

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211913Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

<input checked="" type="checkbox"/> Approval
<input type="checkbox"/> Approval with Post-Marketing Commitment
<input type="checkbox"/> Complete Response

NDA 211913 Assessment 1

Drug Product Name	ABSORICA™ LD (isotretinoin)
Dosage Form	Capsules
Strength	8mg, 16mg, 20mg, 24mg, 28mg, and 32mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Sun Pharmaceutical Industries Limited
US agent, if applicable	Sun Pharmaceuticals Industries, Inc.

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original NDA submission	08/17/2018	All
Proprietary Name Request	10/29/2018	All
Patent and Exclusivity	11/19/2018	Administrative
Response to Quality IR	11/23/2018	OPQ-ONDP-Drug Product
Amendment to Patent	12/21/2018	Administrative
Safety and Efficacy Report	01/24/2019	Clinical
Response to Quality IR	02/19/2019	OPQ-ONDP-Drug Product and Process
Response to Quality IR	03/20/2019	OPQ-ONDP-Biopharm
Response to Quality IR	04/08/2019	OPQ-ONDP-Drug Product
Draft Labeling	05/02/2019	All
Draft Labeling	05/06/2019	All
Clinical Study Report	05/28/2019	Clinical
Draft Labeling	06/11/2019	All
Pediatric Plan – Literature Reference- iPSP	06/17/2019	Clinical
Draft Labeling and Labels	06/20/2019	All
Draft Labeling	07/18/2019	All
Draft Labels	07/19/2019	All
Patent Certification	08/16/2019	Administrative

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sam Bain, Ph.D.	Donna Christner, Ph.D.
Drug Product	Zhengfang Ge, Ph.D.	Moo-Jhong Rhee, Ph.D.
Manufacturing	Mesfin Abdi, Ph.D.	Yubing Tang, Ph.D.
Microbiology	Mesfin Abdi, Ph.D.	Yubing Tang, Ph.D.
Biopharmaceutics	Rajesh Savkur, Ph.D.	Vidula Kolhatkar, Ph.D.
Regulatory Business Process Manager	Bamidele (Florence) Aisida, Pharm. D., BCPS	
Application Technical Lead	Hamid R. Shafiei, Ph.D.	
Laboratory (OTR)	N/A	N/A
Environmental	Zhengfang Ge, Ph.D.	Moo-Jhong Rhee, Ph.D.

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	Isotretinoin	Adequate	Oct 29, 2018	Latest review by Sam Bain, Ph.D.
	III		(b) (4)	-----	-----	Adequate information is provided in the NDA
	III			-----	-----	Adequate information is provided in the NDA

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

Document	Application Number	Description
NDA	21951	ABSORICA Capsules

2. CONSULTS

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

EXECUTIVE SUMMARY

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, purity, strength, and quality of the drug substance and drug product.
- Labels/labeling issues have been **satisfactorily** addressed.
- The Office of Process and Facility has made an overall “**Acceptable**” recommendation regarding the facilities involved in this NDA.
- The claim for categorical exclusion of the environmental assessment is granted.

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

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Sun Pharmaceutical Industries Limited has submitted this (505)(b)(2) application for ABSORICA™ LD (isotretinoin) Capsules, 8mg, 16mg, 20mg, 24mg, 28mg, and 32mg for the treatment of severe recalcitrant nodular acne in patients 12 years of age or older.

Isotretinoin was first approved as the active ingredient of the drug product marketed by Hoffmann La Roche under the brand name, ACCUTANE oral capsules for the same indication, on May 7, 1982 under NDA 18662. However, marketing of ACCUTANE has been discontinued. The discontinuation of ACCUTANE was not because of any safety or efficacy reason. Since the original approval, multiple brand name and generic versions for isotretinoin capsules have been approved for marketing in the United States.

The applicant of this application, Sun Pharmaceutical Industries Limited currently is the holder of the approved application, NDA 21951 for ABSORICA™ (isotretinoin) Capsules, 10mg, 20 mg, 25mg, 30mg, 35mg, and 40mg for oral administration. ABSORICA™ was approved on May 25, 2012 and is also indicated for the treatment of severe recalcitrant nodular acne. ABSORICA™ is used as the referenced listed drug (LD) for this application.

The new oral capsules formulation presented in this application contains isotretinoin that is micronized [REDACTED] (b)(4) The purpose for

The improved solubility and bioavailability have allowed the applicant to reformulate the oral capsules and to reduce the amount isotretinoin in each of the capsule strengths by 20% without impacting efficacy. Based on the review of the results from bioequivalence study of the highest dosage strength of the new capsule formulation and the original ABSORICA capsule formulation as well as similarity of the dissolution profiles of the lower strengths, biowaiver for the lower strengths of ABSORICA™ LD capsules has been granted.

To-be-marketed ABSORICA™ LD capsules for oral use will be packaged in cartons each containing 3 blister cards with 10 capsules per blister card (total of 30 capsules per carton). 8mg strength is an opaque light green capsule printed with “RL 29” on both body and cap. 16mg strength is an opaque dark blue capsule printed with “RL 30” on both body and cap. 20mg strength is opaque dark pink capsule printed with “RL 33” on both body and cap. 24mg strength is an opaque yellow capsule printed with “RL 31” on both body and cap. 28mg strength is an opaque light blue capsule printed with “RL 34” on both body and cap. 32mg strength is an opaque caramel capsule printed with “RL 32” on both body and cap.

Based on the safety risk associated with isotretinoin, ABSORICA and all other brand name and generic drug products containing this active ingredient are only available through a restricted program under a REMS called iPLEDGE. Under this REMS, prescribers, patients, pharmacist, and distributors must be enrolled and be registered in iPLEDGE program.

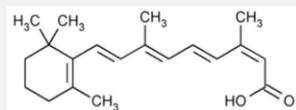
Proposed Indication(s) including Intended Patient Population	Treatment of severe recalcitrant nodular acne in patients 12 years of age or older
Duration of Treatment	15 to 20 weeks
Maximum Daily Dose	1.6 mg/kg/day given in two divided doses
Alternative Methods of Administration	No alternative method of administration

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, isotretinoin is a non-aromatic retinoid and is a compendial active pharmaceutical ingredient with a published USP monograph. Isotretinoin was first approved in 1982 as the active ingredient of the drug product, ACCUTANE indicated for the treatment of severe recalcitrant nodular acne.

Isotretinoin is a yellow to orange crystalline powder. It is very sparingly soluble in water, sparingly soluble in ethanol and isopropanol, and soluble in chloroform and methylene chloride. Isotretinoin has a melting point of 173°C - 178°C and pKa of 5. It is non-hygroscopic with only one known crystalline form. This active ingredient has been classified as a BCS class II drug substance. Isotretinoin has molecular formula of C₂₀H₂₈O₂, molecular weight of 300.44, and molecular structure below:



(b) (4)

(b) (4)

(b) (4)

Isotretinoin manufactured by (b) (4) is tested and released according to a drug substance specification that complies to the USP monograph requirements and ICH Q3A guideline. The proposed drug substance specification includes testing and acceptance criteria for all physical and chemical attributes essential for the determination of the identity, strength, purity and quality of the drug substance at release and throughout its proposed retest date of (b) (4).

In summary, the Drug Substance Reviewer, Dr. Sukhamaya Bain has concluded that the information provided in DMF (b) (4) and in the drug substance section of this application is adequate to support approval of this application from the drug substance perspective. Dr. Bain's review is provided in the Drug Substance Chapter of the IQA.

Drug Product: Adequate

The drug product, ABSORICA™ LD (isotretinoin) Capsules, 8mg, 16mg, 20mg, 24mg, 28mg, and 32mg is indicated for treatment of severe recalcitrant nodular acne in patients 12 years of age or older. The approved drug product ABSORICA™ (isotretinoin) Capsules, 10mg, 20mg, 25mg, 30mg, 35mg, and

40mg also marketed by the same applicant is used as the referenced listed drug (LD) for this application.

Isotretinoin drug substance in the proposed drug product, ABSORICA™ LD is micronized (b) (4) leading to an enhanced the solubility and bioavailability of the active ingredient due to increased surface area (b) (4). Based on the improved bioavailability, API contents for all capsule strengths of ABSORICA™ LD have been reduced by 20% compared to ABSORICA capsules.

The excipients used in the composition of this drug product including the drug substance, capsule shells, and inks are all compendial materials, composed of compendial materials, or materials that complies to the applicable 21 CFR requirement.

The to-be-marketed drug product capsules will be packaged in blisters consisting of (b) (4) and child resistant peelable (b) (4) lid foil configured in blister cards containing 10 capsules. Blister card is further packaged into a blister wallet. Three blister wallets each containing 10 capsules are packaged in an outer carton (30 capsules per carton).

The drug product is tested and released according to a specification that includes testing and acceptance criteria for all physical and chemical attributes essential for assuring the identity, strength, purity, and quality of the drug product at release and throughout its proposed expiration dating period of 24 months. The applicant has provided sufficient stability data in support of the proposed drug product expiration dating period.

The drug product section of this application including the applicant's request for categorical exclusion from preparation of the environmental assessment has been reviewed by the Drug Product Reviewer, Dr. Zhengfang Ge. Dr. Ge has recommended the approval of this application with an expiration dating period of 24 months from the drug product perspective. Dr. Ge has also recommended granting the categorical exclusion to this application. Dr. Ge's review is provided 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 the final PI as well as immediate container and carton labels have satisfactorily resolved all outstanding issues noted in her Labeling Review #1, and therefore, she has recommended the approval of this application from the labeling/labels perspective (see Dr. Ge's addendum dated August 7, 2019 to her Labeling Review # 1).

Biopharmaceutics: Adequate

The biopharmaceutic review of this application was mainly focused on the dissolution method development, dissolution data, dissolution acceptance criteria, and the request for biowaiver for the lower strength of this new drug product.

The comparability of this new drug product formulated using the micronized isotretinoin and manufactured with 20% lower API content in each strengths due to enhanced bioavailability against referenced listed drug ABSORICA™ was evaluated by a bioequivalence study conducted comparing the 32mg strength of the new drug product to the 40mg strength of the LD. Additionally, in support of the request for biowaiver for lower strengths of the new drug product, studies to determine the similarity of dissolution profiles for all strengths of the drug product were conducted.

Based on the results from the bioequivalence study of the highest dosage strength as well as the similarity in the dissolution profiles of all strengths of drug product, the Biopharm Reviewer, Dr. Rajesh Savkur has granted the biowaiver to lower strengths of ABSORICA™ LD. Dr. Savkur has found the information provided in the biopharm section of this new drug application adequate and has recommended the approval of this application from the biopharm perspective. Dr. Savkur's review is provided in the Biopharm Chapter of the IQA.

Microbiology (if applicable): Adequate

The review of microbial limit for this application is reviewed by the Process Reviewer. Refer to the Process Chapter of the IQA for this new drug application.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA		Initial Risk Ranking		Final Risk Evaluation	Lifecycle Considerations/ Comments
Dissolution rate	(b) (4)	H	(b) (4)	L	None

D. L

cies for Compl

e: None

Application Technical Lead
Hamid Shafiei, Ph.D.
 Branch V/ DNDP II/OPND/OPQ



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Shafiei

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LABEL FOR NDA 211913

I. PI

1. Highlights of Prescribing Information



(b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))		
Proprietary name and established name	Absorica LD	Not Adequate Established name for API, isotrenoïn, is not provided

		Established name and dosage form should be provided in the title of the highlight
Dosage form, route of administration	capsules, for oral	Adequate
Controlled drug substance symbol (if applicable)	N/A	
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))		
Summary of the dosage form and strength	Capsules: 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg	Adequate

This section is not adequate

The proprietary name, established name and dosage form in the title of highlight section should be displayed as: **Absorica LD (isotretinoin) capsules**

2. Section 2 Dosage and Administration



Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))		
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	N/A	Adequate

This section is adequate.

3. Section 3 Dosage Forms and Strengths



Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))		
Available dosage forms	capsules	Adequate
Strengths: in metric system	8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Capsule size, color, imprinting are provided	Adequate

This section is adequate.

4. Section 11 Description



Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))		
Proprietary name and established name	established name is not provided	Not Adequate Proprietary name, established name and dosage form should be shown in the 1st paragraph as: ABSORICA LD (isotretinoin) capsules contain ...
Dosage form and route of administration	capsules	Adequate
Active moiety expression of strength with equivalence statement (if applicable)	N/A	Adequate
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	excipients are provided	Adequate
Statement of being sterile (if applicable)	N/A	Adequate
Pharmacological/ therapeutic class	retinoid	Adequate
Chemical name, structural formula, molecular weight	Provided	Adequate
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	(b) (4)	Adequate

This section is not adequate. The following revision should be made:

- Proprietary name, established name and dosage form should be shown in the 1st paragraph as: ABSORICA LD (isotretinoin) capsules contain ...

5. Section 16 How Supplied/Storage and Handling



Item	Information Provided in NDA	Reviewer's Assessment
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))		
Strength of dosage form	8 mg, 16 mg, 20 mg, 24 mg, 28 mg, 32 mg	Adequate
Available units (e.g., bottles of 100 tablets)	30 capsules (3X10 prescription packs)	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	capsules	Adequate
Special handling (e.g., Dispense in tight and light resistant container as defined in USP)	Protect from light	Adequate
Storage conditions	Store at 20° to 25°C (68° to 77°F), excursions permitted between 15°- 30°C (59° - 86°F) [see USP Controlled Room Temperature]	Adequate
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided at after section 17 Manufactured by: M W Encap Ltd United Kingdom Distributed by: Sun Pharmaceutical Industries, Inc. Cranbury, NJ 08512 October 2018	Adequate

This section is adequate.

II. Labels:

1. Immediate Container Label

Labels for 10 count wallets in the strengths of 8 mg, 16mg, 20 mg, 24 mg, 30 mg and 32 mg are provided in the submission. The Figure below is the labels for the 8 mg strength. Labels for the strengths 16 mg, 24 mg 30 mg, 32 mg are the same as 8 mg except the strength, therefore are not displayed below. The front panel of the 20 mg also displayed below contains an important note “

(b) (4)

(b) (4)

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Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	ABSORICA LD (Isotretinoin) Capsules, USP	Not Adequate established name isotretinoin should be displayed all in lower case
Dosage strength Active moiety expression of strength with equivalence statement (if applicable), if space is available	8 mg	Adequate
Net contents	10 capsules	Adequate
“Rx only” displayed prominently on the main panel	Provided	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Adequate
Lot number and expiration date (21 CFR 201.17)	Provided	Adequate
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	This package is child-resistant. Keep out of reach of children. STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) [SEE USP CONTROLLED ROOM TEMPERATURE.] PROTECT FROM LIGHT.	Adequate
Bar code (21CFR 201.25)	Provided	Adequate
Name of manufacturer/distributor	Provided	Adequate
And others, if space is available	N/A	Adequate

This section is not adequate. The following revision should be made:

- Established name isotretinoin should be displayed all in lowercase

2. Carton Label

Carton labels for 30 count capsules in the strengths of 8 mg, 16mg, 20 mg, 24 mg, 30 mg and 32 mg are provided in the submission. The Figure below is the label for the 8 mg

strength. Labels for the strengths 16 mg, 20 mg, 24 mg, 30 mg, 32 mg are the same as 8 mg except the strength.

(b) (4)



Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name, established name (font size, prominence)	ABSORICA LD (Isotretinoin) Capsules, USP	Not Adequate established name isotretinoin should be displayed all in lower case
Dosage strength Active moiety expression of strength with equivalence statement (if applicable) in the side panel.	8 mg	Adequate
Net quantity of dosage form	30 capsules (3X10 prescription packs)	Adequate
“Rx only” displayed prominently on the main panel	Provided	Adequate
Lot number and expiration date	Provided	Adequate
Storage conditions Special handling, e.g., “Dispense in tight and light resistant container as defined in USP”.	STORE AT 20° C - 25° C (68° F - 77° F), EXCURSION PERMITTED BETWEEN 15° C - 30° C (59° F - 86° F) [SEE USP CONTROLLED ROOM TEMPERATURE.] PROTECT FROM LIGHT.	Adequate
Bar code (21CFR 201.25)	Provided	Adequate
NDC number (21 CFR 207.35(b)(3)(i))	Provided	Adequate
Manufacturer/distributor's name	Provided	Adequate
Quantitative ingredient information (injectables)	N/A	Adequate
Statement of being sterile (if applicable)	N/A	Adequate
“See package insert for dosage information”	(b) (4) DOSAGE: (b) (4) (b) (4) prescribing information, (b) (4) (b) (4)	Adequate
“Keep out of reach of children” (Required for OTC in CFR. Optional for Rx drugs)	This package is child-resistant. Keep out of reach of children	Adequate

This section is not adequate. The following revision should be made:

- Established name isotretinoin should be displayed all in lower case

List of Deficiencies:

A. Regarding PI

I. Highlights of Prescribing Information

- The proprietary name, established name and dosage form in the title of highlight section should be displayed as follows:

Absorica LD (isotretinoin) capsules, for oral use

II. Full Prescribing Information

For Section 11, “DESCRIPTION”

- Proprietary name, established name and dosage form should be shown in the 1st paragraph as: Absorica LD (isotretinoin) capsules contain ...

B. Regarding Container/Carton Labels:

- Established name for isotretinoin should be displayed all in lowercase

Overall Assessment and Recommendation:

The labeling and labels are **not** deemed ready for approval in its present form per 21 CFR 314.125 (b)(6) from the CMC labeling perspective until the deficiencies are satisfactorily resolved.

Primary Labeling Reviewer Name and Date:

Zhengfang Ge, Ph. D.

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

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

I agree with Dr. Ge’s assessment and concur with her recommendation that this application is not ready for approval in its present form until the above deficiencies are satisfactorily resolved.

Moo-Jhong Rhee, Ph. D.

*Branch Chief, BRANCH V/DIVISION II
OFFICE OF NEW DRUG PRODUCT*



Zhengfang
Ge

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Moo Jhong
Rhee

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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: Aug. 7, 2019

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

Through: Moo-Jhong Rhee, Ph.D.
Chief, ONDP/Division II/Branch V

To: Labeling Review #1 of NDA 211913

Subject: Final Recommendation for Labeling/Labels

The Labeling review #1 has noted the following pending issues:

A. Regarding PI

I. Highlights of Prescribing Information

- The proprietary name, established name and dosage form in the title of highlight section should be displayed as follows:

Absorica LD (isotretinoin) capsules, for oral use

II. Full Prescribing Information

For Section 11, "DESCRIPTION"

- The proprietary name, established name and dosage form should be shown in the 1st paragraph as: Absorica LD (isotretinoin) capsules contain ...

B. Regarding Container/Carton Labels:

- Established name isotretinoin should be displayed all in lowercase

And because of these deficiencies, in the Labeling Review #1, this NDA was not recommended for approval from the labeling perspective.

The above requests have been implemented as shown in the revised labeling. The revised container/carton labels are satisfactory and provided in the **Attachment**.

Recommendation:

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

Attachment:

Carton Labels:

Carton labels for 30 count capsules in the strengths of 8 mg, 16mg, 20 mg, 24 mg, 30 mg and 32 mg are provided in the submission. The Figure below is the label for the 8 mg strength. Labels for the strengths 16 mg, 20 mg, 24 mg, 30 mg, 32 mg are the same as 8 mg except the strength.



Container Labels:

Labels for 10 count wallets in the strengths of 8 mg, 16mg, 20 mg, 24 mg, 30 mg and 32 mg are provided in the submission. The Figure below is the labels for the 8 mg strength. Labels for the strengths 16 mg, 24 mg 30 mg, 32 mg are the same as 8 mg except the strength, therefore are not displayed below. The front panel of the 20 mg also displayed below contains an important note



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Zhengfang
Ge

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA-211913-ORIG-1

Drug Product Name / Strength: Isotretinoin Capsules, 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, and 32 mg

Route of Administration: Oral

Applicant Name: Sun Pharmaceuticals Industries Ltd.

Review Summary:

The Listed Drug (LD) Absorica® (Isotretinoin capsules, 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg), developed by Sun Pharmaceuticals Industries Inc, a subsidiary of Sun Pharmaceuticals Industries Ltd. was approved by the FDA under NDA N021951 on 12/31/1996. Absorica is indicated for the treatment of severe recalcitrant nodular acne in patients 12 years of age and older.

Using Absorica® as the LD, the Applicant is developing a new formulation of Isotretinoin capsules with reduced dosage strengths of 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, and 32 mg, which are designed to be bioequivalent to the corresponding LD, Absorica - 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, and 40 mg capsules, and has submitted this NDA-211913 under section 505 (b)(2) to the Division of Dermatology and Dental Products for review on 8/17/2018.

The Biopharmaceutics review focuses on the dissolution method development, dissolution data, dissolution acceptance criteria and biowaiver request.

The final dissolution method and acceptance criterion as agreed upon by the Agency and the Applicant are stated below:

Method:	In-house (modified USP monograph test-4)
Apparatus:	Apparatus II (paddles) with spiral coated sinkers
Medium:	50 mM monobasic Potassium phosphate (pH 7.4), containing 70 mg/L of pancreatin, and 2.25% v/v of lauryl dimethylamine oxide as 30% solution
Volume:	900 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Sampling time:	15, 30, 45, 60 and 90 minutes
Acceptance criterion:	Q = ^{(b) (4)} % of the labeled amount is dissolved in 45 minutes

A Bioequivalence study was performed on the 32 mg strength of the test product against the 40 mg strength of the LD. Based on the similarity in the in vitro dissolution profiles between the 32 mg strength and the lower (8 mg, 16 mg, 20 mg, 24 mg and 28 mg) strengths, the Applicant's

request for the biowaiver for the lower strengths has been granted by the Agency provided BE studies are adequate.

From the Biopharmaceutics perspective, this Reviewer concludes that NDA-211913-ORIG-1, Isotretinoin capsules, 8 mg, 16 mg, 20 mg, 24 mg, 28 mg, and 32 mg, is **Adequate** for approval

List Submissions being reviewed:

8/17/2018	Original submission/Sequence 0001
11/22/2018	Information Request – Quality/Sequence 0004
2/19/2019	Information Request – Quality/Sequence 0007
3/20/2019	Information Request – Quality/Sequence 0008
4/8/2019	Amendment Quality/Sequence 0009

Concise Description Outstanding Issues Remaining:

None

Solubility:

The solubility of Isotretinoin API at 25 °C in various aqueous media is presented in Table 1. As seen in Table 1, at the highest proposed dose of 32 mg, Isotretinoin is insoluble in physiological media (from 0.01 N HCl to pH 7.5 phosphate buffer). However, it shows solubility in USP test method 3 (pH 8.0 borate buffer containing 0.5% cetrimide), USP test method 4 (50 mM monobasic potassium phosphate, pH 7.4 containing 70 mg/L pancreatin 4.5% (v/v) lauryl dimethyl amine oxide as a 30% solution), and USP test method 5 (pH 7.7 phosphate buffer containing 50 mg/L pancreatin and 1.5% N,N dimethyldodecylamine-N-oxide) dissolution media. Based on the solubility data, the Applicant has classified Isotretinoin as a BCS class II compound.

Table 1: Solubility data of Isotretinoin at 25 °C

S.No.	Media	Solubility (mg/mL)
1	0.01 N HCl	0.0001
2	pH 4.5 Acetate buffer	0.0002
3	pH 6.8 Phosphate buffer	0.0263
4	pH 7.5 Phosphate buffer	0.0004
5	pH 8.0 Borate Buffer containing 0.5% cetrimide	0.5461
6	50 mM monobasic potassium phosphate at pH 7.4 containing 4.5% (v/v) of lauryl dimethyl amine oxide as 30% solution	6.730
7	pH 7.7 phosphate buffer containing 1.5% N,N-dimethyldodecylamine N-oxide	5.037

Reviewer’s Assessment:

The Reviewer has noted that the Applicant has submitted the solubility data of Isotretinoin in various buffers. However, it was unclear whether the Applicant reported the solubility of the micronized API. In the early Information Request (IR) that was communicated to the Applicant on 10/25/2018, the Applicant was requested to clarify whether the submitted solubility data (reported in Table 10 of the Development Report in the original submission/sequence 0001) was obtained using micronized Isotretinoin. The Applicant responded to the Information Request (IR) on 11/22/2018 that the reported solubility data was obtained from the micronized API. The IR

comments, the Applicant's response to the IR and the Reviewer's assessment are included in Appendix 2.

Permeability:

The Applicant has classified Isotretinoin as a BCS class II compound and has stated that it is a highly permeable drug.

Reviewer's Assessment:

The Applicant has not reported any permeability data in this submission to justify their claim that Isotretinoin is a highly permeable compound.

Dissolution: See the review below

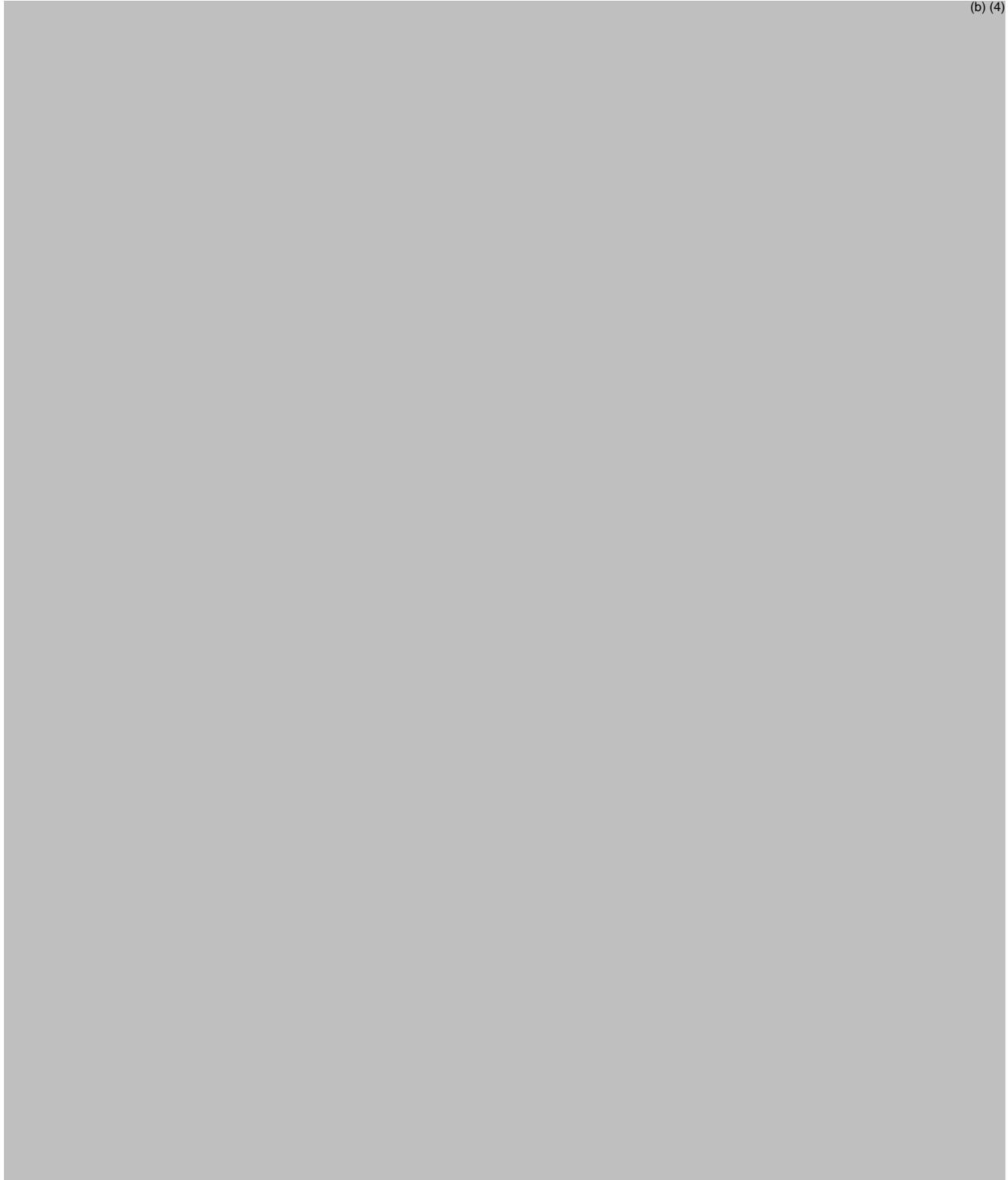
Dissolution Method and Acceptance Criterion**1. Dissolution Method:**

The dissolution method used by the Applicant for the LD, is in accordance with the test-3 method stated in the USP monograph for Isotretinoin capsules. In the original submission (Sequence 0001), for the test product, the dissolution method used by the Applicant is in accordance with test-4 method stated in the USP monograph for Isotretinoin capsules. In response to the IR that was received by the Agency on 2/19/2019 (Sequence 0007), the final dissolution method and the acceptance criterion proposed by the Applicant for routine dissolution testing of the test product at release and stability is stated below:

Method:	In house (modified USP monograph-test 4)
Apparatus:	Apparatus II (paddle) with spiral coated sinkers
Medium:	50 mM monobasic Potassium phosphate (pH 7.4), containing 70 mg/L of pancreatin, and 2.25% v/v of lauryl dimethylamine oxide as 30% solution (see Information Request Quality/Sequence 0007)
Volume:	900 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Sampling times:	15, 30, 45, 60, and 90 minutes.
Acceptance Criterion:	Q = $\frac{(b)}{(4)}$ % in 45 minutes (subsequent to the teleconference that was held between the Applicant and the Agency on 4/2/19; see Amendment - Quality/Sequence 0009)

In the original submission (Sequence 0001), the Applicant submitted data demonstrating that the test-4 was the most optimal dissolution test for the proposed product:

There are 6 dissolution tests mentioned in the USP monograph for Isotretinoin capsules. However, the Applicant has tested 5 of these tests. These are listed in Table 2:



USP Test-4:

The Applicant has evaluated the drug release of the test product (of the strengths 8 mg/16 mg/24 mg/32 mg) in USP Test-4. In the original submission (Sequence 0001), the Applicant proposed a tolerance limit for this dissolution condition as “Not Less than (b) (4) % (Q) of labelled amount of Isotretinoin to be dissolved in (b) (4) minutes”. However, in response to the Information Request (dated 11/22/2018; sequence 0004), the Applicant has revised

the acceptance criterion and proposed a new tolerance limit for the proposed product as “Not Less than (b) (4) % (Q) of labelled amount of Isotretinoin to be dissolved in 45 minutes”. The Applicant has stated that the percentage drug release of test product was found acceptable. The Applicant evaluated the effect of temperature on the test product - the samples were charged on stability and evaluated as per USP dissolution test-4. The dissolution results of stability samples of Isotretinoin capsules as per USP test-4 are summarized below in the Table 5:

Table 5: Drug release of Isotretinoin capsules 8/16/24/32 mg at stability in USP dissolution test-4

Dissolution Parameters	50 mM monobasic potassium phosphate at pH 7.4 containing 70 mg/L of pancreatin and 4.5% (v/v) of lauryl dimethyl amine oxide as 30% solution/ Apparatus 2 with spiral coated sinkers/ 75 RPM/37°C±0.5°C			
Batch No.	HM(6147)011	HM(6147)009	HM(6147)003	HM(6147)001
Strength	8 ma	16 ma	24 ma	32 ma
Condition	(b) (4)			
Specification	NLT (b) (4) % (Q) in (b) (4) minutes			
% Drug release	(b) (4)			

The Applicant has attributed the complete drug release in USP dissolution test-4 media might to having an appropriate concentration of enzymes i.e. pancreatin to enable the uniform disintegration of the hard gelatin capsule shell, and to avoid any cross-linking of gelatin capsule shell on accelerated stability. The Applicant has also stated that the (b) (4) % (v/v) of lauryl dimethyl amine oxide present in this dissolution media also helped to avoid the cross-linking of gelatin capsules on accelerated stability. Based on above results, the Applicant concluded that complete drug release was achieved for 8mg and 16 mg strengths at the 9-month time-period under Long-term conditions and for 24 mg and 32 mg strengths at 6-month time under accelerated conditions. Thus, the Applicant has stated that based on the above results, USP dissolution test-4 was finalized for Isotretinoin capsules and further testing of all initial and stability samples.



(b) (4)

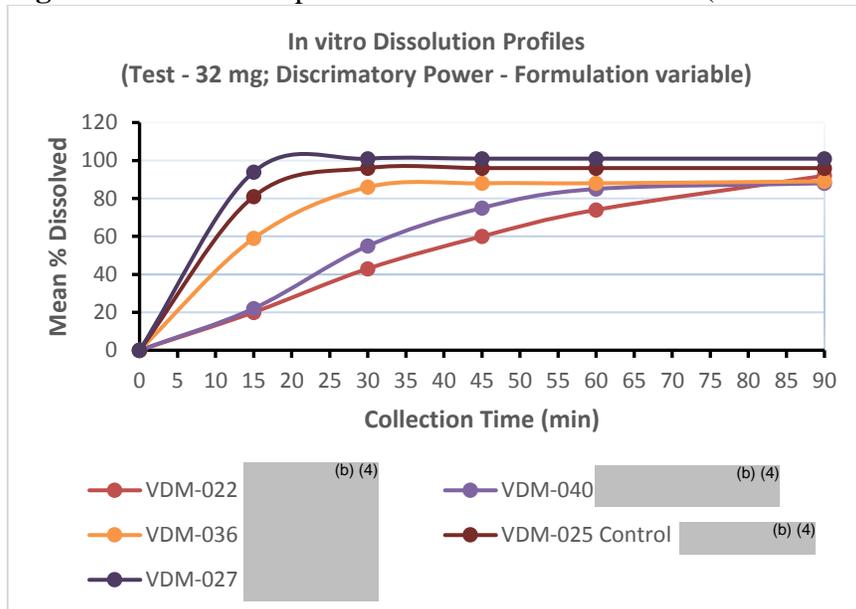
Table 6: Formulation changes to demonstrate discriminatory power of USP-test 4

Batch No.	VDM(6891)022	VDM(6891)040	VDM(6891)036	VDM(6891)025	VDM(6891)027
Concentration of	(b) (4)				
Name of Ingredient	mg per capsule				
(b) (4)					

Table 7: Dissolution data of formulation variable (concentration of (b) (4))

Batch No.	VDM(6891)022	VDM(6891)040	VDM(6891)036	VDM(6891)025	VDM(6891)027
Dissolution Profile (mins.)	% Drug release				
15	20	22	59	81	94
30	43	55	86	96	101
45	60	75	88	96	101
60	74	85	88	96	101
90	92	88	89	96	101

Figure 3: Dissolution profiles of formulation variable (concentration of (b) (4))



f_2 comparison between VDM-025/Control (b) (4) and VDM-040 (b) (4) = 21
 f_2 comparison between VDM-025/Control (b) (4) and VDM-022 (b) (4) = 19

Based on the dissolution data and profiles, the Reviewer calculated the f_2 values between the Target/Control formulation and the altered formulations. The Reviewer concluded that the dissolution profiles are similar between the (b) (4)% target/control and a (b) (4)% change in the formulation variables. An f_2 comparison between VDM-025 ((b) (4)% w/w) and VDM-027 ((b) (4)% w/w) was not possible because $> (b) (4) \%$ of the drug was released in 15 minutes suggesting that the dissolution profiles between the two were similar; an f_2 comparison between VDM-025 ((b) (4)% w/w) and VDM-036 ((b) (4)% w/w) was also not possible because $> (b) (4) \%$ of the drug was released in 30 minutes. The f_2 values between VDM-025 (b) (4) %

w/w) and VDM-040 ((b) (4) % w/w) was 21, and between VDM-025 ((b) (4) % w/w) and VDM-022 ((b) (4) % w/w) was 19 indicating that the dissolution profiles are different, and that the dissolution method adopted by the Applicant (USP-test 4) was capable of detecting larger ((b) (4) % and greater) changes but not smaller ((b) (4) %) changes in the formulation variable in the drug product composition.

Intentional changes in manufacturing process variable:

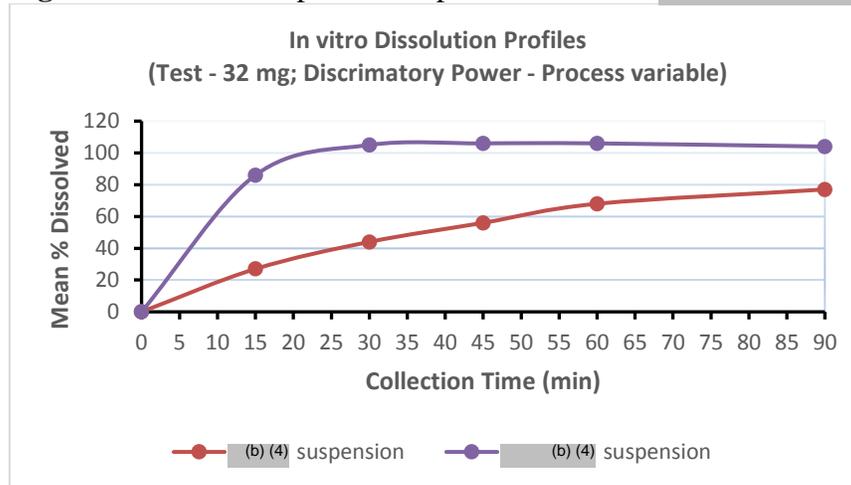
Isotretinoin capsules 32 mg batch [RD(6535)010] was manufactured with an intentional modifications ((b) (4)) and the dissolution profile was compared against target/control formulation batch [HM(219)02] that was manufactured with ((b) (4)) suspension. The process variable is shown in Table 8, and the dissolution data and profiles are shown in Table 9 and Figure 4, respectively.

Table 8: Process changes to demonstrate discriminatory power of USP-test 4

Process	((b) (4))	
Strength	32 mg	
Batch No.	RD(6535)010	HM(219)02
Ingredients	mg per capsule	mg per capsule
((b) (4))		

Table 9: Dissolution data of process variable ((b) (4) suspension)

Process	((b) (4))	
Strength	32 mg	32 mg
B.No.	RD(6535)010	HM(219)02
Time (min)	Limit: NLT ((b) (4))% (Q) at ((b) (4)) minutes	
15	27	86
30	44	105
45	56	106
60	68	108
90	((b) (4))	

Figure 4: Dissolution profiles of process variable ((b) (4) suspension)

f_2 comparison between (b) (4) process = 15.6

Based on the dissolution data and profiles, the Reviewer calculated the f_2 values between the Target/Control formulation and the altered formulation. The Reviewer calculated f_2 value between the (b) (4) process alteration was 15.6, indicating that the dissolution profiles are different, and that the dissolution method adopted by the Applicant (USP-test 4) was capable of detecting this extreme change (b) (4) in the manufacturing process variable.

Reviewer's Assessment:

There are 6 dissolution tests mentioned in the USP monograph for Isotretinoin capsules. The Applicant has evaluated 5 of these tests. (b) (4)

The Applicant had further selected USP test 4 as the preferred dissolution method for the test product. The dissolution method initially used by the Applicant (test 4) was able to demonstrate its discriminatory ability with respect to intentional changes in the formulation (different amounts of (b) (4) added to the product) and manufacturing process (product manufactured with (b) (4) API). However, the discriminatory ability of the method was seen only when these variations exceeded the Agency's recommended $\pm 10\%$ - 20% change in the specification ranges of the tested variables, and hence were not considered as meaningful variations. In the early Information Request (IR) that was communicated to the Applicant on 10/25/2018, the Applicant was requested to submit data to demonstrate the discriminating ability of the proposed dissolution method for drug products that are intentionally manufactured with meaningful variations (e.g. products manufactured with API within proposed PSD and outside PSD) comprising a $\pm 10\%$ - 20% change in the specified values or ranges for these variables. In addition, the Applicant was also requested to submit data (if available) showing the capability of the selected dissolution method to reject batches that were not bioequivalent to the target product. The Applicant responded to the Information Request (IR) on 11/22/2018. The IR comments, the Applicant's response to the IR and the Reviewer's assessment are included in Appendix 2. Based on the Applicant's

response to the IR of 11/22/2018, it appeared that a dissolution media with a lower % of surfactant demonstrated meaningful discriminating ability. the Agency communicated an additional IR to the Applicant on 1/18/2019, wherein the Applicant was recommended to conduct the dissolution testing of the proposed product in the USP Test-4 media containing a lower % of surfactant (e.g. 2.25% LDAO). The Applicant responded to the IR on 2/19/2019 (Sequence 0007) and submitted the dissolution data for the test product using USP Test-4 media containing 2.25% LDAO as dissolution media.

2. Acceptance Criterion:

The dissolution data for all the strengths of the test product in the USP test-4 media (Original Submission/Sequence 0001) are presented as a link in Appendix 1.

In the IR response dated 2/19/2019 (Sequence 0007), the Applicant conducted the dissolution testing in the USP test-4 media containing 2.25% lauryl dimethyl amine oxide (LDAO). The Applicant stated that based on the acceptable dissolution results for the exhibit batches, the Applicant has concurred with the Agency's proposal to use the dissolution method with lower (2.25%) of surfactant (LDAO) for the routine testing of the test product during release and stability. Based on these results, the Applicant had proposed a new acceptance criterion of "NLT (b) (4) % of the labeled amount is dissolved in (b) (4) minutes". The dissolution data in the newly proposed media is presented in Appendix 2 (Tables 14-19/Figures 12-17).

Reviewer's Assessment:

In the Original Submission (Sequence 0001), the Applicant proposed an acceptance criterion as "Not Less than (b) (4) % (Q) of labeled amount of Isotretinoin to be dissolved in (b) (4) minutes".

In the response to the Information Request (dated 11/22/2018; Sequence 0004), the Applicant revised the acceptance criterion and proposed a new tolerance limit for the proposed product as "Not Less than (b) (4) % (Q) of labeled amount of Isotretinoin to be dissolved in 45 minutes".

In the response to the Information Request (dated 2/19/2019; Sequence 0007), as recommended by the Agency, the Applicant performed the dissolution testing in the USP test-4 media containing less surfactant (2.25% LDAO) and submitted the dissolution data for all the batches of all the strengths. However, the Applicant did not submit the complete 12-unit dissolution data. Instead, the Applicant submitted the Mean, Range and %CV for all the six strengths of the product. Based on the data submitted in Sequence 0007, the Applicant had further revised the acceptance criterion and proposed a new tolerance limit for the proposed product as "Not Less than (b) (4) % (Q) of labeled amount of Isotretinoin to be dissolved in (b) (4) minutes". The Applicant's data shown in Appendix 2:Table 13. The Reviewer has summarized and presented this data in Appendix 2:Tables 14-19/Appendix 2:Figures 12-17.

Based on the Reviewer’s assessment — for the 32 mg, 28 mg, 24 mg, 20 mg, and 16 mg strength products, > (b) (4) % of the test product is dissolved in 45 minutes (with a dissolution range of (b) (4) %). Hence, the acceptance criterion proposed by the Applicant was liberal. For these strengths, in the teleconference that transpired between the Applicant and the Agency on 4/2/19 (Amendment Quality dated 4/8/2019/Sequence 0009), the following acceptance criterion was recommended:

“Q = (b) (4) % of the labeled amount of Isotretinoin is dissolved in 45 minutes”.

For the 8 mg strength, the Reviewer has analyzed the data for the three batches using the Monte Carlo based sampling method with a normal distribution as its probability function (see table below).

Batch/Recommended acceptance criterion	Q = (b) (4) % in 45 min		
	% Passing S1	% Passing S2	% Passing S3
Test; 8 mg (batch# 3677B16A)	22	100	100
Test; 8 mg (batch# 3673B16A)	25	100	100
Test; 8 mg (batch# 3669B16A)	-	36	61

However, because the 8 mg strength exhibits a high degree of inter-capsule variability and because the Applicant did not submit the complete 12-unit data for the 8 mg strength, and also because the Applicant has attributed this high variability at the early time-points in dissolution data of the 8 mg capsule, in the third IR that was communicated to the Applicant, the Applicant was requested to submit individual capsule dissolution data from each of the 12 capsules tested at release in the newly proposed dissolution method (USP-test 4 containing 2.25% LDAO) for all the three batches of the 8 mg strength. Furthermore, the Applicant was also requested to submit data on the individual capsule disintegration time from each of the 12 capsules tested in the newly proposed dissolution method for the three batches of the 8 mg strength and the 32 mg strength biobatch. The Applicant responded to the IR on 3/20/2019 (Sequence 0008). The IR comments, the Applicant’s response, and the Reviewer’s assessment are included in Appendix 2. Based on the Monte Carlo analysis for batches# 3677B16A and 3673B16A, since 100% of the samples pass stage 2 with an acceptance criterion set at Q = (b) (4) % in 45 minutes and Q = (b) (4) % in (b) (4) minutes, an acceptance criterion of “Q = (b) (4) % in 45 minutes” was recommended for the 8 mg strength. Although batch# 3669B16A did not pass QC with an acceptance criterion set at Q = (b) (4) % in 45 minutes, in the teleconference that transpired between the Applicant and the Agency on 4/2/19 (Amendment - Quality dated 4/8/2019/Sequence 0009), the following acceptance criterion was also recommended for the 8 mg strength:

“Q = (b) (4) % of the labeled amount of Isotretinoin is dissolved in 45 minutes”.

The Applicant stated that batch# 3669B16A would pass the Agency’s proposed acceptance criterion at the stage 3 level of testing. The Applicant agreed to the Agency’s proposed acceptance criterion. As stated in the Amendment that was submitted on 4/8/2019 (Amendment - Quality dated 4/8/2019/Sequence 0009), the following acceptance criterion has been finalized for all the strengths

“Q = (b) (4) % of the labeled amount of Isotretinoin is dissolved in 45 minutes”.

Clinical relevance of dissolution method & acceptance criterion (e.g., IVIVR, IVVC, In Silico Modeling, small scale in vivo)

Reviewer’s Assessment:

The Applicant has not performed an in vitro-in vivo correlation. The dissolution method proposed by Applicant is to ensure batch-to-batch consistency, and this is acceptable.

Bridging of Formulations

Reviewer’s Assessment:

The Applicant has presented data on a single formulation for the exhibit and clinical (bio) batch. The proposed commercial formulation in the exhibit batches is identical to the formulation used in the clinical (bio) batch. Hence, there is no need for bridging of formulations.

Stability Data

Reviewer’s Assessment:

The Applicant has performed stability studies under three conditions – Accelerated (6 months), Intermediate (12 months), and Controlled Room Temperature/Long Term (24 months for the 8 mg, 24 mg and 32 mg strengths; and 18 months for the 16 mg, 20 mg and 28 mg strengths). The dissolution data does not suggest any loss of stability. In accordance with the recommended specification of “Q = $\frac{(b)}{(a)}$ % of the labeled amount is dissolved in 45 minutes” for all strengths of the proposed product the Applicant was requested to revise the acceptance criterion for the dissolution data at stability. The stability data will be further reviewed by the DS or DP reviewer.

Biowaiver Request

There are six strengths of the test product – 8 mg, 16 mg, 20 mg, 24 mg, 28 mg and 32 mg. The Bioequivalence study was performed on the 32 mg strength of the test product against the 40 mg strength of the LD. The Applicant has stated that, under fed conditions, 90% CI for C_{max}, AUC_{0-t}, and AUC_{0-∞} was found between the BE criterion of 80% - 125%. The BE study is being evaluated by the Division of Clinical Pharmacology. The Applicant has provided data on the qualitative and quantitative composition of the test product is proportional for the six strengths (Table 10).

Table 10: Quantitative composition of drug product

i) Quantitative Composition of Drug Product (Unit Composition)							
Ingredients	% w/w	8 mg	16 mg	20 mg	24 mg	28 mg	32 mg
		mg/capsule	mg/capsule	mg/capsule	mg/capsule	mg/capsule	mg/capsule
Isotretinoin* USP	(b) (4)	8.0000	16.0000	20.0000	24.0000	28.0000	32.0000
Butylated hydroxyl anisole, USP-NF							(b) (4)
Polysorbate 80 USP-NF							
Soybean Oil [†] USP- (Part-I)	(b) (4)						
Soybean Oil ^{††} USP- (Part-II)							
Final Target Fill Weight							

Based on the acceptable bioequivalence study of the 32 mg strength and the comparative dissolution profiles of the 32 mg strength and the 8 mg, 16 mg, 20 mg, 24 mg and 28 mg strengths, the Applicant has requested a biowaiver for the 8 mg, 16 mg, 20 mg, 24 mg and 28 mg strengths.

Reviewer's Assessment:

Based on the data presented in Table 10, this Reviewer has concluded that the qualitative and quantitative composition of the test product is proportional through all the strengths. In response to the IR dated 2/19/2019 (Sequence 0007), the Applicant conducted the dissolution testing in the USP test-4 media containing 2.25% LDAO. The Applicant has further stated that USP test-4 media containing 2.25% LDAO would be used for the routine dissolution testing of the drug product during release and stability. Based on the dissolution data in the newly proposed dissolution media (USP test-4 media containing 2.25% LDAO), the Reviewer has compared the dissolution profile of the 32 mg biobatch (batch# 3679B16A) with - 3 batches of the 8 mg strength (Appendix 2:Table 14, Appendix 2:Figure 12), 1 batch of the 16 mg strength (Appendix 2:Table 15, Appendix 2:Figure 13), 1 batch of the 20 mg strength (Appendix 2:Table 16, Appendix 2:Figure 14), 3 batches of the 24 mg strength (Appendix 2:Table 17, Appendix 2:Figure 15) and 1 batch of the 28 mg strength (Appendix 2:Table 18, Appendix 2:Figure 16). The Reviewer has calculated the f_2 values for these comparisons and has concluded that the dissolution profiles between the 32 mg biobatch are similar to the 28 mg, 24 mg, 20 mg and 16 mg strengths (f_2 values are >50). Based on the acceptable BE study between the 32 mg strength of the test product and the 40 mg strength of the LD (this study is being currently evaluated by the Division of Clinical Pharmacology), this Reviewer is able to grant the Applicant's request for the biowaiver for the 16 mg, 20 mg, 24 mg and 28 mg strengths.

The dissolution profile of one of the batches of the 8 mg strength (batch# 3669B16A) differs from the dissolution profile of the 32 mg biobatch (f_2 value is <50), whereas that of the other two batches (batch# 3673B16A and batch# 3677B16A) are 50 and 52.6, respectively. This suggests that the dissolution profiles of one of the batches of the 8 mg strength (batch# 3669B16A) is not similar to the 32 mg strength biobatch. Furthermore, the inter-capsule variability in the dissolution of the 3 batches of the 8 mg strength (especially batch# 3669B16A) is very high. However, since all the strengths of the Isotretinoin capsules are manufactured from the same common suspension mix and subsequently filled into the various size gelatin capsules to deliver 8 mg, 16 mg, 20 mg, 24 mg, 28 mg and 32 mg doses, respectively, and also because the acceptance criterion for the 8 mg strength is the same as that of the 32 mg strength biobatch, the Reviewer does not expect any dissolution problems specifically to the 8 mg strength, and is also able to grant the Applicant's request for the biowaiver for this lowest strength.

(b) (4)

. Furthermore, the lower (8 mg - 28 mg) strengths are compositionally proportional to the 32 mg strength, the Reviewer anticipates that a linear relationship between the PK parameters and the dose would exist between all the strengths.

The dissolution studies of the proposed product demonstrate the immediate release properties of the Isotretinoin capsule dosage form. The Applicant has stated that the test product is a BCS class II drug. The Applicant has stated that since the API is a BCS Class II compound, the (b) (4)

The Applicant stated that the PSD specifications are as follows:

(b) (4)

(b) (4) There are no additional concerns for the PSD.

APPENDIX 1

Data Tables and Figures

The 12-capsule in vitro dissolution data for the test product (8mg, 16 mg, 20 mg, 24 mg, 28 mg and 32 mg) using the USP monograph test-4 (Original submission/Sequence 0001) is presented in the link below:

[Comparative dissolution data for Isotretinoin capsules using the USP monograph test-4 method](#)

APPENDIX 2

List of Deficiencies

IR comments and Applicant's Response to IR:

(b) (4)

Based on the data submitted in the IR response dated 3/20/2019 (Sequence 0008), in the teleconference that was held between the Applicant and the Agency on 4/2/19, the following acceptance criterion was proposed for all the strengths:

“Q = $\frac{(b)}{(4)}$ % of the labeled amount of Isotretinoin is dissolved in 45 minutes”.

On 4/8/2019, the Applicant submitted an Amendment to the NDA (Amendment Quality/Sequence 0009). The Amendment was submitted in response to the teleconference that transpired between the Applicant and the Agency on 4/2/2019. As per the Amendment, the Applicant agreed to the acceptance criterion that was proposed by the Agency. The final dissolution method and acceptance criterion (for all the strengths) as agreed by the Applicant and the Agency is stated below:

Method:	In-house (modified USP monograph-test 4)
Apparatus:	Apparatus II (paddle) with spiral coated sinkers
Medium:	50 mM monobasic Potassium phosphate (pH 7.4), containing 70 mg/L of pancreatin, and 2.25% v/v of lauryl dimethylamine oxide as 30% solution
Volume:	900 mL
Temperature:	37.0 ± 0.5 °C
Speed:	75 rpm
Sampling times:	15, 30, 45, 60, and 90 minutes.
Acceptance Criterion:	Q = $\frac{(b)}{(4)}$ % of the labeled amount is dissolved in 45 minutes

Primary Biopharmaceutics Reviewer Name and Date:

Rajesh Savkur, Ph.D.

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

Vidula Kolhatkar, Ph.D.



Vidula
Kolhatkar

Digitally signed by Vidula Kolhatkar
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Rajesh
Savkur

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Date: 4/16/2019 04:20:09PM
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