	N/A

statements such as “latex-free.”		
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.
Please include your comments about other sections of labeling if they contain product quality information.

Assessment: There is no other sections of labeling.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Manufactured (b) (4): Formosa Pharmaceuticals, Inc. Taipei, Taiwan, (b) (4) (no street address)	See comment(s) to the labeling team

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Labeling will be finalized through OND during labeling negotiations with the applicant.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

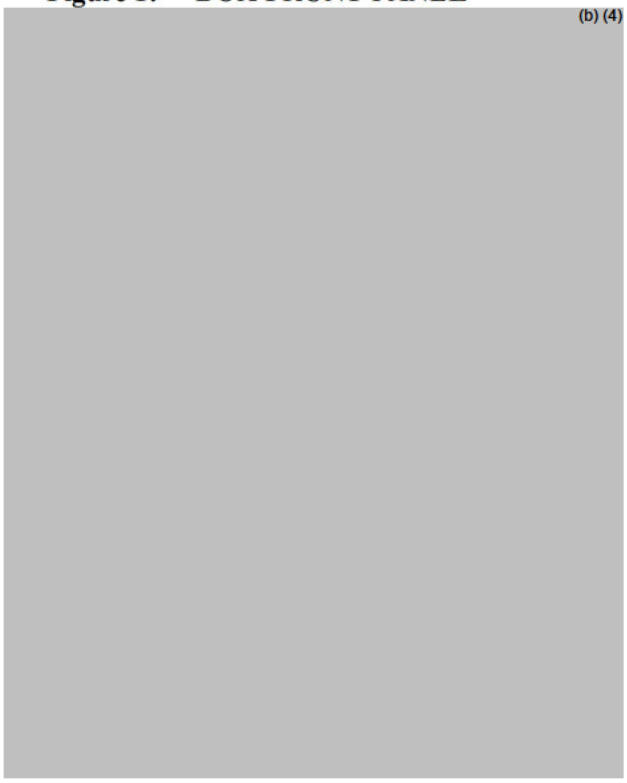
3.1 Container Label

(Representative examples of a proposed containers)

Figure 1 to Figure 6 show the proposed text on the 6 panels of the carton box. Figure 7 shows the text of the label affixed to the bottle itself. Figure 8 represents the final folded carton.

Carton Label (5-mL bottle, 3.5 mL drug product)

Figure 1: BOX FRONT PANEL



3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	(b) (4)	Pending review by DMEPA
Dosage strength	0.5 mg/mL (0.05% (b) (4) (b) (4)	Adequate
Route of administration	Topical (b) (4)	Adequate
Net contents (e.g., tablet count)	(b) (4)	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Labels contain space for NDC number	Adequate
Lot number and expiration date	Labels contains space for Lot number and expiration date	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 15°C to 25°C (59°F to 77°F). Do not freeze	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use).	N/A	N/A

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	The product does not contain alcohol.	Adequate
Bar code	Labels have space for bar code	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Manufactured for: Formosa Pharmaceuticals, Inc. Taipei, Taiwan, (b) (4)	Adequate
Medication Guide (if applicable)	There is a statement of See (b) (4)	Adequate
No text on Ferrule and Cap Overseal	N/A	N/A
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	N/A
And others, if space is available	N/A	N/A

Assessment of Carton and Container Labeling:

The product labels have all the relevant information in accordance with regulatory requirements from a CMC perspective, except the followings, which have been conveyed to the labeling team:

1. Drug product labeling review of Full Prescribing Information, in section 11 Description, also provide the Pharmacological/therapeutic class.

2. In Section 16.1 How Supplied, after (b) (4) clobetasol propionate ophthalmic (b) (4) suspension, 0.05%, add 0.5 mg/mL.

3. The draft labeling missing 1.2.6 Manufacturing Information After Section 17 (for drug product). Amend the label with 1.2.6 for the Name and location business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer.

Labeling will be finalized through OND during labeling negotiations with the applicant.

ITEMS FOR ADDITIONAL ASSESSMENT

None.

Overall Assessment and Recommendation:

The product labels are acceptable from a CMC perspective other than those in comments. Labeling will be finalized through OND during labeling negotiations with the applicant.

Primary Labeling Assessor Name and Date: Elise Luong, Ph.D., 12/18/2023. Secondary Assessor Name and Date (and Secondary Summary, as needed): ChunChun Zhang, Ph.D., 12/18/2023, I concur with the reviewer's assessment.

Elise Luong

Digitally signed by Elise Luong
Date: 12/18/2023 06:04:46AM
GUID: 537253e70005b48ebb030e8b349f32e6

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 12/18/2023 07:24:25AM
GUID: 51269608000064178e75377202fe6c5d

CHAPTER VI: BIOPHARMACEUTICS

NDA Number	NDA-218158-ORIG-1
Submission History	5/4/2023 (Seq 0001): Original submission 7/24/2023 (Seq 0004): Response to Biopharmaceutics IR#1 10/3/2023 (Seq 0009): Response to Biopharmaceutics IR#2
Drug Product Name/ Strength	Clobetasol Propionate (APP13007) Ophthalmic Nanosuspension, 0.05%
Route of Administration	Ophthalmic/Topical
Applicant Name	Formosa Pharmaceuticals Inc.
Therapeutic Classification/ OND Division	DO
Proposed Indication	Clobetasol Propionate Ophthalmic Nanosuspension is indicated for the treatment of post-operative inflammation and pain in patients following ocular surgery.
IND Number	IND-128133
Primary Reviewer	Rajesh Savkur, Ph.D.
SPQA	Kevin Wei, Ph.D.
Assessment Recommendation	**Adequate**

EXECUTIVE SUMMARY

In this submission, the Applicant seeks approval of Clobetasol Propionate (APP13007) Ophthalmic Nanosuspension, 0.05%. Clobetasol Propionate (also known as Clobetasol 17-Propionate), a synthetic analog of Prednisolone, has potent glucocorticoid activity and weak mineralocorticoid activity. The proposed drug product is indicated for the treatment of post-operative inflammation and pain in patients following ocular surgery. NDA-218158-ORIG-1 was initially submitted to the Division of Ophthalmology on 5/4/2023 under section 505(b)(2). The proposed drug product is intended to be an immediate release product, and is available as a 0.05% nanosuspension. The proposed dosing regimen is to instill 1 drop in the [redacted] (b) (4) operated eye twice daily for 14 days.

The Listed Drug (LD) product, Temovate® 0.05%, is available as a cream and an ointment (Clobetasol Propionate cream, 0.05% [NDA-019322; approved on 12/27/1985] and Clobetasol Propionate ointment, 0.05% [NDA-019323; approved on 12/27/1985]). In addition to referencing the safety and efficacy information from the LD products, the Applicant proposes to conduct non-clinical pharmacology, pharmacokinetics and toxicology studies. In addition, clinical studies have been conducted to evaluate the systemic exposure of the drug following ocular instillation, and assess the efficacy and safety of the drug product.

***Assessment Summary*:**
The Biopharmaceutics assessment focuses on evaluating (i) the proposal to exclude the *in vitro* drug release method/acceptance criterion from the QC testing and (ii) the bridging data between the clinical, registration and commercial/to-be-marketed drug products.

- ***In vitro drug release (IVR) test and acceptance criterion*:**
  The Applicant proposes to exclude the IVR test from the quality control (QC) testing of the proposed drug product. According to the Applicant, the particle size distribution (PSD) of the clobetasol propionate active pharmaceutical ingredient (API) is the only critical bioavailability attribute (CBA) for the proposed drug product that may impact the ocular bioavailability and it has been controlled and maintained using a Dynamic Light Scattering method, the IVR test/specifications offer no additional benefit over the current approach (Dynamic Light Scattering method) of monitoring and controlling this CBA, and in mitigating the risk towards maintaining product quality at release and through the stability period. Considering that the efficacy and safety of the proposed topical ophthalmic drug product have been demonstrated by the submitted clinical studies and in light of the FDA's Draft Guidance for Industry: *Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry* (October 2023), the IVR test/acceptance criterion as part of the drug product release specifications are not deemed necessary for approval of this drug product. However, the Applicant has been encouraged to develop a discriminating and bio-predictive IVR method for the proposed drug product to assess product sameness for the minor and/or moderate post-approval change(s). The adequacy of the information and the requirement for an IVR test in support of the post-approval change(s) would be determined upon future submission.

- ***Product Bridging*:**
  Bridging of formulations: The proposed drug product for registration and commercialization has the same composition as that used in the pivotal Phase 3 studies and the pivotal toxicology study. The Phase 3 clinical batches and registration batches were manufactured with the same process under cGMP. The formulation used in the clinical studies, registration and proposed commercial batches is the same. A bridging of formulations is not required.

  Bridging of batch sizes: The sizes of the clinical/registration and the proposed commercial batch are (b) (4) kg. A bridging of the batch sizes is not required.

  Bridging of manufacturing sites: The final drug product used in the clinical studies/registration batches is manufactured at a single site – (b) (4) A bridging of manufacturing sites is not required.

***List of Submissions being assessed*:**

5/4/2023	NDA-218158-ORIG-1/Original Submission (Sequence 0001)

7/24/2023	Response to Information Request# 1/Biopharmaceutics (Sequence 0004)
10/3/2023	Response to Information Request# 2/Biopharmaceutics (Sequence 0009)

Concise Description of Outstanding Issues *(list bullet points with key information and update as needed*):
None

OVERALL BIOPHARMACEUTICS RECOMMENDATION:
From a Biopharmaceutics perspective, NDA-218158-ORIG-1 for Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%, is **ADEQUATE** and is **RECOMMENDED FOR APPROVAL**.

B.1. BCS DESIGNATION:
Assessment: Not Applicable

Solubility and Permeability:
The solubility of the clobetasol propionate API (Response to IR#1; sequence 0004; Appendix 1) across the drug product and physiological pH range of 5.0–7.4 is shown below in Table 1.

Table 1: Solubility of the clobetasol propionate drug substance in buffers at various pH

API Lot No.	Solubility (µg/mL) pH 5.0	Solubility (µg/mL) pH 6.0	Solubility (µg/mL) pH 7.4
202002140007	1.77	1.44	1.07
202002140008	1.59	1.20	1.14
202008060002	1.52	1.23	1.02
Average	1.63	1.29	1.08
RSD	7.86%	10.0%	5.82%

***Reviewer's assessment*:**
At the strength of 0.5 mg (i.e., 0.05% suspension; 0.05 g/100 mL) and the lowest solubility of 0.00108 mg/mL (i.e., 1.08 µg/mL at pH 7.4), the volume of solvent required to dissolve the drug substance is 0.5/0.00108 = 462.9 mL. Hence, the clobetasol propionate API can be considered as a low-solubility drug substance. Since the drug product is intended to be administered via the ophthalmic (topical) route, the intestinal permeability and BCS classification of the API are not applicable.

B.2. IN VITRO DRUG RELEASE METHOD AND ACCEPTANCE CRITERIA:
Assessment: Adequate

In vitro drug release (IVR) test and acceptance criterion:
The Applicant proposes to exclude the IVR test from the quality control (QC) testing of the proposed drug product. In response to IR#1 (sequence 0004; Appendix 1), the Applicant stated that the API-particle size distribution (PSD) was the only CBA and well-controlled. Thus, the IVR test was unnecessary and not physiologically relevant to correlate with the *in vivo* performance of the nanosuspension formulation of clobetasol propionate for topical ophthalmic administration.

***Reviewer's assessment*:**
The composition of the drug product is shown below in Table 2.

Table 2: Composition of Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%

Component	Quality Standard	Function	Formulation Composition (%w/v) [a]
Clobetasol Propionate	USP	Active ingredient	0.05 [b]
Sodium Chloride	USP		(b) (4)
Hydrogenated Soybean Lecithin	NF		
Citric Acid (b) (4)	USP		
Glycerin	USP		
Poloxamer 407	NF		
Polyvinyl Alcohol	USP		
Boric Acid	NF		
Edetate Disodium Dihydrate	USP		
Benzalkonium Chloride	NF	Preservative	0.0036
Methylcellulose	USP		(b) (4)
Tri-Sodium Citrate (b) (4)	USP		
Water for Injection	USP		

Based on the low-solubility of the API and the final drug product being a suspension, the IVR test as part of the finished drug product specifications at release and through stability are useful in ensuring consistent product quality. In addition, the IVR test/specifications are also useful in assessing product "sameness" for certain post-approval changes (e.g., formulation and/or manufacturing process changes, product scale-up). Thus, in the IR (IR#1), the Applicant was recommended to develop a discriminating and bio-predictive IVR method or provide a justification for excluding the IVR test from the quality control (QC) testing of the proposed drug product. The details of the IR, the Applicant's response and the Reviewer's assessment are provided in Appendix 1. Based on the information submitted in the IR response, the Reviewer notes that the API has been micronized and nano-milled from ~40,000 nm to ~(b) (4) nm (Appendix 1; Figure 1A). Prior to the nano-milling process, the unprocessed API clobetasol propionate particles are practically insoluble (b) (4) (b) (4). Thus, the API-PSD is a critical bioavailability attribute (CBA) that impacts drug release and ocular bioavailability of the "solubilized" API. A comparison of the PSD of the API in the drug product batches (Table 3) indicates a variability (%RSD) of (b) (4) in the API-PSD between batches.

Table 3: API-PSD data of all GMP batches manufactured throughout the development of APP13007

PSD	Specification at Release	Lot. A0501	Lot. A0507	Lot. TR010	Lot. TR011	Lot. TR016	Lot. TR022	Lot. TR023	Lot. TR049	%RSD
Mean (nm)	(b) (4)	151	134	142	132	144	166	160	134	(b) (4)
D90 (nm)									(b) (4)	
D50 (nm)										
D10 (nm)										

*acceptance criteria were tightened from report value to current value starting from Lot TR022

The ocular and systemic bioavailability of the drug (two drops; 100 µL, 50 µL/eye) upon administration in rabbits (PK study: APP13007-ADME-001; Table 4A) is shown below in Table 4B.

Table 4A: APP13007-ADME-001: Study Design

Group	Treatment	Dose Volume (µL/eye)	Dose Frequency	Treated Eye	Terminal Time Points (hours post-dose)	Number of Males
1	0.05% APP13007	50	Once	OS and OD	0.25, 0.5, 1, 2, 4, 8, 12, 24	24

Table 4B: PK parameters of clobetasol propionate in the plasma and ocular tissues following a single bilateral instillation of 0.05% APP13007 in rabbits

Matrix	C_{max} (ng/mL or ng/g)	t_{max} (h)	AUC_{0-t} (h*ng/mL or h*ng/g)	$t_{1/2}$ (h)	t_{last} (h)
Plasma	2.19± 0.0877	0.25	2.36± 0.0807	3.17	12
Cornea	3240± 369	0.25	4240± 237	5.42	24
Palpebral Conjunctiva	1720± 199	0.25	997± 83.3	4.52	24
Bulbar Conjunctiva	1390± 163	0.25	778± 49.3	4.45	24
Sclera	59.2± 6.91	0.25	97.8± 3.53	3.3	24
Aqueous Humor	46.9± 9.77	0.5	68.9± 4.72	1.05	12
Iris/Ciliary Body	117± 13.3	0.5	231± 12.2	1.72	12
Lens	8.05± 0.493	2	86.8± 7.20	15	24
Vitreous Humor	0.0595± 0.0287	0.25	0.0570± 0.0126	NR	4
Retina/Choroid/RPE	6.36± 0.707	0.5	22.6± 0.830	3.65	12
Optic Nerve	5.59± 0.922	0.5	22.6± 4.94	NR	12

Based on the submitted data, the drug is quantifiable and reaches the maximum concentration in the rabbit ocular tissues within 30 minutes of administration (C_{max} in the cornea, palpebral conjunctiva, bulbar conjunctiva and sclera = 0.25 hours; C_{max} in aqueous humor and iris/ciliary body = 0.5 hours). The concentration of the drug in the ocular tissues is higher than in the plasma. Although the bioavailability of the drug in human ocular tissues is not known, based on the information on the PK parameters in rabbits, this Reviewer concludes that the nano-milled API would penetrate through the human ocular tissues upon surface instillation. Based on the totality of the information, including the low inter-batch variability ((b) (4) RSD) in the API-PSD, this Reviewer concludes that PSD of the API is controlled, and the IVR test/specifications would offer no additional benefit over the current approach (Dynamic Light Scattering method) of monitoring and controlling this CBA when maintaining product quality at release and through the stability period.

Considering that the efficacy and safety of the proposed topical ophthalmic drug product have been demonstrated by the submitted clinical studies and in light of the FDA's Draft Guidance for Industry: *Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry* (October 2023), the IVR test/specifications may not be required at the current stage for approval of the drug product nor are they required as a routine batch-to-batch quality control test. However the IVR test is still useful to assess product "sameness" for post-approval changes (e.g., minor and moderate formulation and/or manufacturing process changes, product scale-up). Thus, in the IR (IR#2), the Applicant was encouraged to develop a discriminating and bio-predictive IVR method for the proposed drug product. The details of the IR, the Applicant's response and the Reviewer's assessment are provided in Appendix 1. In the IR response, the Applicant reiterated that since the API-PSD was the only CBA that may impact the ocular bioavailability, this attribute was well-controlled, and an IVR test is unnecessary for the QC testing of their

product. In addition, the Applicant stated that they have examined the literature for available IVR tests/methods for ophthalmic suspensions. However, none of the methods could be meaningfully applied to a nanosuspension drug product like APP13007 that has a mean particle size in the (b) (4) nm range, due to the pore size of the dialysis membrane larger than the product PSD. The Applicant further stated that the current quality control processes are robust and comprehensive, and align with the current regulatory standards, and are sufficient to assure the quality of the product. In addition, they will monitor and assess the necessity of an appropriate and feasible IVR test/method as a relevant quality control measure as circumstances evolve. This Reviewer concludes that the adequacy of the information and the requirement for an IVR test in support of the post-approval change(s) would be determined upon future submission.

B.12. BRIDGING OF PRODUCTS:
B.12a. BRIDGING OF PROPOSED PRODUCT TO THE LD PRODUCT:
Assessment: Adequate

***Reviewer's assessment*:**
The Listed Drug (LD) product Temovate® 0.05% is available as a cream and an ointment (Clobetasol Propionate cream, 0.05% [NDA-019322] and Clobetasol Propionate ointment, 0.05% [NDA-019323]).

In addition to conducting non-clinical pharmacology, pharmacokinetics and toxicology studies, the Applicant references the information submitted in the LD products.

The Applicant has conducted one Phase 1 (to evaluate the systemic exposure of the drug following ocular instillation), one Phase 2 (to assess the safety, tolerability and preliminary efficacy) and two Phase 3 (to evaluate the efficacy and safety) studies. A waiver of the *in vivo* pharmacokinetic, safety and efficacy studies has not been requested. The *in vivo* BA studies are being evaluated by the Office of Clinical Pharmacology.

B.12b. BRIDGING OF FORMULATIONS, BATCH SIZES AND MANUFACTURING SITES:
Assessment: Adequate

Bridging of formulations:
***Reviewer's assessment*:**
The proposed drug product for registration and commercialization has the same composition (Table 2) as that used in the pivotal Phase 3 studies and the pivotal toxicology study. The Phase 3 clinical batches and registration batches were manufactured with the same process under cGMP. The formulations used in the clinical studies, registration and proposed commercial batches are the same. A bridging of formulations is not required.

Bridging of batch sizes:
***Reviewer's assessment*:**
The sizes of the clinical/registration and the proposed commercial batch are (b) (4) kg. A bridging of the batch sizes is not required.

Bridging of manufacturing sites:
***Reviewer's assessment*:**
The final drug product used in the clinical studies/registration batches is manufactured at a single site – (b) (4). A bridging of manufacturing sites is not required.

B.13. BIOWAIVER REQUEST:
Assessment: Not Applicable

***Reviewer's assessment*:**
The proposed drug product exists in one strength – 0.05%. A Phase 1 study was conducted to evaluate the systemic exposure of the drug following ocular instillation. In addition, two Phase 3 studies were conducted to evaluate the efficacy and safety of the drug product. A waiver of the *in vivo* pharmacokinetic, safety and efficacy studies has not been requested. The *in vivo* BA studies are being evaluated by the Office of Clinical Pharmacology.

R. REGIONAL INFORMATION:
Life Cycle Management Considerations and Risk Mitigation Strategies

***Reviewer's assessment*:**
Based on the low-solubility of the API, the API-PSD is a CBA that impacts drug dissolution and ocular bioavailability of the drug product. As part of the risk mitigation strategy, the Applicant proposes a three-tier PSD specification (Table 3) to control the API particle size, ensure consistent *in vivo* drug release, and maintain the quality of the drug product through the shelf-life. The Applicant proposes to use a Dynamic Light Scattering method to monitor and control API particle size in lieu of an IVR test. Based on the totality of the information, including the low inter-batch variability ((b) (4) RSD) in the API-PSD (Table 3), this Reviewer concludes that PSD of the API is controlled and the IVR test/specifications offer no additional benefit over the current approach (Dynamic Light Scattering method) of monitoring and controlling this CBA when maintaining product quality at release and through the stability period. Thus, considering that the efficacy and safety of the proposed topical ophthalmic drug product have been demonstrated by the submitted clinical studies and in light of the FDA's Draft Guidance for Industry: *Quality Considerations for Topical Ophthalmic Drug Products Guidance for Industry* (October 2023), the Biopharmaceutics risk for the proposed topical ophthalmic drug product is considered low and the IVR test as part of the drug product release specifications are not deemed necessary for approval of this drug product.

Although the IVR test/specifications may not be required at the current stage for approval of the drug product nor are they required as a routine batch-to-batch quality control test, the IVR test is still useful to assess product "sameness" for post-approval changes (e.g., minor and/or moderate formulation and/or manufacturing process changes, product scale-up). The Applicant has been encouraged to develop a discriminating and bio-predictive IVR method for the proposed drug product to assess product sameness for any post-

approval change(s). The adequacy of the information and the requirement for an IVR test in support of the post-approval change(s) would be determined upon future submission.

BIOPHARMACEUTICS LIST OF DEFICIENCIES:
None

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CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	218158
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Clobetasol Propionate Ophthalmic Nanosuspension, 0.05% multi-dose bottle
Route of Administration	Topical ophthalmic solution
Applicant Name	Formosa Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Division of Ophthalmology in the Office of Specialty Medicine
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:
The drug product is (b) (4) filled into 5 mL eye dropper bottles.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0001	May 4, 2023
eCTD Seq #0004	July 24, 2023
eCTD Seq #0012	October 27, 2023
eCTD Seq #0014	November 28, 2023
eCTD Seq #0015	December 14, 2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product is supplied as a solution in 5 mL bottles.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed): None.

Supporting Documents: None

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** A preserved multi-dose solution of a nanosuspension filled into 5 mL opaque eyedropper bottles with opaque nozzle.

- **The applicant provided the following drug product composition summary table (3.2.P.1, SEQ0005, Description and composition of the drug product_Aug2023(APP13007, Nanosuspension), page 2):**

Table 3.2.P.1.1 The Composition of APP13007 (Clobetasol Propionate Ophthalmic Nanosuspension, 0.05%)

Component	Quality Standard	Function	Formulation Composition (%w/v) [a]	Formulation Composition (mg/mL)	Amount Per Drop (mg) [c]
Clobetasol Propionate	USP	Active ingredient	0.05 [b]	0.5	(b) (4)
Sodium Chloride	USP	(b) (4)			
Hydrogenated Soybean Lecithin	NF				
Citric Acid (b) (4)	USP				
Glycerin	USP				
Poloxamer 407	NF				
Polyvinyl Alcohol	USP				
Boric Acid	NF				
Edetate Disodium Dihydrate	USP				
Benzalkonium Chloride	NF	Preservative	0.0036	0.036	
Methylcellulose	USP	(b) (4)			
Tri-Sodium Citrate (b) (4)	USP				
Water for Injection	USP				
(b) (4)					

- **Description of container closure system:**

Component	Description	Manufacturer
Bottle	Round eye dropper LDPE bottle, 5 mL white opaque color (b) (4)	(b) (4)
Nozzle	LDPE nozzle for 5 mL eye dropper bottle, white opaque color (b) (4)	
Cap	HDPE cap for 5 mL eye dropper bottle, pink color (b) (4)	

Adequate

Reviewer's Assessment:
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

P.2 Pharmaceutical Development

(b) (4)

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(b) (4)

Adequate

Reviewer's Assessment:
The applicant provided acceptable instructions for the drug product which are comparable to the refence listed drug product.

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date:
David Bateman, Ph.D. (December 15, 2023)

Secondary Assessor Name and Date
Laura Wasil, Ph.D. (December 15, 2023)

Laura Wasil

Digitally signed by Laura Wasil
Date: 12/15/2023 11:21:41AM
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David Bateman

Digitally signed by David Bateman
Date: 12/15/2023 11:19:48AM
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/s/

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