

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214510Orig1s000

PRODUCT QUALITY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 4, 2022
From: Hamid Shafiei, Ph.D.
Application Technical Lead, Branch IV
Division of New Drug Products 2
Office of New Drug Products

To: To Executive Summary, IQA for Assessment # 1 of NDA 214510

Subject: Amendment #1: Final Recommendation of Approval

In the original IQA review #1 dated April 7, 2021, this application was not recommended for approval from the OPQ perspective because of the pending required preapproval inspection of the drug product manufacturing facility, [REDACTED] (b) (4) [REDACTED] which had been deferred due to the travel restrictions associated with COVID-19 pandemic. The inspection of this facility was complete on February 17, 2022, and the facilities involved in this application have received an overall recommendation of adequate from the Office of Pharmaceutical Manufacturing Assessment (OPMA) which now supports the approval of this application from the facilities perspective. The OPMA's review is attached as an Appendix to this memorandum.

Therefore, from the OPQ perspective this application is now recommended for **approval** with the expiration dating period of **24 months**.

Application Technical Lead:
Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ

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/s/

HAMID R SHAFIEI
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RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response
☒ Approval Pending Successful Completion of the Required Pre-Approval Inspection

NDA 214510 Assessment # 1

Drug Product Name	EPSOLAY (benzoyl peroxide)	
Dosage Form	Cream	
Strength	5%	
Route of Administration	Topical	
Rx/OTC Dispensed	Rx	
Applicant	Sol-Gel Technologies, Ltd.	
US agent, if applicable	B&H Consulting Services, Inc.	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA Submission	06/26/2020	All
Proprietary Name Request	07/07/2020	All
Response to Quality Information Request	08/28/2020	ONDP and OPMA
Response to Quality Information Request	09/08/2020	OPMA-DMA
Response to Clinical Information Request	09/11/2020	Clinical
Response to Quality Information Request	11/16/2020	ONDP and OPMA-DMA
Response to Clinical Information Request	11/17/2020	Clinical
Draft Labeling	12/04/2020	All
Response to Clinical Information Request	12/08/2020	Clinical
Response to Quality Information Request	12/09/2020	ONDP
Response to Quality Information Request	12/15/2020	ONDP and OPMA

Response to Quality Information Request	01/21/2021	ONDP and OPMA
Response to Quality Information Request	01/26/2021	OPMA
Response to Quality Information Request	01/29/2021	ONDP and Biopharm
Response to Quality Information Request	02/22/2021	OPMA
PI Labeling	03/18/2021	All

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Zhixing Shan, Ph.D.	Donna Christner, Ph.D.
Drug Product	Zhengfang Ge, Ph.D.	Wendy Wilson-Lee, Ph.D.
Manufacturing	Allison Aldridge, Ph.D.	Rose Xu, Ph.D.
Microbiology	Alifiya Ghadiali, Ph.D.	Samata Tiwari, Ph.D.
Biopharmaceutics	Leah Falade, Ph.D.	Tapash Ghosh, Ph.D.
Regulatory Business Process Manager	Melinda Bauerlien, M.S.	
Application Technical Lead	Hamid Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Zhengfang Ge, Ph.D.	Wendy Wilson-Lee, Ph.D.

EXECUTIVE SUMMARY

[IQA NDA Assessment Guide Reference](#)

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

- The applicant of this 505(b)(2) new drug application **has** provided **sufficient CMC information** to assure the identity, strength, purity, and quality of the drug substance, benzoyl peroxide, and the drug product, EPSOLAY (benzoyl peroxide) Cream, 5% for topical use.
- Facilities **have not** been cleared **pending the required preapproval inspection** of the drug product manufacturing facility, (b) (4) which has been deferred due to current travel restrictions associated with COVID-19 pandemic.
- The CMC issues on labels/labeling have been satisfactorily resolved in this review cycle.
- The applicant request's for categorical exclusion from the environmental assessment has been granted.

Therefore, from the OPQ perspective, the **APPROVAL** of this application is **deferred** to the successful completion of the required inspection of the drug product manufacturing site, (b) (4) as per 21 CFR 314.125(b)(13).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Sol-Gel Technologies, Ltd. has submitted this 505(b)(2) new drug application for EPSOLAY (benzoyl peroxide) Cream, 5% for topical use. EPSOLAY is indicated for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. EPSOLAY is intended for topical administration as a thin layer once daily to the affected skin area.

Rosacea is a chronic inflammatory disease that primarily affects the facial skin of adults. Benzoyl peroxide is an oxidizing agent that has been marketed for more than 50 years as the active ingredient of over-the-counter products at strengths of 2.5% to 10% for the treatment of acne vulgaris. Benzoyl peroxide has also been used as an active ingredient in multiple approved topical combination drug products.

Each gram of EPSOLAY cream contains 50mg of (b) (4) benzoyl peroxide as the active ingredient and silicone dioxide, cetrimonium

chloride, polyquaternium-7, lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, glycerin, mono and di-glycerides, macrogol stearate type 1 (b) (4), edetate disodium, cyclomethicone, cetyl alcohol, phenoxyethanol, and purified water as the inactive ingredients. The benzoyl peroxide in EPSOLAY is in a solid form that is incorporated into a microcapsule composed of silicon dioxide, cetrimonium chloride and polyquaternium-7.

EPSOLAY is white to off-white cream and will be packaged in as 50g in a 50-mL (commercial drug product) and as (b) (4)g in a 30-mL (physician sample) high-density polyethylene bottles with (b) (4) airless pumps and (b) (4) caps. This drug product should be stored at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F).

Proposed Indication(s) including Intended Patient Population	Treatment of inflammatory lesions of rosacea in adults 18 years of age and older
Duration of Treatment	As prescribed by physician
Maximum Daily Dose	A peas size amount should be applied as a thin layer to the affected skin area once daily.
Alternative Methods of Administration	None

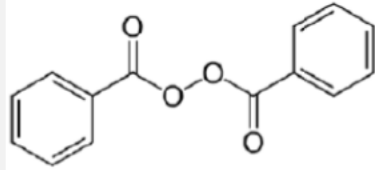
B. Quality Assessment Overview

Drug Substance: Adequate

The active ingredient, benzoyl peroxide is a compendial drug substance and has been classified as an oxidizing agent. Benzoyl peroxide has been marketed for more than 50 years as the active ingredient of topical over-the-counter products for the treatment of acne vulgaris. It has also been used as the active ingredient of multiple approved combination drug products for topical use.

Benzoyl peroxide is a white granular powder with a melting range of 103°C to 106°C and no observed polymorphic forms. It is sparingly soluble in water or alcohol and soluble in benzene, chloroform, and ether.

The IUPAC chemical name for benzoyl peroxide is benzoyl benzenecarboxylate. It has a molecular formula of $C_{14}H_{10}O_4$, a molecular weight of 242.23g/mol, and the chemical structure provided below:



Benzoyl peroxide, USP for this application is manufactured in accordance current Good Manufacturing Practices (cGMP) (b) (4)

(b) (4)
(b) (4). It

is tested, released, and accepted according to the USP compliant specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its currently assigned retest date of (b) (4). The detailed manufacturing process as well as supporting stability data for benzoyl peroxide supplied (b) (4) have been provided in DMF (b) (4). This DMF has been previously reviewed multiple times and recently on April 25, 2018 by LCAP Reviewer, Mst Hasina Akter and has been found to be adequate.

Relying of the previous reviews of DMF (b) (4) and the review of the information provided in the drug substance module of this application, the Drug Substance Reviewer, Dr. Zhixing Shan concluded that the drug substance information submitted is adequate to support the approval of this application from the drug substance perspective. Dr. Shan's review is provided in the Drug Substance Chapter of the Integrated Quality Assessment (IQA).

Drug Product: Adequate

The drug product, EPSOLAY (benzoyl peroxide) Cream, 5% is a white to off white cream containing 50mg of benzoyl peroxide per each gram. It will be packaged as 50g in a 50-mL (commercial drug product) and as (b) (4) in a 30-mL (physician sample) high-density polyethylene (HDPE) bottles with (b) (4) airless pumps and (b) (4) caps. This drug product is intended for topical administration as a thin layer to the affected skin area and it is indicated for the treatment of inflammatory lesions of rosacea in adults 18 years of age and older.

The active ingredient, benzoyl peroxide in this drug product (b) (4)
(b) (4). The encapsulation is intended to allow slow migration of the benzoyl peroxide through the microcapsules' shells leading to continuous release of this active ingredient over time and delivery to the affected skin area. (b) (4)

(b) (4)
(b) (4)
(b) (4). The inactive ingredients used in the manufacture of

EPSOLAY cream are silicone dioxide, cetrimonium chloride, polyquaternium-7, lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, glycerin, mono and di-glycerides, macrogol stearate type 1 (b) (4), edetate disodium, cyclomethicone, cetyl alcohol, phenoxyethanol, and purified water. Inactive ingredient used in this drug product are all compendial excipients with the exception of cetrimonium chloride (CTAC) and polyquaternium-7 (PDAC). The applicant has submitted information including specification and testing procedures in support of the qualification of these two non-compendial excipients for use in the formulation of the drug product. The information regarding CTAC and PDAC has been reviewed and evaluated from the CMC and Pharm/Tox perspectives and has been found to be adequate.

EPOSLEY cream is manufactured (b) (4) for Sol-Gel. The applicant has submitted the certificate that (b) (4) manufactures EPOSLEY cream for Sol-Gel in accordance to cGMP requirements. However, due travel restrictions associated with COVID-19 pandemic, this manufacturing facility cannot be inspected to confirm the site's compliance with the cGMP.

EPSOLAY cream is tested and released against a drug product specification that assures the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. The proposed expiration dating period of 24 months is supported by the stability data submitted in the application and is granted.

The applicant has also submitted a comparability protocol (b) (4) to (b) (4) be reviewed during the first review cycle of this NDA. Based on the adequacy determination of the comparability protocol, the applicant plans to submit a CBE-30 supplement post-approval (b) (4) (b) (4). The applicant comparability protocol has been reviewed and found to be adequate to support the post-approval submission of a CBE-30.

In summary, the drug product module of this application has been reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge has found the information provided in the application adequate and has recommended the approval of this application from drug product perspective. Dr. Ge's review is provided in the drug product chapter of the IQA.

The applicant's request for categorical exclusion from the preparation environmental assessment has also been reviewed by Dr. Zhengfang Ge. Dr. Ge has found the applicant's request valid and has recommended

granting the categorical exclusion for this application. The review of the categorical exclusion is also captured in the Drug Product Chapter of the IQA.

Labeling: Adequate

The CMC section of prescribing information (PI) labeling as well as the immediate container and carton labels were reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge identified multiple CMC labeling deficiencies in the PI as well as the immediate container and carton labels. These labeling/labels deficiencies were communicated to the applicant.

The applicant has submitted revised PI as well as the container closure and carton labels that have satisfactorily addressed the deficiencies noted in Dr. Ge's labeling review # 1. Based on the applicant response Dr. Ge has now recommended the approval of this application from the labeling perspective. Dr. Ge's labeling review # 1 and her addendum to labeling review # 1 dated April 6, 2021 are provided in Labeling Chapter of the IQA.

Manufacturing: Inadequate

(b) (4)

The applicant has provided batch records for three exhibits batches of drug product. The critical process parameters and (b) (4) controls have been adequately selected based on process development and are supported by the developmental data. The exhibit batches met the final drug product specification.

The manufacturing facilities have also been reviewed and found to be adequate with the exception of the drug product manufacturing facility, (b) (4). It has been determined that pre-approval inspection (PAI) (b) (4) is required before,

the overall manufacturing facilities for this application are cleared for approval.

The manufacturing process and the facilities have been reviewed by the Office of Pharmaceutical Manufacturing Assessment (OPMA) Reviewer, Dr. Allison Aldrich. Dr. Aldrich has found the manufacturing process adequate, but she has deferred the recommendation for the approval of this application from the manufacturing perspective until successful inspection of (b) (4) manufacturing facility is performed per 21 CFR 314.125(b)(13). Dr. Aldrich's review is provided in the Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The biopharmaceutics review of EPSOLAY cream was mainly focused on the proposed dissolution method, dissolution acceptance criteria, and the need for any bridging studies.

The proposed dissolution method was developed using USP apparatus 2 (paddle) at the rpm of 200 in 500mL of 2% Tween 60 in phosphate buffer with the pH of 6.8 at 37°C. The method has shown discriminating ability toward an aberrant formulation manufactured (b) (4) although the discriminating ability was not demonstrated toward the formulation manufactured (b) (4).

The applicant's proposed dissolution acceptance criteria of (b) (4)% - (b) (4)% in 1 hour, (b) (4)% - (b) (4)% in 6 hours, and not less than (b) (4)% in 24 hours are based on the results from the pivotal clinical and registration batches of drug product and are supported by the IVRT data. The proposed dissolution acceptance criteria are deemed adequate. Since the drug product formulation used in the pivotal studies is the same as the formulation of the to-be-marketed drug product and is manufactured at the proposed commercial manufacturing facilities, no formulation bridging study is needed.

The biopharmaceutics section of this applicant has been reviewed by the Biopharmaceutical Reviewer, Dr. Leah Falade. Dr. Falade has found the biopharmaceutics information provided in this application adequate and has recommended the approval of this application from the biopharmaceutics perspective. Dr. Falade's review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

This drug product is a non-sterile cream drug product for topical use that is packaged in a multi-use high-density polyethylene (HDPE) bottles with

(b) (4) airless pumps. Therefore, the microbiology review of this application was mainly focused on the critical aspects such as release testing (b) (4).

The applicant has provided sufficient data that supports the suitability of the method for microbial limits testing for TAMC and TYMC according to USP <61>, S. aureus and P. aeruginosa according to USP <62>, and BCC according to modified USP <62>. The applicant has also provided sufficient data in support (b) (4).

The microbiology section of this application has been reviewed by the Microbiology Reviewer, Dr. Samata Tiwari. Dr. Tiwari has found the information provided in the microbiology section of this application adequate to support the approval of this NDA from the Microbiology perspective. Dr. Tiwari's review is provided in the Microbiology Chapter of the IQA.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
Encapsulation of Benzoyl Peroxide	Release of Benzoyl Peroxide	M	(b) (4)	Acceptable	None

D. List of Deficiencies for Complete Response

Manufacturing Deficiencies

Facilities have not been cleared pending the required preapproval inspection of the drug product manufacturing facility, (b) (4).

(b) (4) which has been deferred due to current travel restrictions associated with COVID-19 pandemic.

Application Technical Lead:

Hamid Shafiei, Ph.D.
Branch IV/DNDP 2/ONDP/OPQ



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Shafiei

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QUALITY ASSESSMENT DATA SHEET

[IQA NDA Assessment Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	Adequate	25-APR-2018	Reviewed by Mst Hasina Akter Additional Information has been included in the NDA
	III			_____	_____	Sufficient information is provided in the NDA

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
N/A	N/A	N/A

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH-ODE	N/A			
CDRH-OC	N/A			
Clinical	N/A			
Other	N/A			

CHAPTER IV: LABELING

[IQA NDA Assessment Guide Reference](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The Prescribing Information is deemed not ADEQUATE as proposed until it is revised satisfactorily to meet the regulatory requirements (See the **List of Deficiencies** at the end of this review).

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	EPSOLAY	Adequate
Established name(s)	(b) (4) benzoyl peroxide) Cream	Not Adequate (b) (4) should be removed from the established name
Route(s) of administration	for topical use	Adequate
Dosage Forms and Strengths Heading in Highlights		

Summary of the dosage form(s) and strength(s) in metric system.	Cream, 5%. Each gram of Cream contains 50 mg (5%) (b) (4) benzoyl peroxide	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)



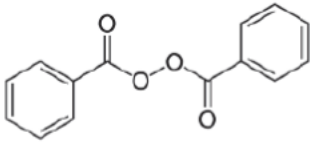
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) for topical use only. Not for oral, ophthalmic, or intravaginal use	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)	cream	Adequate
Strength(s) in metric system	5%	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	(b) (4) benzoyl peroxide in a white to off white (b) (4)	Not adequate Delete (b) (4)
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	EPSOLAY (b) (4) benzoyl peroxide)	Not Adequate - delete (b) (4) from the established name
Dosage form(s) and route(s) of administration	Cream	Not Adequate Add "for topical use"
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	Adequate
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	silicon dioxide, cetrimonium chloride, polyquaternium 7, lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, glycerin, mono and di glycerides, macrogol stearate Type I, edetate disodium, cyclomethicone, cetyl alcohol, phenoxyethanol and purified water	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	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Not provided	Adequate Per pharmacology review team leader Dr. B. Hill, there is no established PTC for benzoyl peroxide. Its function for antibacterial and keratolytic should be listed in section 12.

Chemical name, structural formula, molecular weight	Name: benzoyl benzenecarboperoxoate formula $C_{14}H_{10}O_4$ and molecular weight 242.23 	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)		

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	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	(b) (4)	Not Adequate This is promotional information and should be deleted

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)	cream	Adequate
Strength(s) in metric system	(b) (4)	Adequate
Available units (e.g., bottles of 100 tablets)	50 gram pump	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	white to off-white Cream NDC space holder is provided	Adequate Replace NDC space holder with actual number when available
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	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	
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.)	• Keep away from heat. • Do not freeze. (b) (4)	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	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F) with excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].	Not Adequate Add "discard unused cream 30 days after first use"
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	N/A	

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

1.2.5 Other Sections of Labeling

N/A

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	Marketed by Sol-Gel Technologies Inc. 110 South Jefferson Rd. Suite (b) (4) Whippany, NJ 07981 Product of Canada	Adequate

2.0 PATIENT LABELING

The following CMC information is provided in the Patient Labeling



The following Changes should be made:

1. The How should I store section should add “discard unused cream 30 days after first use”
2. Delet (b) (4) from the Active Ingredient section

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (blister wallet)



(b) (4)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence)	Epsolay (b) (4) benzoyl peroxide) cream	Not Adequate delet (b) (4) from the established name
Dosage strength	5%	Adequate
Route of administration	For topical use only. Not for ophthalmic, oral, or intravaginal use	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	50 g 3 g for physician sample	Adequate
"Rx only" displayed on the principal display	Provided	Adequate
NDC number	Provided	Adequate
Lot number and expiration date	Provided	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store at 68° to 77°F (20° to 25°C); excursions permitted to 59° to 86°F (15° to 30°C).	Not Adequate Add "discard unused cream 30 days after first use"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Provided	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Provided	Adequate
Medication Guide (if applicable)	(b) (4) (b) (4) is provided on container label	Not Adequate Revise to "Recommended Dosage: See prescribing information" on carton/container labels to be consistent with PI via DMEPA
No text on Ferrule and Cap overseas	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	
And others, if space is available	Each gram of EPSOLAY cream contains 50 mg (5%) of (b) (4) benzoyl peroxide Package is not child-resistant. Keep out of reach of children, are provided in carton label.	Not Adequate

Assessment of Carton and Container Labeling: *Inadequate*

1. Delete (b) (4) from the established name
2. Add "discard unused cream 30 days after first use" for the storage conditions
3. Delete (b) (4) from "Each gram of EPSOLAY cream contains 50 mg (5%) of (b) (4) benzoyl peroxide"

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

The following changes have been implemented in the PI

For Prescribing Information:

1. Delete (b) (4) from established name

Section 11 Description

2. Add “for topical use” after dosage form
3. Add pharmacological/therapeutic category “Benzoyl peroxide is an antibacterial and keratolytic agent”
4. Delete (b) (4)

Section 16: How Supplied

5. Add “discard unused cream 30 days after first use”

Patient Labeling:

6. The How should I store section should add “discard unused cream 30 days after first use”
7. Delete (b) (4) from the Active Ingredient section

The following deficiencies in the carton/container labels need to be conveyed to the applicant

1. Delete (b) (4) from the established name
2. Add “discard unused EPSOLAY 30 days after first use” for the storage conditions
3. Delete (b) (4) from “Each gram of EPSOLAY cream contains 50 mg (5%) of (b) (4) benzoyl peroxide”

Overall Assessment and Recommendation:

The NDA is not ready for approval in its present form per CFR 314.125(b)(6) until the outstanding labeling issues listed in the **List of Deficiencies** are satisfactorily resolved.

Primary Labeling Assessor Name and Date:

Zhengfang Ge, Ph. D.

*Reviewer, BRANCH IV/DIVISION II
OFFICE OF NEW DRUG PRODUCT*

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Wendy Wilson, Ph. D.
*Director/DIVISION II
OFFICE OF NEW DRUG PRODUCT*



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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 5, 2021

From: Zhengfang Ge, Ph.D.
ONDP/Division II/Branch IV

Through: Wendy Wilson, Ph.D.
Director, ONDP/Division II

To: Labeling Review of NDA 214510: EPSOLAY (benzoyl peroxide) cream

Subject: Final Recommendation for Labeling/Labels

The CMC related deficiencies have been adequately addressed in the revised labeling. The [REDACTED] (b) (4) has been removed from the established name, PI and PPI. The applicant includes “The benzoyl peroxide in EPSOLAY is in a solid form that is incorporated into a microcapsule composed of silicon dioxide, cetrimonium chloride and polyquaternium-7” in Section 11 of the labeling, which is similar to a microcapsule description in the approved drug product Carac (fluorouracil cream) cream and is acceptable. The revised container/carton labels are satisfactory and provided in the **Attachment**.

Recommendation:

This NDA is **now** recommended for **Approval** from the labeling perspective.

CHAPTER VI: BIOPHARMACEUTICS

[IQA NDA Assessment Guide Reference](#)

NDA Number	NDA-214510-ORIG-1
Drug Product Name/ Strength	Benzoyl Peroxide Cream, 5%
Route of Administration	Topical
Applicant Name	Sol-Gel Technologies Ltd.
Therapeutic Classification/ OND Division	Antiacne/Division of Dermatology and Dentistry
RLD/RS Number	N/A
Proposed Indication	For the topical treatment of inflammatory lesions of rosacea in adults 18 years and older.
Primary Reviewer	Leah W. Falade, Ph.D.
Secondary Reviewer	Tapash Ghosh, Ph.D.

Assessment Recommendation: Adequate

Background:

Sol-Gel Technologies is seeking approval for its Benzoyl Peroxide (BPO) Cream, 5% for topical administration for the treatment of inflammatory lesions of rosacea in adults 18 years and older. The proposed product is a cream formulation containing microcapsules of benzoyl peroxide. The microcapsules are designed to allow a slower release of benzoyl peroxide to be released over time than conventional release dosage forms administered by the same route.

The Applicant has submitted this NDA to the Division of Dermatology and Dentistry under the 505(b)(2) pathways relying on the documented clinical history of benzoyl peroxide in humans, with no noted cardiovascular safety signals. Benzoyl peroxide is generally recognized as safe and effective (GRASE) and is an active ingredient that has been on the market for decades for the over-the-counter (OTC) topical treatment of acne and is used off-label for patients with rosacea. The Applicant has submitted a request for a waiver for a clinical QT/QTc study.

Assessment Summary:

The Biopharmaceutics review focuses on the evaluation and acceptability of 1) the proposed dissolution method and acceptance criteria, and 2) the bridging throughout the product development, with key findings summarized below:

- 1) **Dissolution Method and Acceptance Criteria:** The Applicant proposed a dissolution method using USP Apparatus 2 (paddle) at 200 rpm in 500 mL of 2% Tween 60 in pH 6.8 phosphate buffer at 37°C. The proposed dissolution method was demonstrated to have

discriminating ability toward an aberrant formulation manufacture (b) (4). However, the method was not shown to be discriminating towards a formulation manufactured (b) (4).

The acceptance criteria include three time-points at early (1-hr), middle (6-hr), and late (24-hr) of the dissolution profiles. The proposed acceptance criteria were based on the mean dissolution profile data of the pivotal clinical batch and registration batches. Generally, $\pm 10\%$ swing across the mean is allowed without any supportive data. In this case, $\pm 15\%$ swing for the 6 hr time point is allowed based on provided IVRT data. The Applicant justified widening the acceptance criterion at the 6-hr timepoint with IVRT data demonstrating similarity between the batches. The proposed acceptance criteria (1 hr (b) (4)%, 6 hr (b) (4)% and 24 hr: NLT (b) (4)%) are deemed appropriate.

The Applicant's proposed dissolution method and acceptance criteria are deemed acceptable for batch release and stability testing of the proposed drug product.

- 2) Bridging of Formulations:** The pivotal studies used the to-be-marketed (TBM) formulation manufactured at the same site where the commercial batches will be manufactured. Therefore, additional formulation bridging is not necessary.

Recommendation

From the Biopharmaceutics perspective, NDA-214510-ORIG-1 for Benzyl Peroxide Cream, 5% is adequate.

FDA-Approved Dissolution Method and Acceptance Criteria for Benzyl Peroxide Cream, 5%

Apparatus	Speed	Medium/Temperature	Volume	Dissolution Acceptance Criteria
2 (Paddle)	200 rpm	2% Tween 60 in Phosphate Buffer, pH 6/37°C	500 mL	1 hr (b) (4)% 6 hr (b) (4)% 24 hr: NLT (b) (4)%

List Submissions being assessed:

Document(s) Assessed	Date Received
Seq 0001	06/26/2020

Seq 0011	12/15/2020
Seq 0014	01/29/2021

Highlight Key Issues from Last Cycle and Their Resolution:

This is the first review cycle.

Concise Description of Outstanding Issues: None

B.1 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

In a Type B Pre-NDA meeting held with the Agency on February 24, 2020, it was recommended to develop an IVRT method and establish acceptance criteria for a QC tool as well as to bridge pre- and post-approval CMC changes. As per the meeting discussion, the Applicant stated that the IVRT method was developed and validated specifically for evaluating sameness of pre- and post-approval changes to the drug product. A QC method was developed and validated for routine QC release and stability testing. The QC dissolution-based method evaluates the dissolution rate of the particles to demonstrate release over time while the IVRT method evaluates the dissolution rate of the whole cream and particles. The Applicant proposes to use the dissolution-based QC method as it is more appropriate for routine analyses, i.e., release of benzoyl peroxide from the microcapsules over time.

The Applicant developed a dissolution method to determine the release of BPO from encapsulated benzoyl peroxide (E-PBO) over time. The development of the method was based on the USP general chapter <1092> (b) (4) (b) (4) since the drug product is designed to release BPO over time on the skin.



Acceptance Criteria

The acceptance criteria were proposed based on the dissolution data available at release and stability (stored at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60 \pm 5\% \text{ RH}$). Eight batches (R&D batches 17034, 17036, Phase 3 clinical batches 17091 and 18035, and 4 registration batches) were produced a (b) (4) scale, which is identical to the TBM drug product. Based on the collective data, the Applicant proposes the following acceptance criteria:

1 hr: NMT (b) (4)%

6 hr: NMT (b) (4)%

24 hr: NLT (b) (4)%

This Reviewer has summarized the dissolution data at release. The data is presented in Table 5 and the release profiles are presented in Figure 2. Based

on the data at release, the following acceptance criteria were recommended in an IR on 12/11/2020:

1 hr (b) (4) %

6 h (b) (4) %

24 hr: NLT (b) (4) %

Table 5. Dissolution data at release

Batch No.	Time (hr)		
	1	6	24
17034	(b) (4)		
17036			
17091			
18035			
19001			
19002			
19003			
19003A			
Mean			
Low	(b) (4)		
High	(b) (4)		

* Not tested

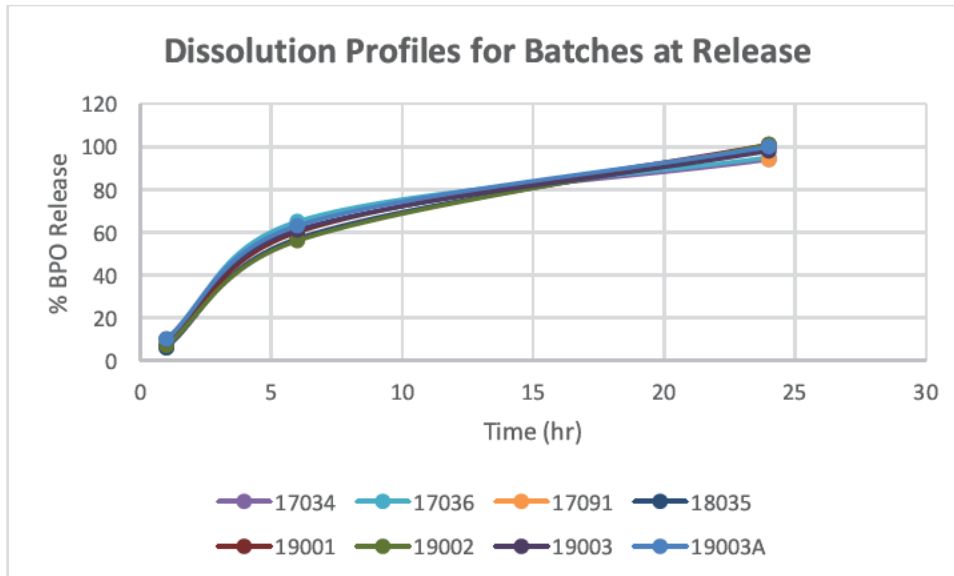


Figure 2. Dissolution profiles at release

In response to the IR¹, the Applicant propose (b) (4) the acceptance criteria for the 1-h (b) (4) and 6-h (b) (4) timepoints. In support of the proposal, the Applicant referred to the IVRT results from 4 of the registration batches which showed that the batches are considered to be equivalent. The supportive IVRT data was deemed inadequate because dissolution testing is used as the QC method. The stability data submitted also had a (b) (4) trend for the 6-hr timepoint, which was not seen for the 1-hr and 12-hr timepoints. A second IR was then sent to the Applicant denying the proposal of the (b) (4) acceptance criterion at 6-hr and to investigate the root-cause for the (b) (4) trend at the 6-hr timepoint observed during the long-term stability.

In response to the IR², the Applicant states that the 3 timepoints were selected because the test product is designed to have an extended release profile. The most important factor for the characteristics of the formulation is that the release starts after the application (1 hour) and is completed within 24 hours (daily application). The 6-hr timepoint was selected to demonstrate approximately (b) (4) of the drug release and is an additional QC check that is of less importance to the bioavailability of the drug substance. The IVRT method is not planned to be used as the QC method but demonstrates the sameness between the exhibit

¹ NDA 214510 Seq 0011 \\CDSESUB1\evsprod\nda214510\0011\m1\us\111-information-amendment\quality-information-amendment-sn0011.pdf

² NDA 214510 SEQ 0014 \\CDSESUB1\evsprod\nda214510\0014\m1\us\111-information-amendment\quality-information-amendment-sn0014.pdf

batches and a batch that exhibited (b) (4) release at the 6-hr timepoint (Applicant's Tables 1 and 2 below). The Applicant proposed to tighten the acceptance criterion for the 6-hr timepoint to (b) (4), which is a +/-15% swing. From a Biopharmaceuticals perspective, the applicant's proposal is acceptable because the IVRT method showed that a batch that falls outside the Biopharm proposed acceptance criterion of (b) (4) in 6 hours (b) (4) release in 6 hours) is equivalent to the bio/clinical batch. The long-term stability data meet the Applicant's proposed acceptance criteria³.

Table 1: Sameness Evaluation Between Exhibit Batches and Clinical Backup Batch

Test Batch Nos.	% Release of Benzoyl Peroxide at the 6-Hour Timepoint at the Time of Testing ^a	90% Confidence Interval	Sameness Results vs. Reference Batch ^b RD-18035
GMP-19001	(b) (4)	(b) (4)	Pass
GMP-19002	(b) (4)	(b) (4)	Pass
GMP-19003A	(b) (4)	(b) (4)	Pass
RD-18035	(b) (4)	(b) (4)	

^a Method accuracy as was defined in Validation is up to (b) (4) of label amount.

^b This 90% confidence interval falls within the limits of (b) (4) in accordance with FDA SUPAC-SS guidance.

Table 2: Sameness Evaluation of Clinical Batches

Test Batch Nos.	% Release of Benzoyl Peroxide at the 6-Hour Timepoint at the Latest Available Stability Timepoint ^a	90% Confidence Interval	Sameness Results vs. Reference Batch ^b RD-17091
RD-18035	(b) (4)	(b) (4)	Pass
RD-17091	(b) (4)	(b) (4)	

^a Method accuracy as was defined in Validation is up to (b) (4) of label amount.

^b This 90% confidence interval falls within the limits of (b) (4) in accordance with FDA SUPAC-SS guidance.

The Applicant explained that the (b) (4) trend observed at the 6-hr timepoint for long-term stability was due to the (b) (4) and that (b) (4) affects the dissolution at 6 hours (b) (4) (b) (4). This (b) (4) trend is not observed at the 1-hr and 24-hr timepoints (b) (4). The Applicant provided batches that were manufacture (b) (4).

³ NDA 214510 Seq 0011 Justification of Specifications \\CDSESUB1\evsprod\nda214510\0011\m3\32-body-data\32p-drug-prod\encapsulated-benzoyl-peroxide-cr-topical-cream (b) (4)\32p5-contr-drug-prod\32p56-justif-spec\justification-of-specifications.pdf

(b) (4)

The Applicant's explanation does not support the (b) (4) trend observed at 6 hours during long-term stability. The Applicant should investigate the formulation and process and drug product reviewer should take that into consideration for determination of expiry period.

(b) (4)

Discriminating Ability of the Dissolution Method

Two test formulations were manufactured to compare to the target formulation (lot #582-126-01). (b) (4)

(b) (4)

(b) (4). The similarity factor (f2) between the target formulation and the (b) (4) formulation was 54. Therefore, the dissolution profiles are considered similar. The f2 for th (b) (4) is 18. Therefore, the dissolution method is able to discriminate against changes in the percent of encapsulation materials used. The dissolution profiles for the three formulations are presented in Figure 3 below.

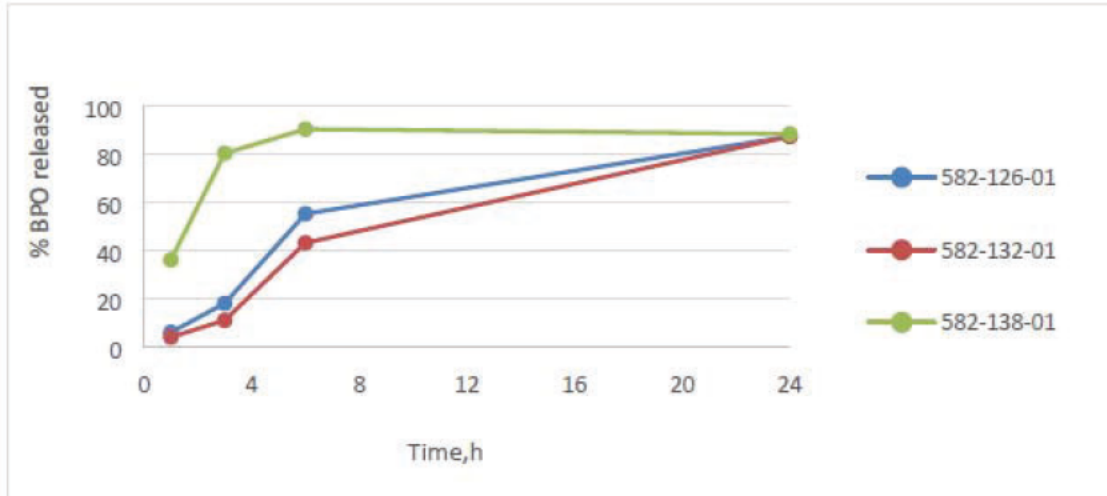


Figure 3. BPO release profile in target and altered formulations

B.2 BRIDGING OF FORMULATIONS

Assessment: Adequate

The Phase 3 clinical studies used the to-be-marketed (TBM) formulation of benzyl peroxide cream, 5% while the Phase 2 study used a different formulation with minor changes (manufacturing process, composition, source of raw material, scale, and manufacturing site). The primary objective of the Phase 2 study was to identify the lowest efficacious dose of the cream that was safe and effective and to establish the basis for performing power calculations in the Phase 3 studies. The Applicant submitted an in vivo release test (IVRT) to compare the pre and post-change formulations. However, based on internal discussion with the clinical and pharm/tox teams, the Phase 2 formulation will not impact the approvability and bridging of the formulations is therefore not necessary.

BIOPHARMACEUTICS LIST OF DEFICIENCIES

None



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Ghosh

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MICROBIOLOGY

Product Information	Indicated in the treatment of inflammatory lesions of rosacea in adults 18 years of age and older. 505(b)(2)
NDA Number	214510
Assessment Cycle Number	01
Drug Product Name / Strength	Encapsulated Benzoyl Peroxide Cream; 5%
Route of Administration	Topical
Applicant Name	Sol-Gel Technologies Ltd
Therapeutic Classification/ OND Division	CDER/OND/ODEIII/DDDP
Manufacturing Site(s)	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: Adequate

Assessment Summary: The subject drug product is a non-sterile multi-use drug product for topical administration. The critical aspects of the process from the quality microbiology perspective are the release test in (b) (4). These aspects were reviewed and deemed acceptable. The Applicant has provided sufficient data to support the microbial limits method suitability for TAMC and TYMC as per USP <61>, *S. aureus* and *P. aeruginosa* as per USP <62> and BCC as per modified USP <62>. The Applicant has also provided sufficient data to support (b) (4)

List Submissions Being Assessed

Document(s)	eCTD	SDN	Date Received
NDA-214510-ORIG-1	0001	1	06/26/2020
NDA-214510-ORIG-1	0003	3	08/28/2020
NDA-214510-ORIG-1	0004	4	09/08/2020
NDA-214510-ORIG-1	0006	6	11/16/2020

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

Remarks: N/A

Concise Description of Outstanding Issues: The Division of Microbiology Assessment has no deficiencies or additional comments.

Supporting Documents: N/A

APPEARS THIS WAY ON ORIGINAL

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product

The subject drug product is a white to off-white, homogenous cream packaged in a (b) (4),
airless pump system consisting of a high-density polyethylene bottle with a pump and (b) (4)
cap.

Drug product composition



Final qualitative and quantitative composition (3.2.P.1. description-and-composition.pdf; eCTD 0003)		
Component	Amount [% (w/w)]	Function
(b) (4) benzoyl peroxide, USP	5.0	API
Silicon dioxide, NF	(b) (4)	(b) (4)
Cetrimonium chloride, In-house		
Polyquaternium-7, In-house		
Lactic acid, USP		
Anhydrous citric acid, USP		
Hydrochloric acid, NF		
Sodium hydroxide, NF		
Glycerin, USP		
Mono and Di-glycerides, NF		
Macrogol stearate Type (b) (4) Ph. Eur.		
Edetate disodium, USP		
Cyclomethicone, NF		
Cetyl alcohol, NF		
Phenoxyethanol, NF		
Purified Water, USP		

Description of container closure system

Configuration	Component	Description	DMF	Manufacturer
3g* fill	Container	30 mL (b) (4) white round bottle	(b) (4)	(b) (4)
50g fill		50 mL (b) (4) white round bottle		
3g and 50g fill	Closure	(b) (4) airless pump		

* Physician's sample

Assessment: Adequate

The Applicant has provided an adequate description of the drug product composition and the container closure system.

(b) (4)

R REGIONAL INFORMATION

Executed Batch Records

Executed lot #(s): GMP-19001, GMP-19002 and GMP-19003 (50g fill)
GMP-19003A (3g fill)

Assessment: Adequate

The Applicant has provided batch manufacturing record for only one exhibit batch (#GMP-19003).

Comparability Protocols

(3.2.R. comparability-protocol.pdf)

The comparability protocol provides for (b) (4)

The release and stability specifications, and analytical procedures will remain as currently proposed.

The Applicant propose (b) (4)

(b) (4)

(b) (4) The stability data will be provided in Annual Reports.

The proposed reporting category is Changes Being Effected in 0 days (CBE-0). The Applicant also states that (b) (4) the same protocol will also be submitted as a CBE-0 supplement, if the data meet the same criteria.

Note to reviewer: From a product quality microbiology perspective, the proposed changes do not present any added risk to the drug product.

Assessment: Adequate

The Applicant has provided adequate information regarding the comparability protocol (b) (4)

(b) (4)

2 ASSESSMENT OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

(1.14.1.3. pdf.pdf)

Storage temperature: 20-25°C (68-77°F)
Route of administration: Topical
Container: Multiple-use

Assessment: Adequate

In the stability summary (3.2.P.8.1.), the Applicant has stated that the drug product is intended for up to (b) (4) days use. However, this is not indicated in the labeling. Drug product reviewer, Zhengfang Ge, has communicated that the Applicant will be asked to revise the labeling to reflect the (b) (4)-day in-use instructions will be reflected in the labeling.

Deficiency issued on 11/27/2020; response expected on 12/9/2020. This section will be updated once the labeling has been updated.

As per the applicant's response (12/09/2020): The applicant states that Samples at the 36-month stability timepoint from the clinical batch will be tested for in-use stability to confirm that the aged drug product continues to meet the in-use acceptance criteria throughout the shelf-life. Data will be provided in the Annual Report. The product label will be updated with the instruction to discard the unused product 30 days after first opening. In the e-mail correspondence dated January 05, 2021, between Samata Tiwari (Microbiology Secondary Reviewer) and Zhengfang Ge (CMC reviewer), the CMC reviewer has communicated that the response is acceptable.

MICROBIOLOGY LIST OF DEFICIENCIES

Micro deficiencies are: Major Minor

The Division of Microbiology Assessment has no deficiencies or additional comments.

Primary Microbiology Assessor Name and Date:

Alifiya H. Ghadiali, Ph.D.; November 30, 2020

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Samata Tiwari, Ph.D.; January 13, 2021



Samata
Tiwari

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