CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214902Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214902
Assessment # 1

Drug Product Name	TWYNEO (tretinoin/benzoyl peroxide)
Dosage Form	Cream
Strength	0.1%/3%
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 Submission	10/01/2020	All
Proprietary Name Request	10/06/2020	All
Response to Clinical Information Request and Draft Labeling	11/25/2020	All
Response to Quality and Clinical Information Request	11/23/2020	Clinpharm, Biostatistics, and Quality Microbiology
Response to Clinical Information Request	12/01/2020	Clinical and Quality Biopharm
Draft Labeling	12/21/2020	All
Response to Clinical Information Request	02/24/2021	Clinical
Response to Quality Information Request	03/15/2021	ONDP, OPMA, and Microbiology
Response to Quality Information Request	04/12/2021	OPMA
Response to Quality Information Request	05/04/2021	OPMA
Clinical Information Amendment	05/24/2021	Clinical
Response to Clinical Information Request	05/28/2021	Clinical

Clinical Information Amendment	06/03/2021	Clinical
Response to Quality Information Request	06/10/2021	OPMA

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Zhixing Shan, Ph.D.	Donna Christner, Ph.D.
Drug Product	Zhengfang Ge, Ph.D.	Wendy Wilson-Lee, Ph.D.
Manufacturing	Yan Xu, Ph.D.	Ying Zhang, Ph.D.
Microbiology	Samata Tiwari, Ph.D.	Yuansha Chen, Ph.D.
Biopharmaceutics	Kaushalkumar Dave, 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

For more details about the items in this template, please see the Executive Summary chapter of the NDA IQA Guide

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 substances, tretinoin and benzoyl peroxide, and the drug product, TWYNEO® (tretinoin/benzoyl peroxide) Cream, 0.1%/3% for topical use.
- The Office of Pharmaceutical Manufacturing Assessment has made an overall "**Acceptable**" recommendation regarding the facilities involved in this NDA.
- The CMC issues on labels/labeling have been **satisfactorily** addressed in this review cycle.
- The applicant request's for categorical exclusion from the environmental assessment has been **granted**.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The applicant, Sol-Gel Technologies, Ltd. has submitted this 505(b)(2) new drug application for a fixed-dose combination drug product, TWYNEO® (tretinoin/benzoyl peroxide) Cream, 0.1%/3% for topical use. TWYNEO® is indicated for the treatment of acne vulgaris in patients 9 years of age or older. TWYNEO® is intended for topical administration as a thin layer once daily to the affected skin area.

The active ingredient, tretinoin is a retinoid approved since 1973 for the treatment of acne vulgaris. Since its original approval, tretinoin has been used as the active ingredient of multiple approved brand name and generic drug products. Tretinoin has also been used as the active ingredient of multiple approved topical combination drug products.

The active ingredient, 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 TWYNEO® contains 1mg of tretinoin and 30mg of benzoyl peroxide as the active ingredients and polyquaternium-7, silicon dioxide, cetrimonium chloride, (S)-lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, white wax, tetraethyl ortho silicate, squalane, butylated hydroxytoluene, glycerin, macrogol stearate, cetyl alcohol, mono and di-glycerides, edetate disodium, cyclomethicone, imidurea, carbomer homopolymer type C and purified water as inactive ingredients.

The formulation of this drug product uses silica (silicon dioxide) core shell structures to separately micro-encapsulate benzoyl peroxide crystals and tretinoin crystals enabling simultaneous inclusion of the two active ingredients in the cream.

TWYNEO® is a yellow cream packaged as 50g in 50-mL (commercial drug product) and as 6g in 30-mL (physician sample) high-density polyethylene bottles with (b) (4) pumps and transparent caps. This drug product should be stored at 2ºC – 8ºC (36ºF – 46ºF) prior to dispensing to patients and at 20ºC – 25ºC (68ºF – 77ºF) for up to 12 weeks after dispensing. The unused drug product should be discarded 30 days after opening. The physician sample should be discarded 5 days after opening.

Proposed Indication(s) including Intended Patient Population	Treatment of acne vulgaris in patients 9 years of age or older
Duration of Treatment	As prescribed by a physician
Maximum Daily Dose	Should be applied topically as a thin layer to the dry clean affect skin area
Alternative Methods of Administration	None

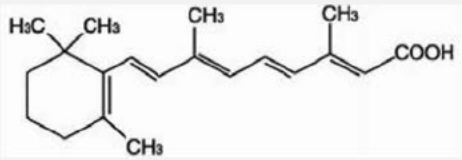
B. Quality Assessment Overview

Drug Substance: Adequate

The drug product, TWYNEO® Cream is fixed-dose combination containing two drug substances, tretinoin and benzoyl peroxide.

1) The active ingredient, tretinoin is retinoid and it was first approved on January 26, 1973 as the active ingredient of RETIN-A topical cream under NDA 017340 for the treatment of acne vulgaris. Since its original approval, multiple brand name and generic drug products containing this active ingredient have approved for marketing in the United States. Tretinoin is a compendial drug substance. It is a yellow to yellow-orange crystalline powder with melting range of 182ºC with decomposition. It very sparingly soluble in water with the logP of 3.46. Tretinoin has two polymorphic forms, a monoclinic form and a triclinic form. The manufacture of the tretinoin for this application has confirmed that

the manufacturing process used produces the [(b) (4)] form of this drug substance.
Tretinoin has the chemical name, all trans (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8-nonate traenoic acid, a chemical formula of $C_{20}H_{28}O_2$, a molecular weight of 300.44 g/mol, and the chemical structure provided below:



Tretinoin, USP for this application is manufactured in accordance to the current good manufacturing practices (cGMP) requirements by [(b) (4)]. It is packaged in [(b) (4)] for the storage at [(b) (4)]. The details of the manufacturing process, packaging, release testing, and stability for tretinoin produced by [(b) (4)] is provided in DMF [(b) (4)] This DMF was originally submitted on [(b) (4)] and since then has been reviewed multiple times and found to be adequate. The most recent review of this DMF was performed by the Drug Substance Reviewer, Dr. Zhixing Shan of February 20, 2021 and was found adequate to support this application.

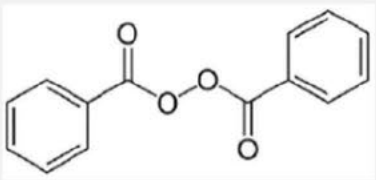
Tretinoin, USP is tested, released, and accepted according to the USP compliant specification that assures the identity, strength, purity, and quality of the drug substance at release and throughout its assigned retest date of [(b) (4)] months. Sufficient stability data that supports the retest date of [(b) (4)] months is provided in the referenced DMF.

2) 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 benzenecarboperoxoate. 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 to the cGMP requirements by [redacted] (formerly known as [redacted] and packaged and stored in [redacted]. The details of manufacturing process, packaging, release testing, and stability for benzoyl peroxide supplied by [redacted] is provided in DMF [redacted] This DMF was originally submitted on [redacted] and since then has been reviewed multiple times and found to be adequate. The most recent review of this DMF was performed on April 25, 2018 by LCAPI Reviewer, Mst Hasina Akter and was found adequate with additional comments. The comments were adequately addressed in the drug substance section of the referenced NDA 214510.

Benzoyl peroxide, USP 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 [redacted] months. Sufficient stability data that supports the retest date of [redacted] months is provided in the referenced DMF.

In summary, relying on the previous reviews of the referenced DMF [redacted] DMF [redacted] and NDA 214510 as well as the review of the drug substance information provided in this application, the Drug Substance Reviewer, Dr. Zhixing Shan has found the drug substance section of this application 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, TWYNEO® (tretinoin/benzoyl peroxide) Cream, 0.1%/3% is a yellow cream containing 1mg of tretinoin and 30mg of benzoyl peroxide per each gram. It will be packaged as 50g in 50-mL (commercial drug product) and as 6g in 30-mL (physician sample) high-density polyethylene (HDPE) bottles with [redacted] pumps and transparent caps. This drug product is intended for topical administration as a thin layer to dry clean affected skin area and for the treatment of acne vulgaris in patients 9 years of age and older.

Both active ingredients of this drug product, tretinoin and benzoyl peroxide are first encapsulated separately into microcapsules consisting of silica (b) (4) before formulation into the topical cream dosage form. The encapsulation enables simultaneous inclusion of the two active ingredients in the cream product. It provides for the slow migration of the active ingredients through the microcapsules' shells leading to continuous release of this active ingredient over time and delivery to the affected skin area.

TWYNEO® cream also contains the following inactive ingredients: polyquaternium-7, silicon dioxide, cetrimonium chloride, (S)-lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, white wax, tetraethyl ortho silicate, squalane, butylated hydroxytoluene, glycerin, macrogol stearate, cetyl alcohol, mono and di-glycerides, edetate disodium, cyclomethicone, imidurea, carbomer homopolymer type C and purified water.

TWYNEO® cream is manufactured by (b) (4) for Sol-Gel in accordance to the cGMP requirements. It is tested and release according to a 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. Sufficient stability data in support of expiration dating period has been submitted.

The applicant has also submitted a comparability protocol for a (b) (4) (b) (4) of a (b) (4) to 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 for (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 sections of the Prescribing Information (PI) as well as the immediate container and carton labels have been reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge has found that the final PI as well as immediate container and carton labels submitted to this application satisfactory and recommended the approval of this application from the labeling/label perspective. Dr. Ge's labeling/label review is provided in the Labeling Chapter of the IQA.

Manufacturing: Adequate

TWYNEO® cream is produced and as (b) (4). The manufacturing of TWYNEO® begins with separate encapsulation of tretinoin and benzoyl peroxide in silicon dioxide. The cream is formed by (b) (4) The cream is filled into as 6g in 30-mL (physician samples) and as 50g in 50-mL (commercial drug product) high-density polyethylene (HDPE) bottles with (b) (4) pumps and transparent caps.

Executed batch records for four exhibit (registration) batches of drug product at the scale of (b) (4) kg have been provided. The applicant intends to scale up the product to (b) (4) scale for the commercial manufacturing. The scale up process the commercial manufacturing has been adequately described in the comparability protocol for the equipment and process parameters.

The manufacturing process and acceptability of the facilities involved in this application have been reviewed by the Office of Pharmaceutical Manufacturing Assessment Reviewer, Dr. Yan Xu. Dr. Xu has found the manufacturing process described in this application adequate and the overall manufacturing facilities acceptable to support the approval of this application. Dr. Xu's review is provided in Manufacturing Chapter of the IQA.

Biopharmaceutics: Adequate

The biopharmaceutics review of TWYNEO® cream was mainly focused on the proposed in-vitro release testing (IVRT) method and acceptance criteria and the formulation bridging studies.

The applicant has developed two IVRT methods, one for the release of encapsulated benzoyl peroxide and the other for the release of encapsulated tretinoin. Both IVRT method have been shown to be

discriminating method toward formulation and critical process parameter changes. The applicant's selection the IVRT methods critical attributes and corresponding acceptance criteria is supported by the data provided in the application. Based on IVRT data collected from the clinical and registration batches at release and during stability, it is concluded that the proposed IVRT methods and acceptance criteria are adequate for QC testing of the drug product.

Although the drug product formulation used in Phase 3 clinical trials is the same as the to-be-marketed formulation, manufacturing changes and changes to the (b) (4) between the Phase 3 clinical batches and registration batches were made. Based on the SUPAC-SS guidance these changes were classified as the LeveL-3 changes requiring that the changes be supported IVRT bridging studies. The applicant has provided sufficient IVRT data from the formulation and manufacturing process bridges studies that demonstrates the sameness of the drug product before and after the changes. The proposed IVRT methods and acceptance criteria can also be adequately used as a tool for the determination of the drug product sameness when post-approval changes are made.

The biopharmaceutics section of this application has been reviewed by the Biopharmaceutic Reviewer, Dr. Kaushalkumar Dave. Dr. Dave has found that IVRT methods and acceptance criteria as well as the data from bridging studies provided adequate to support the approval of this application from the biopharmaceutics perspective. Dr. Dave review is provided in the Biopharmaceutics Chapter of the IQA.

Microbiology (if applicable): Adequate

TWYNEO® (tretinoin/benzoyl peroxide) Cream, 0.1%/3% for topical use is a (b) (4) non-sterile drug product.

Th applicant has provided sufficient information that demonstrates the suitability of the methods for microbial limits test corresponding acceptance criteria for TAMC and TYMC in according USP <61>, for *S. aureus* and *P. aeruginosa* according to USP <62>, and BCC according to USP <60>. Supporting data from testing of batches of drug product for microbial limits has been submitted to the application. Additionally, the applicant has submitted data from the antimicrobial testing of the drug product for all organisms listed in USP <51> and 3 strains of BCC.

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 of the application adequate to support the approval of this application 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**
Content Uniformity, Assay, IVRT, and Microbial Limits	Efficacy and Safety from Drug Product Quality Perspective	Medium to High	(b) (4)	Low Acceptable	None

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies

   None

Application Technical Lead:

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

Hamid Shafiei

Digitally signed by Hamid Shafiei
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QUALITY ASSESSMENT DATA SHEET

For more details about the items in this template, please see the Quality Assessment Data Sheet chapter of the NDA IQA Guide

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	20-Feb-2021	Zhixing Chen
	II			Adequate	25-APR-2018	Reviewed by Mst Hasina Akter Additional Information has been included in this NDA and referenced NDA 214510
	III			———	———	Sufficient information is provided in the NDA

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

Document	Application Number	Description
NDA	214510	Drug substance information referenced

2. CONSULTS

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

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

The CMC information in the Prescribing Information is deemed ADEQUATE. The NDA is recommended for approval from labeling perspective.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

[redacted]

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	TWYNEO	**Adequate**
Established name(s)	(tretinoin and benzoyl peroxide) cream	**Adequate** • "(b) (4)" has been removed from the established name at the Agency's request removed from the established • the order of benzoyl peroxide and tretinoin has been changed to be consistent with other approved combination

		products containing benzoyl peroxide
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, [redacted] (3)	**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)

[redacted]

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)	Apply a thin layer of TWYNEO (b) (4) to the affected areas once daily on clean and dry skin. Avoid contact with the eyes, lips and mucous membranes. TWYNEO (b) (4) is for topical use only. Not for oral, ophthalmic or intravaginal use.	**Adequate**

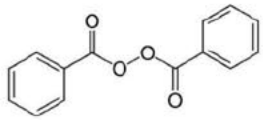
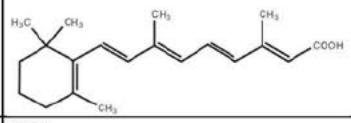
1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(b) (4)

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	0.1%/3%	**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	Each gram of TWYNEO contains 1 mg (0.1%) of tretinoin and 30 mg (3%) of benzoyl peroxide in a yellow cream in a 50 gram pump bottle	**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 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)	TWYNEO (tretinoin and benzoyl peroxide) cream	**Adequate**
Dosage form(s) and route(s) of administration	- cream - for topical use	**Adequate**
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	polyquaternium-7, silicon dioxide, cetrimonium chloride, (S)-lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, white wax, tetraethyl ortho silicate, squalane, butylated hydroxytoluene, glycerin, macrogol stearate, cetyl alcohol, mono and di-glycerides, edetate disodium, cyclomethicone, imidurea, carbomer homopolymer type C and purified water	**Adequate** - A comment has been added to recommend the applicant to display the inactive ingredients in alphabetical order
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	Tretinoin is a retinoid and benzoyl peroxide is an oxidizing agent	**Adequate**

Chemical name, structural formula, molecular weight	Benzoyl peroxide Name: benzoyl benzenecarboperoxoate Formula $C_{14}H_{10}O_4$ Molecular weight 242.23  Tretinoin Name: all-trans-retinoic acid, also known as (all-E)-3,7-dimethyl-9-(2,6,6-trimethyl-1-cyclohexen-1-yl)-2,4,6,8nonatetraenoic acid Formula $C_{20}H_{28}O_2$ Molecular weight 300.44 	**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"	The formulation uses silica (silicon dioxide) core shell structures to separately micro encapsulate benzoyl peroxide crystals and tretinoin crystals enabling (b) (4) inclusion of the two active ingredients in the cream.	**Adequate** This is acceptable as the same information stated in the benzoyl peroxide cream in NDA 214510

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

(b) (4)

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	0.1%/3%	**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	yellow (b) (4) cream NDC number is provided	**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	
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.)	• Do not freeze.	**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	• Prior to Dispensing: Store TWYNEO between	**Adequate**

rather than storage at a single temperature.	2°C to 8°C (36°F to 46°F) until dispensed to the patient. • After Dispensing: S tore TWYNEO at room temperature 20°C to 25°C (68°F to 77°F). Discard 12 weeks after date of dispensing or 30 days after first opening, whichever is sooner. • Do not freeze.	
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 statements such as "latex-free."	N/A	
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 203 Whippany, NJ 07981 Product of New Zealand	**Adequate**

2.0 PATIENT LABELING

The following CMC information is provided in the Patient Labeling

Important: TWYNEO (b) (4) ***is for use on the*** (b) (4) ***only. Do not use TWYNEO*** (b) (4) ***in your eyes, mouth or vagina.***

How should I use (b) (4) ***Cream?***

- ***Use TWYNEO*** (b) (4) ***exactly as your healthcare provider tells you to use it.***

- (b) (4)
- ***TWYNEO*** (b) (4) ***comes in a pump. Press down on (depress) the pump to dispense a small amount of TWYNEO*** (b) (4) ***and apply a thin layer of TWYNEO*** (b) (4) ***to the affected areas once daily. Avoid contact with eyes, lips and*** (b) (4).
- ***Wash your hands after applying TWYNEO*** (b) (4).

How should I store TWYNEO (b) (4)***?***

- ***Store TWYNEO*** (b) (4) ***at room temperature between 68°F to 77°F (20°C to 25°C)***
- ***Throw away (discard)*** (b) (4) ***12 weeks after the date*** (b) (4) ***or 30 days after first opening, whichever is sooner.***
- ***Do not freeze.***
- ***Keep TWYNEO Cream and all medicines out of reach of children.***

What are the ingredients in TWYNEO Cream?

Active ingredient: (b) (4) ***benzoyl peroxide and*** (b) (4) ***tretinoin***
Inactive ingredients: polyquaternium-7, silicon dioxide, cetrimonium chloride, (S)-lactic acid, anhydrous citric acid, hydrochloric acid, sodium hydroxide, white wax, tetraethyl orthosilicate, squalane, butylated hydroxytoluene, glycerin, mocrogol stearate, cetyl alcohol, mono and di-glycerides, edetate disodium, cyclomethicone, imidurea, carbomer homopolymer type C and purified water.

Reviewer Note: rearrange the order of inactive ingredients has been recommended to the applicant

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

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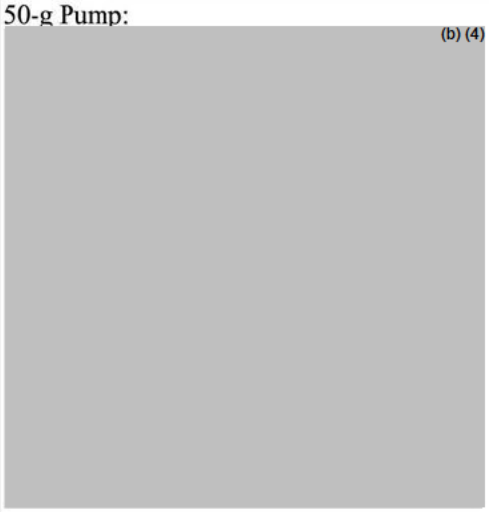
Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	TWYNEO (tretinoin and benzoyl peroxide) (b) (4)	**Adequate** Change the established name to (tretinoin and benzoyl peroxide) at the Agency's request
Dosage strength	0.1% /3%	**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 pump 6 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.	50-g Pump: (b) (4)  Physician Sample: (b) (4) 	**Adequate**
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)	Apply once daily or as directed by physician. See Package Insert for full product details.	**Adequate**
No text on Ferrule and Cap overseal	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 TWYNEO® cream contains 1 mg (0.1%) of tretinoin and 30 mg (3%) of (b) (4) benzoyl peroxide. May bleach colored fabric or hair.	**Adequate**

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

List of Deficiencies

None

Overall Assessment and Recommendation:

The labeling is adequate from CMC perspective. The NDA is ready for approval in its present form per CFR 314.125(b)(6).

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

Zhengfang Ge

Digitally signed by Zhengfang Ge
Date: 6/15/2021 11:16:06AM
GUID: 508da7210002a030e76df4f60ccd142a

Wendy Wilson- Lee

Digitally signed by Wendy Wilson- Lee
Date: 6/15/2021 12:12:21PM
GUID: 50816dbc000085595ca3284bbca465a8

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BIOPHARMACEUTICS

Application No: NDA 214902; 505(b)(2)
Drug Product Name/Strengths: Encapsulated Benzoyl Peroxide and Encapsulated Tretinoin (TWYNEO®) Cream; (b)(4)%/(b)%
Route of Administration: Topical
Indication: Treatment for acne vulgaris (acne) in patients nine years of age and older
Applicant Name: Sol-Gel Technologies Ltd.
Date of Submission: 10/10/2020 (Original)

Primary Reviewer: Kaushalkumar Dave, Ph.D.
Secondary Reviewer: Tapash Ghosh, Ph.D.

REVIEW SUMMARY

Submission: The Applicant submitted the NDA for Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1% under the 505(b)(2) pathway with its reliance on the prior safety and efficacy findings of the Agency for the Listed Drug (LD) Retin-A® (Tretinoin Topical Cream, 0.1% approved under NDA 022117 on 01/26/1973). The proposed drug product is indicated for the treatment of acne vulgaris (acne) in patients nine years of age and older. The proposed drug product is recommended to be applied once daily to the skin area affected with acne vulgaris.

Review Objective: The Biopharmaceutics review is focused on the evaluation of (1) in vitro drug release testing (IVRT) methods and acceptance criteria for benzoyl peroxide (BPO) and tretinoin (also known as all-trans-retinoic acid, ATRA) components of the proposed combination drug product, and (2) formulation bridging.

IVRT Method: The Applicant developed two separate IVRT methods for release testing of BPO and ATRA from the proposed fixed-dose combination drug product. The Applicant conducted various studies and provided justifications for selection of the suitable IVRT testing conditions for BPO and ATRA. The provided IVRT data show that the proposed IVRT method for BPO is discriminating toward the tested critical formulation variable (b) (4) and critical process parameter (b) (4) Similarly, the Applicant demonstrated that the proposed IVRT method for ATRA is discriminating toward (b) (4) . The Applicant has also adequately justified the selection of the critical attributes and their levels for testing the discriminating ability of the IVRT methods. Based on the provided information/data and justifications, as well as the demonstrated discriminating ability, the proposed IVRT methods for BPO and ATRA are deemed adequate for quality control testing of the proposed drug product.

IVRT Acceptance Criteria: Based on the IVRT data for the clinical and registration batches collected at the time of batch release and the additional full-profile IVRT data collected over the stability testing period, the Applicant's newly proposed IVRT acceptance criteria are deemed adequate for QC testing of the proposed drug product.

The final and approved IVRT method and agreed-upon IVRT acceptance criteria for QC testing of the proposed drug product at batch release and during stability testing are as follows:

FDA approved IVRT method and acceptance criteria for the proposed drug product

IVRT Parameter	For BPO	For Tretinoin
Apparatus	USP Apparatus 2 (Paddle)	USP Apparatus 2 (Paddle)
Paddle Speed	200 rpm	200 rpm
Medium	2 % of Tween 60 in phosphate buffer pH 6.7	2 % of Tween 80 in phosphate buffer pH 6.2, mixed with 4g/L BHT in IPA (66.7%: 33.3% w/w)
Volume	500 mL	500 mL
Temperature	37.0 ± 0.5°C	32.0 ± 0.5 °C
Acceptance Criteria	2 hours: (b)(4) to (b)(4)% 7 hours: (b)(4) to (b)(4)% 24 hours: NLT (b)(4)%	0.5 hour: (b)(4) to (b)(4)% 2 hours: (b)(4) to (b)(4)% 6 hours: NLT (b)(4)%

Formulation Bridging: All clinical studies were performed using the to-be-marketed composition of E-BPO/E-ATRA Cream, 3%/0.1%. However, multiple changes in the manufacturing process and (b)(4)) were introduced between the clinical phase III batches and registration batches. As per the SUPAC-Semisolid Guidance, these changes are Level-3 changes which should be supported by IVRT bridging data. The Applicant provided these data in the submission. The Applicant developed separate IVRT methods for benzoyl peroxide and tretinoin and provided comparative IVRT data to support the sameness in drug release between the pre-change and post-change drug products. The Applicant adequately demonstrated suitability of these methods for bridging. The comparative IVRT data collected and analyzed by the Applicant as per the SUPAC-SS guidance show that there is no significant difference in drug release between the pre-change and post-change drug products. From a Biopharmaceutics perspective, the proposed IVRT based bridging is deemed adequate.

RECOMMENDATION:

From a Biopharmaceutics perspective, NDA 214902 for Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1%, is adequate and recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

LIST OF SUBMISSIONS REVIEWED

Submissions Reviewed		
eCTD sequence #	**Received date**	**Document**
0001	10/01/2020	Original NDA Submission
0008	03/15/2021	Quality/Response to Information Request

BACKGROUND

SolGel Technologies Ltd. has developed the proposed Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1% as a fixed-dose combination drug product for the topical (dermal) treatment of acne vulgaris in patients ages nine and above. Benzoyl peroxide (BPO) is an oxidizing agent with bactericidal, keratolytic and anti-inflammatory effects. Tretinoin is a metabolite of vitamin A that binds with high affinity to specific retinoic acid receptors located in both the cytosol and nucleus. It has not been established whether the clinical effects of tretinoin are mediated through activation of retinoic acid receptors, other mechanisms, or both. Although the exact mode of action of tretinoin in acne treatment is unknown, current evidence suggests that topical tretinoin decreases cohesiveness of follicular epithelial cells with decreased microcomedo formation. Additionally, tretinoin stimulates mitotic activity and increased turnover of follicular epithelial cells causing extrusion of the comedones.

The Applicant has developed the proposed Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1% as a fixed-dose combination drug product to overcome the irritation potential of benzoyl peroxide and degradation potential of tretinoin. To achieve a stable, fixed-dose, topical formulation, both active ingredients undergo encapsulation in silica microcapsules, which form a barrier between the active ingredients and between each active ingredient and the skin. The microcapsule is designed to allow controlled release of the drugs from the encapsulation. The proposed E-BPO/E-ATRA Cream is formed by (b) (4)

(b) (4)

1.

Table 1. Composition of the proposed drug product

Component	Reference	Function	Amount [%(w/w)]
Benzoyl Peroxide	USP	Active	3.00
Tretinoin	USP	Active	0.10
Polyquaternium-7	In-House		(b) (4)
Silicon Dioxide	NF		
Cetrimonium Chloride	In-House		
Lactic Acid	Ph. Eur.		
Anhydrous Citric Acid	USP		
Hydrochloric Acid	NF		
Sodium Hydroxide	NF		
TEOS	In-House		
White Wax	NF		
Squalane	NF		
Butylated Hydroxytoluene	NF		
Glycerin	USP		
Macrogol stearate (b) (4) ((b) (4))	Ph. Eur.		
Cetyl Alcohol	NF		
Mono and Di-glyceride	NF		
Edetate Disodium	USP		
Cyclomethicone	NF		
Imidurea	NF		
Carbomer Homopolymer Type C	NF		
Purified Water	USP		

To support the NDA, the Applicant conducted four Phase 1, one Phase 1b, one Phase 2 and two Phase 3 studies. The Phase 1 program included four separate Phase 1 studies (SGT-65-06, SGT-65-07, SGT-65-08 and SGT-65-09) that evaluated local tolerability (through the assessment of cumulative skin irritation, skin sensitization, phototoxicity and photoallergy) and one Phase 1b study (SGT-65-03) that evaluated pharmacokinetics (PK), safety and tolerability as well as maximal use systemic exposure (MUSE) to tretinoin and its metabolites in order to establish a clinical bridge to the listed drug (LD), Retin-A® (tretinoin) Cream, 0.1%, using the relative bioavailability approach. The Phase 2 study (SGT-65-02) was a dose-ranging, safety and efficacy evaluation. The pivotal Phase 3 studies included two identically designed, parallel, pivotal safety and efficacy evaluations (SGT-65-04 and SGT-65-05).

The Biopharmaceutics review is focused on the evaluation of the (1) proposed in vitro drug release testing (IVRT) methods and acceptance criteria for BPO and tretinoin components of the proposed combination drug product, and (2) formulation bridging, as presented below.

PROPOSED IVRT METHOD AND ACCEPTANCE CRITERIA

The Applicant developed two different IVRT methods for quality control (QC) testing (at batch release and during stability testing period) of each of the drug components of the proposed combination drug product. The proposed QC methods (Table 2) use USP Apparatus 2 and are different from the IVRT methods used to collect comparative drug release data between pre-change and post-change drug products (discussed in the following section).

The Applicant's proposed IVRT methods for BPO (Method TM0775) and tretinoin (Method TM0821) are summarized in Table 2.

Table 2: IVRT methods proposed by the Applicant

IVRT Parameter	For BPO	For Tretinoin
Apparatus	USP Apparatus 2 (Paddle)	USP Apparatus 2 (Paddle)
Paddle Speed	200 rpm	200 rpm
Medium	2 % of Tween 60 in phosphate buffer pH 6.7	2 % of Tween 80 in phosphate buffer pH 6.2, mixed with 4g/L BHT in IPA (66.7%: 33.3% w/w)
Volume	500 mL	500 mL
Temperature	37.0 ± 0.5°C	32.0 ± 0.5 °C
Acceptance Criteria	2 hours: (b)(4) to (b)(4)% 7 hours: (b)(4) to (b)(4)% 24 hours: NLT (b)(4)%	0.5 hour: (b)(4) to (b)(4)% 2 hours: (b)(4) to (b)(4)% 6 hours: NLT (b)(4)%

For selection of the proposed IVRT study conditions, the Applicant performed the following studies:

For Benzoyl Peroxide

The Applicant developed method TM0775 for QC drug release testing of BPO and provided e method development report 09-05-154 in Module 3.2.P.2 of the submission. The Applicant selected the proposed IVRT method based on the following studies:

(b) (4)

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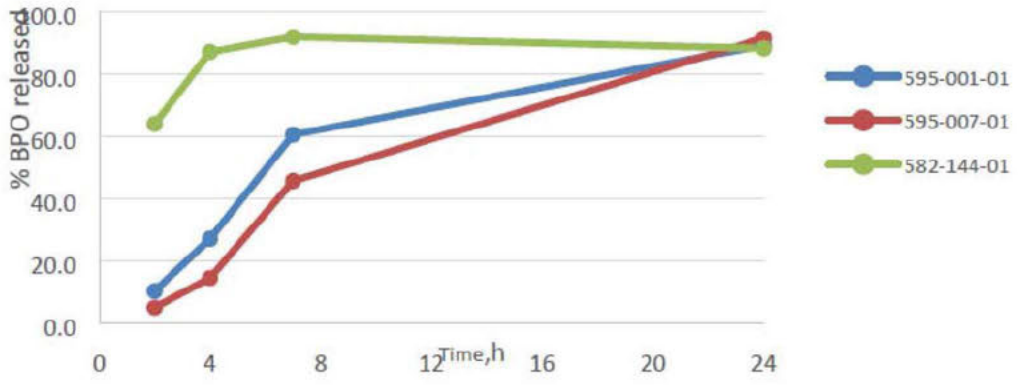
Discriminating ability of the IVRT Method

In the original submission, the Applicant provided data investigating discriminating ability of the proposed method towards process and formulations variables (Table 8 and Figure 1). However, the Applicant did not provide justification for selection of these parameters. Therefore, via an IR (dated 03/03/2021), the Applicant was recommended to justify the selection of critical attributes/parameters and their levels for testing discriminating ability of the proposed QC IVRT method.

Table 8. Description of the E-BPO/ E-ATRA cream, Reference and Test batches used to test discriminating ability of the proposed IVRT method for BPO

E-BPO/E-ATRA Cream, 3%/0.1% Batch No.	**Purpose**	**Process Variant/ Batch size/Reactor**	**E-BPO Suspension, (b) (4) % used in DP Manufacturing, Batch No.**	**Process Variant/ Batch Size/Reactor**
595-001-01	Reference	Standard/ (b) (4)	568-081-01	Standard/ (b) (4)
595-007-01	Test-1	Standard/ (b) (4)	568-085-01	A process under an (b) (4)
582-144-01	Test-2	Standard/ (b) (4) (b) (4)	568-086-01	(b) (4) % of the encapsulation materials (b) (4) / (b) (4)

Figure 1. BPO release profile from reference and test drug products used to test discriminating ability of the proposed IVRT method for BPO



(b) (4)

Based on the above study, the Applicant concluded that the proposed IVRT method is discriminating and suitable for QC testing of the proposed drug product.

Reviewer's Assessment: The Applicant has adequately justified the selection of the release medium for IVRT. The provided data show that the Applicant has appropriately selected the surfactant type, level and pH for the release medium ensuring maintenance of sink condition during IVRT. Similarly, the Applicant provided sufficient data to support the selection of the temperature (37°C) during IVRT. The Applicant did not provide data supporting the selection of the IVRT apparatus (USP Apparatus 2) or paddle speed (200 rpm); however, the selection of these parameters is acceptable based on the following.

The proposed Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1% is a semisolid drug product where both active ingredients undergo encapsulation in silica microcapsules. The microcapsule is designed to allow controlled release of the drugs from the encapsulation. Considering the semisolid state and release controlling characteristic of the formulation, it is challenging to develop a suitable QC IVRT test for the proposed drug product. The provided data show that with the proposed IVRT method, the Applicant was able to not only achieve nearly complete release of BPO but was also able to demonstrate discriminating ability of the method. The Applicant's provided data clearly show that the proposed IVRT method is discriminating towards the tested critical formulation variable and critical process parameter. The Applicant has adequately justified the selection of the critical parameters and their levels for testing discriminating ability of the proposed method. Based on the totality of the data/evidence, the Applicant's proposed IVRT method is deemed adequate for QC testing of the proposed drug product.

IVRT Acceptance Criteria

IVRT acceptance criteria are recommended based on the full-profile drug release data from pivotal clinical batches. In the original submission, the Applicant did not provide adequate data from these batches. Therefore, via an IR (dated 03/03/2021), the Applicant was informed/reminded that the IVRT acceptance criteria should be setup based on clinical batches and was recommended to provide these data. The Applicant provided the requested data in the submission dated 03/15/20201[1]. The Applicant also revised their originally proposed IVRT acceptance criteria for BPO as follows:

(b) (4)

Table 9: IVRT Acceptance criteria for BPO

Originally Proposed	Newly Proposed
2 hours: (b) (4)%	2 hours: (b) (4)%
7 hours: (b) (4)%	7 hours: (b) (4)%
24 hours: NLT (b) (4)%	24 hours: NLT (b) (4)%

Upon reviewing the IVRT data from clinical and registration/stability batches, this Reviewer determines that the Applicant's newly proposed IVRT acceptance criteria are appropriately selected and adequate for QC testing of BPO component of the proposed drug product.

For Tretinoin

The Applicant developed method TM0821 for QC drug release testing of tretinoin and provided a method development report 09-05-153 in Module 3.2.P.2 of the submission. The Applicant selected the proposed IVRT method based on the following studies:

IVRT Method Parameters

(b) (4)

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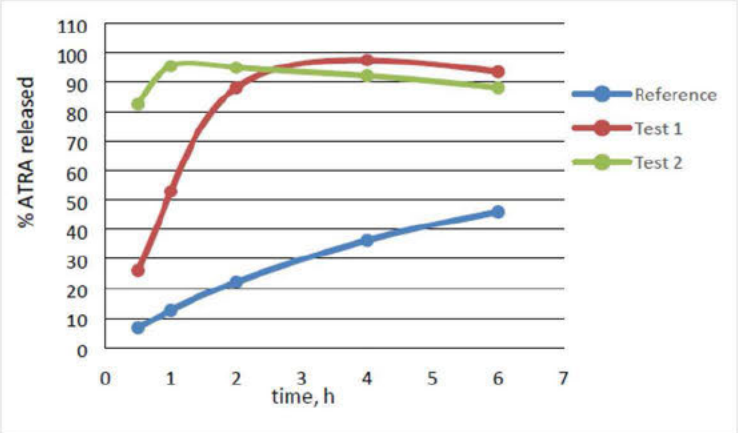
Discriminating ability of the IVRT Method

In the original submission, the Applicant provided data investigating discriminating ability of the proposed method towards process and formulations variables (Table 14 and Figure 2). However, the Applicant did not provide justification for selection of these parameters. Therefore, via an IR (dated 03/03/2021), the Applicant was recommended to justify the selection of critical attributes/parameters and their levels for testing discriminating ability of the proposed QC IVRT method.

Table 14. Description of the E-BPO/ E-ATRA cream, Reference and Test batches used to test discriminating ability of the proposed IVRT method for ATRA

E-BPO/E-ATRA Cream, Batch No.	Purpose	Process Variant/ Batch Size/ Reactor	E-ATRA Suspension, (b) (4) % used in DP Manufacturing, Batch No.	Process Variant/ Batch Size/ Reactor
601-119-01	Reference	Standard/ (b) (4) / (b) (4)	568-100-01	Commercial/ (b) (4) (b) (4)
601-128-01	Test-1	Standard/ (b) (4) (b) (4)	568-100-02	(b) (4) kg of Reference batch (b) (4)
601-135-01	Test-2	Standard/ (b) (4) / (b) (4)	601-126-01	(b) (4) kg of Reference batch 568-100-01 (b) (4)

Figure 2. ATRA release profile from reference and test drug products used to test discriminating ability of the proposed IVRT method for ATRA



In response (dated 03/15/2021) to the IR, the Applicant clarified that the process parameter that was altered in Test-1 is (b) (4) (b) (4)

(b) (4)

The provided data clearly show that the variant batches have significantly different release profile from the reference/target batch.

Based on the above study, the Applicant concluded that the proposed IVRT method is discriminating and suitable for QC testing of the proposed drug product.

Reviewer's Assessment: The Applicant has adequately justified the selection of the release medium for IVRT. The provided data show that the Applicant has appropriately selected the surfactant type, level and pH for the release medium ensuring maintenance of sink condition during IVRT. Similarly, the Applicant provided sufficient data to support the selection of the organic solvent (IPA), antioxidant (DHT), and their levels in the release medium for IVRT. The Applicant did not provide data supporting the selection of the IVRT apparatus (USP Apparatus 2) or paddle speed (200 rpm); however, the selection of these parameters is acceptable based on the following.

The proposed Encapsulated Benzoyl Peroxide (E-BPO) and Encapsulated Tretinoin (E-ATRA) Cream, 3%/0.1% is a semisolid drug product where both active ingredients undergo encapsulation in silica microcapsules. The microcapsule is designed to allow controlled release of the drugs from the encapsulation. Considering the semisolid state and release controlling characteristic of the formulation, it is challenging to develop a suitable QC IVRT test for the proposed drug product. The provided data show that with the proposed IVRT method, the Applicant was able to not only achieve nearly complete release of ATRA but was also able to demonstrate discriminating ability of the method. The Applicant's provided data clearly show that the proposed IVRT method is discriminating towards the tested critical process parameter. The Applicant has adequately justified the selection of the critical parameters for testing discriminating ability of the proposed method. Based on the totality of the data/evidence, the Applicant's proposed IVRT method is deemed adequate for QC testing of the proposed drug product.

IVRT Acceptance Criteria

IVRT acceptance criteria are recommended based on the full-profile drug release data from pivotal clinical batches. In the original submission, the Applicant did not provide adequate data from these batches. Therefore, via an IR (dated 03/03/2021), the Applicant was informed/reminded that the IVRT acceptance criteria should be setup based on clinical batches and was recommended to provide these data. The Applicant provided the requested data in the submission dated 03/15/2020[2]. The Applicant also revised their originally proposed IVRT acceptance criteria for ATRA as follows:

Table 15: IVRT Acceptance criteria for BPO

Originally Proposed	Newly Proposed
0.5 hour: (b) (4) to (b) (4)%	0.5 hour: (b) to (b) (4)%
2 hours: (b) (4) to (b) (4)%	2 hours: (b) (4) to (b) (4)%
6 hours: NLT (b) (4)%	6 hours: NLT (b) (4)%

(b) (4)

[redacted] Upon reviewing the IVRT data from clinical and registration/stability batches, this Reviewer determines that the Applicant's newly proposed IVRT acceptance criteria are appropriately selected and adequate for QC testing of ATRA component of the proposed drug product.

The following IVRT method and acceptance criteria are approved by the FDA for quality control testing of the proposed product.

IVRT Parameter	For BPO	For Tretinoin
Apparatus	USP Apparatus 2 (Paddle)	USP Apparatus 2 (Paddle)
Paddle Speed	200 rpm	200 rpm
Medium	2 % of Tween 60 in phosphate buffer pH 6.7	2 % of Tween 80 in phosphate buffer pH 6.2, mixed with 4g/L BHT in IPA (66.7%: 33.3% w/w)
Volume	500 mL	500 mL
Temperature	37.0 ± 0.5°C	32.0 ± 0.5 °C
Acceptance Criteria	2 hours: [redacted] to [redacted]% 7 hours: [redacted] to [redacted]% 24 hours: NLT [redacted]%	0.5 hour: [redacted] to [redacted]% 2 hours: [redacted] to [redacted]% 6 hours: NLT [redacted]%

FORMULATION BRIDGING

IVRT Method Development for Bridging

As per the Applicant, all clinical studies were performed using the to-be-marketed formulation of E-BPO/E-ATRA Cream, 3%/0.1%. However, several changes in the manufacturing process and excipients [redacted] were introduced between the manufacturing of the E-BPO and E-ATRA cream, 3%/0.1%, clinical phase III batches to the manufacturing of the registration batches (refer to Appendix 1 for the list of manufacturing process related changes and Appendix 2 for the list of [redacted]). As per the SUPAC-Semisolid Guidance[3], these changes are Level-3 changed which should be supported by IVRT bridging data. The Applicant provided these data in the submission.

The Applicant developed separate IVRT methods for benzoyl peroxide (Module 3.2.P.2.; Report 09-05-151) and tretinoin (Module 3.2.P.2.; Report 09-05-152), and provided comparative IVRT data to support the sameness in drug release between the pre-change and post-change drug products (Module 3.2.P.2.; Report 09-05-161). It is noted that the proposed IVRT methods use [redacted] instead

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/supac-ss-nonsterile-semisolid-dosage-forms-scale-and-post-approval-changes-chemistry-manufacturing

of commonly used [redacted] (b) (4) as the drug release testing apparatus. Therefore, via an IR (dated 03/03/2021), the Applicant was recommended to explain why the proposed QC IVRT methods for benzoyl peroxide and tretinoin differ from the methods used for bridging studies to support the changes between the phase 3 clinical batches and the registration batches of the proposed drug product. In response (dated 03/15/2021, the Applicant stated that the IVRT analytical methods were developed based on the Agency's SUPAC-SS guidance while the QC release methods were developed to monitor the changes within individual batches throughout the product's shelf-life. The SUPAC-SS based IVRT methods are designed to evaluate the sameness between batches. As demonstrated in the discriminating ability of the QC release methods (09-05-154 and 09-05-153 for benzoyl peroxide and tretinoin, respectively) the methods are sensitive to changes in the quality of the encapsulation system, while the SUPAC-SS based IVRT methods can evaluate the impact of changes in the entire drug product in comparison to a reference drug product batch. Based on the provided information/clarification, this Reviewer determines that the Applicant's response is adequate, and they may continue evaluation by both methods as they relate to their intended uses described above. The following methods were developed as per SUPAC-SS guidance for IVRT testing of BPO and ATRA to support the changes during the product development:

Table 16: IVRT parameters for bridging studies for BPO

Test parameter	Value
Membrane	GH Polypro, 0.45 µm, 25 mm
Receptor media	mixture of ACN and Water in ratio 60 : 40 (v/v)
Receptor media treatment	Soniction for 20 minutes, dispensing into vessels and equilibration at the test conditions for 15 minutes
Receptor media volume	100 mL
Paddle height	1.0 ± 0.2 cm above the membrane surface
Stirring rate	100 ± 4 rpm
Temperature	32± 0.5°C
Test duration	5 hours
Sampling points	1, 2, 3, 4 and 5 hours
Sample volume	1 mL

* [redacted] (b) (4) was used as the diffusion apparatus

Table 17: IVRT parameters for bridging studies for ATRA

Test parameter	Value
Membrane	GH Polypro, 0.45 µm, 25 mm
Receptor media	mixture of BHT in IPA and phosphate buffer pH 7.9 in ratio 50 : 50 (v/v)
Receptor media treatment	Soniction for 20 minutes, dispensing into vessels and equilibration at the test conditions for 15 minutes
Receptor media volume	100 mL
Paddle height	1.0 ± 0.2 cm above the membrane surface
Stirring rate	100 ± 4 rpm
Temperature	32± 0.5°C
Test duration	4 hours
Sampling points	1.5, 2, 2.5, 3, and 4 hours
Sample volume	1 mL

* [redacted] (b) (4) was used as the diffusion apparatus

The provided data in the IVRT method development reports for benzoyl peroxide (Module 3.2.P.2.; Report 09-05-151) and tretinoin (Module 3.2.P.2.; Report 09-05-152) show that the Applicant has adequately developed and validated these methods. The IVRT method was found to provide acceptable precision and linearity over the range of BPO concentrations studied at 0.5 to 150% of maximal release of BPO at the end of the test ((b)(4)%), and ATRA concentrations studied at 1 to 165% of maximal release of ATRA by the end of the test ((b)(4)%). Also, The IVRT method for BPO could identify changes in different concentrations of BPO in the product and in the encapsulation process. The data also shows that the IVRT method for ATRA could identify different concentrations of ATRA and to differentiate changes in the manufacturing process and product composition. The data also show that the IVRT methods for BPO and ATRA are robust for stirring rate ± 10 rpm, for test temperature to ± 0.5°C and for the change in pH of the receptor media buffer to ±0.05 units. Based on the provided information/data, the proposed IVRT methods are deemed adequate for bridging studies.

Bridging Studies using IVRT

The IVRT data for bridging studies were collected as per the SUPAC-SS guidance following the above described methods for BPO and ATRA. To support the changes, according to SUPAC-SS and USP <1724>, a 'two-step' sameness evaluation by IVRT was performed using batches of comparable age (age similarity within 6 months) as follows:

	'T'	'R'
First Step	**Batch A6741** Registration batch (April 2019 campaign), following 16 months of storage at 2-8°C	**Batch A5270** Phase 3 batch, following 22 months of storage at 2-8°C
Second Step	**Batch A7378** Registration batch (October 2019 campaign), following 10 months of storage at 2-8°C	**Batch A6741** Registration batch (April 2019 campaign), following 16 months of storage at 2-8°C

The experiments ran with six replicates per each tested article and the amounts of released benzoyl peroxide and tretinoin were determined by HPLC against external standards. The average amount released ($\mu g/cm^2$) at a given time-point was calculated and plotted versus the square root of time. The resulting slopes (one for each chamber) were analyzed and the results were compared. The Applicant performed two-step analysis of the results.

For the first step, the cumulative release of benzoyl peroxide and tretinoin from 'T' and 'R' batches versus the square root of time, per each vessel, was modeled by a linear regression, and the slopes were determined, as summarized in Tables 18 and 19, respectively. A plot of the mean cumulative release of benzoyl peroxide and tretinoin per unit membrane area versus the square root of time and the mean liner regression equations for the 'T' and 'R' batches are presented in Figures 3 and 4, respectively.

Table 18 - Linear regression slopes for cumulative benzoyl peroxide release vs. the square root of time per IVRT vessel – First step of IVRT testing

Vessel Number	'T' Batch A6741	'R' Batch A5270
1	(b) (4)	(b) (4)
2		
3		
4		
5		
6		
Mean ± SD	806.15 ± 22.62	743.76 ± 111.85
RSD	2.8	15.0

Table 19 - Linear regression slopes for cumulative tretinoin release vs. the square root of time per IVRT vessel – First step of IVRT testing

Vessel Number	'T' Batch A6741	'R' Batch A5270
1	(b) (4)	(b) (4)
2		
3		
4		
5		
6		
Mean ± SD	31.65 ± 0.88	30.45 ± 2.71
RSD	2.8	8.9

Figure 3 - Mean linear regression curves of the cumulative release of benzoyl peroxide versus the square root of time – First step of IVRT testing

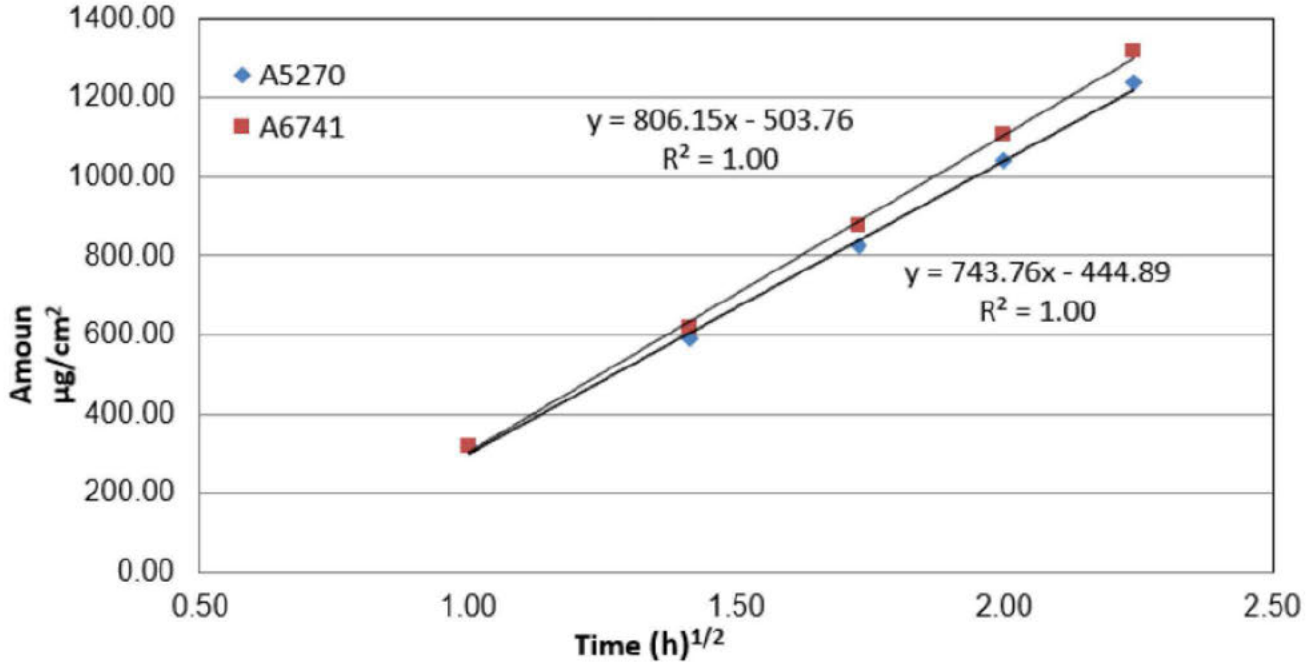
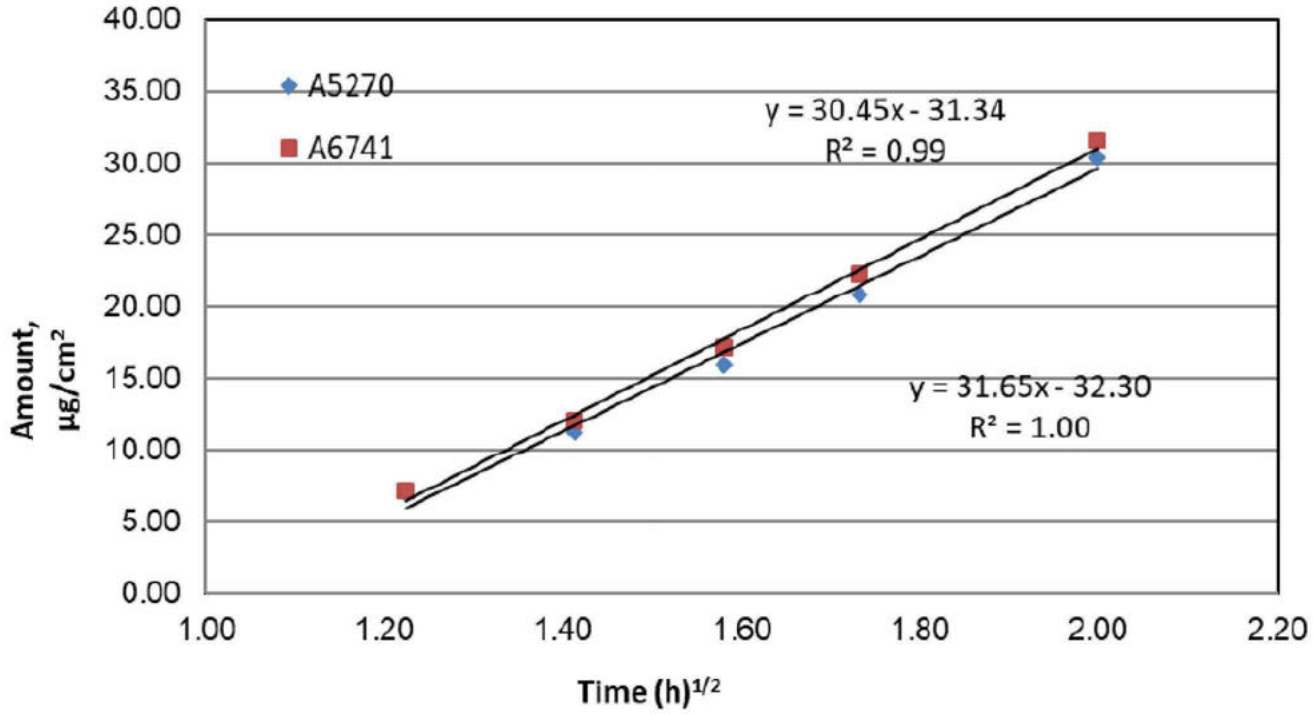


Figure 4 - Mean linear regression curves of the cumulative release of tretinoin versus the square root of time - First step of
IVRT testing



For the second step, a similar analysis was performed for batches A7378 and A6741. The data for the analysis from batches A7378 and A6741 is provided in the Report 09-05-161[4].

Following this, the 'T'/'R' slope ratio values, for both IVRT steps, were calculated for each pair of test-to-reference slope and ranked from the lowest to the highest. The 8th and the 29th 'T'/'R' ratios were identified and converted to percent (multiplied by 100). These values represent the 90% confidence interval and are presented in Table 20 and Table 21, below.

Table 20. T'/'R' slope ratio ranges - First step of IVRT testing

Tretinoin	A5270 (R)	Benzoyl peroxide	A5270 (R)
A6741 (T)	95.84-113.53%	A6741 (T)	98.23-114.67%

Table 21. 'T'/'R' slope ratio ranges - Second step of IVRT testing

Tretinoin	A6741 (R)	Benzoyl peroxide	A6741 (R)
A7378 (T)	101.30-121.75%	A7378 (T)	88.19-109.47%

The provided data show that a 90% confidence interval for the ratio of six release rates of the tested batch A6741 to six release rates of the reference batch A5270 is within the range of 75%–133.33%. Similarly, a 90% confidence interval for the ratio of six release rates of the tested batch A7378 to six release rates of the reference batch A6741 is within the range of 75%–133.33%. Based on these data,

(b) (4)

both tested products A6741 and A7378 are deemed same to the reference phase III clinical batch in terms of in vitro drug release. The statistical analysis data is provided by the Applicant in Appendix 4 of the Report 09-05-161[4]. These data were verified by this Reviewer and were found acceptable. Based on the provided data, the pre-change and post-change drug products are deemed adequately bridged. From a Biopharmaceutics perspective, the proposed IVRT based bridging is deemed adequate.

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Kaushalkumar Dave

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FDA U.S. FOOD & DRUG ADMINISTRATION

MICROBIOLOGY

Product Information	Indicated in the treatment for acne vulgaris (acne) in patients nine years of age and older.
NDA Number	214902
Assessment Cycle Number	01
Drug Product Name / Strength	Encapsulated Benzoyl Peroxide and Encapsulated Tretinoin Cream; 3%/0.1%
Route of Administration	Topical
Applicant Name	Sol-Gel Technologies Ltd
Therapeutic Classification/ OND Division	CDER/OND/OII/DDD
Manufacturing Site(s)	(b) (4)
Method of Sterilization	Non-sterile

Assessment Recommendation: **Adequate**

Assessment Summary: The submission is **recommended** for approval on the basis of sterility assurance. 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 testing and the effectiveness of the antimicrobial agent. 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 USP <60>. The Applicant has also provided sufficient data to support the antimicrobial effectiveness of the drug product (b) (4) to all the organisms listed in USP<51> and 3 BCC strains.

List Submissions Being Assessed

Document(s)	eCTD	SDN	Date Received
NDA-214510-ORIG-1	0001	1	10/01/2020
NDA-214510-ORIG-1	0004	4	11/23/2020
NDA-214510-ORIG-1	0008	8	03/15/2021

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

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Samata Tiwari

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Yuansha Chen

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