CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204141Orig1s000

CHEMISTRY REVIEW(S)

MEMORANDUM DEPATMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTARTION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 21, 2013

TO: NDA 204141 CMC Review # 1

FROM: Hamid R. Shafiei, Ph.D., CMC Reviewer
(ONDQA/Division II/Branch IV)

THROUGH: Moo-Jhong Rhee, Ph.D., Branch Chief
(ONDQA/Division II/Branch IV)

SUBJECT: Final CMC Recommendation

In the Review # 1 of NDA 204141 for Topicort (desoximetasone) Topical Spray, 0.25%, this NDA was not recommended for approval from the CMC perspective due to the following reasons:

1) CMC related label/labeling issues were ***not*** resolved
2) An overall recommendation of "Acceptable" from the Office of Compliance regarding the facilities involved in this NDA was ***not*** yet issued

The CMC label/labeling issues have been resolved via the amendments dated February 22, 2013 and March 15, 2013 (see the **Attachment -2**).

The Office of Compliance has also made an overall recommendation of "Acceptable" for the facilities involved in this NDA on March 20, 2013 (see the **Attachment-1**).

Recommendation:

This NDA is now recommended for **approval** from the ONDQA perspective with the product expiation dating period of 24 months.

Attachment 1:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 204141/000
Stamp Date: 12-JUN-2012
Regulatory: 12-APR-2013

Action Goal:
District Goal: 11-FEB-2013

Applicant: TARO PHARMS (US)
3 SKYLINE DR
HAWTHORNE, NY 10532

Brand Name: Topicort (desoximetasone) Spray, 0.25%
Estab. Name: (desoximetasone) Spray, 0.25%
Generic Name:

Priority: 3
Org. Code: 540

Product Number; Dosage Form; Ingredient; Strengths
001; SPRAY; DESOXIMETASONE; .25%

Application Comment:

FDA Contacts:	C. TRAN-ZWANETZ	Project Manager	(HFD-800)	3017963877
	H. SHAFIEI	Review Chemist		3017962326
	S. DING	Team Leader		3017961349

Overall Recommendation:	ACCEPTABLE	on 20-MAR-2013	by M. HEAYN	(HFD-320)	3017964753
	PENDING	on 31-JAN-2013	by EES_PROD		
	PENDING	on 26-DEC-2012	by EES_PROD		
	PENDING	on 26-DEC-2012	by EES_PROD		
	PENDING	on 26-DEC-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		
	PENDING	on 20-JUL-2012	by EES_PROD		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
OC RECOMMENDATION	23-JUL-2012			ACCEPTABLE	SAFAAIJAZIR
				BASED ON PROFILE	
SUBMITTED TO DO	26-DEC-2012	10-Day Letter			SAFAAIJAZIR
PDUFA DATE IS 12-APR-2013. EXTENSION REQUESTED.					
ASSIGNED INSPECTION TO IB	(b) (4)	GMP Inspection			PHILPYE
UNDER REVIEW	05-MAR-2013				STOCKM
WORK ID 67260					
DO RECOMMENDATION	20-MAR-2013			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	20-MAR-2013			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: FINISHED DOSAGE OTHER TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO DO	23-JUL-2012	10-Day Letter			SAFAAIJAZIR
STATUS STILL INITIAL.					
UNDER REVIEW	26-JUL-2012				PHILPYE
DO RECOMMENDATION	18-DEC-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	26-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE (b) (4)

Establishment Comment: (b) (4)

Profile: (b) (4) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO DO	23-JUL-2012	10-Day Letter			SAFAAIJAZIR
UNDER REVIEW	26-JUL-2012				PHILPYE
DO RECOMMENDATION	25-NOV-2012			ACCEPTABLE	PHILPYE
SHOULD BE CRU				BASED ON FILE REVIEW	
OC RECOMMENDATION	03-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: CONTROL TESTING LABORATORY **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
OC RECOMMENDATION	23-JUL-2012			ACCEPTABLE	SAFAAIJAZIR
				BASED ON PROFILE	
OC RECOMMENDATION	26-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE LABELER
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Establishment Comment: (b) (4)

Profile: NON-STERILE API BY CHEMICAL SYNTHESIS **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
OC RECOMMENDATION	23-JUL-2012			ACCEPTABLE	SAFAAIJAZIR
				BASED ON PROFILE	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9610271 **FEI:** 3002808385

TARO PHARMACEUTICAL INDUSTRIES LTD

14 HAKITOR STREET
HAIFA BAY, , ISRAEL

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

DRUG SUBSTANCE STABILITY TESTER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: ALTERANTE TESTING FACILITY IN THE TESTING OF EXCIPIENTS, API , FINISHED DRUG PRODUCT AND PACKAGING COMPONENT. (on 20-JUL-2012 by K. JENNINGS () 3017962919)

Profile: CONTROL TESTING LABORATORIES "ALSO" (DRUGS) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
OC RECOMMENDATION	23-JUL-2012			ACCEPTABLE	SAFAAIJAZIR
				BASED ON PROFILE	
SUBMITTED TO DO	26-DEC-2012	10-Day Letter			SAFAAIJAZIR
EER RE-EVAL EXPIRED. PDUFA DATE 12-APR-2013. WERE TESTING/LAB COVERED DURING 28-MAY-2010 INSPECTION?					
DO RECOMMENDATION	30-DEC-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	31-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Establishment: **CFN:** 9614240 **FEI:** 3002808384

TARO PHARMACEUTICALS, INC.

130 EAST DRIVE
BRAMPTON, ON, CANADA

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE RELEASE TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE PACKAGER

FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER

Establishment Comment: MANUFACTURING, PACKAGING, RELEASE TESTING AND STABILITY TESTING (on 29-JUN-2012 by A. CUFF (HF-01) 3017964061)

Profile: NON-STERILE LIQUID (OTHER THAN SUSP & EMULSIONS) **OAI Status:** NONE

Milestone Name	Milestone Date	Request Type	Planned Completion	Decision	Creator
Comment				Reason	
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO OC	20-JUL-2012				JENNINGSK
SUBMITTED TO DO	23-JUL-2012	10-Day Letter			SAFAAIJAZIR
DO RECOMMENDATION	26-JUL-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	02-AUG-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	
SUBMITTED TO DO	26-DEC-2012	10-Day Letter			SAFAAIJAZIR
PDUFA DATE 12-APR-2013. REUQESTING AN EXTENSION.					
DO RECOMMENDATION	30-DEC-2012			ACCEPTABLE	PHILPYE
				BASED ON FILE REVIEW	
OC RECOMMENDATION	31-DEC-2012			ACCEPTABLE	SAFAAIJAZIR
				DISTRICT RECOMMENDATION	

Attachment 2

1) **Final labeling:** The applicant has submitted final labeling on March 15, 2013 addressing all CMC labeling issues that were documented in CMC review #1 of this NDA.

HIGH LIGHTS **ACCEPTABLE**

TOPICORT® (desoximetasone) Topical Spray, 0.25%

FULL PRESCRIBING INFORMATION **ACCEPTABLE**

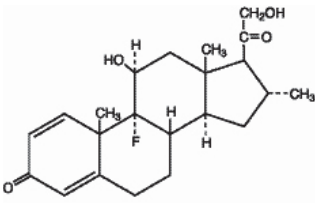
#3. Dosage Forms and Strengths:

Topical Spray, 0.25%. Each gram of Topicort® Topical Spray contains 2.5 mg of desoximetasone in a clear, colorless liquid

#11. Description:

Topicort® (desoximetasone) Topical Spray, 0.25% contains desoximetasone as the active ingredient. Desoximetasone is a corticosteroid with the chemical name of pregna-1, 4-diene-3, 20-dione, 9-fluoro-11, 21-dihydroxy-16-methyl-, (11ß,16a)-. Desoximetasone has the molecular formula of C22H29FO4 and a molecular weight of 376.47. The CAS Registry Number is 382-67-2.

The structural formula is:



Each gram of Topicort® Topical Spray contains 2.5 mg of desoximetasone in a clear, colorless liquid with the following inactive ingredients: glyceryl oleate, isopropyl alcohol (23.4%), isopropyl myristate, L-menthol, and mineral oil. Topicort® Topical Spray is co-packaged with a manual spray pump for installation by the pharmacist prior to dispensing to patients.

#16. How Supplied/Storage and Handling:

16.1 How Supplied / Storage:

Topicort® (desoximetasone) Topical Spray, 0.25% is a clear colorless liquid supplied in white, opaque bottles with white, opaque screw caps in the following sizes:

- 30 mL (NDC 51672-5281-3)
- 50 mL (NDC 51672-5281-4)
- 100 mL (NDC 51672-5281-7)

Store at controlled room temperature between 20°C to 25°C (68°F to 77°F), excursions permitted to 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature] Spray is flammable; avoid heat, flame or smoking when using this product.

Each unit is co-packaged with a manual spray pump for installation by the pharmacist.

16.2 Instructions for the Pharmacist:

1. Remove the spray pump from the wrapper
2. Remove and discard the cap from the bottle
3. Keeping the bottle vertical, insert the spray pump into the bottle and turn clockwise until well-fastened
4. Dispense the bottle with the spray pump inserted
5. Label the bottle with “discard the product 30 days after dispensing

Patient Counseling Information: See FDA-approved patient labeling (Patient Information and Instructions for Use)

Inform patients of the following:

- Use this medication as directed by the physician.
- Topicort® Topical Spray is for external use only. Avoid use on the face, axilla or groin.
- Do not to use this medication for any disorder other than that for which it was prescribed.
- Do not bandage or otherwise cover or wrap the treated skin so as to be occlusive.
- Report any signs of local or systemic adverse reactions to the physician.
- Do not use other corticosteroid-containing products with Topicort® Topical Spray without first consulting with the physician.
- Discontinue therapy when control is achieved. If no improvement is seen within 4 weeks, contact the physician.
- This medication is flammable; avoid heat, flame, or smoking when applying this product.
- Discard this product 30 days after dispensed by pharmacist.

2) **Final immediate container/carton label:** The applicant has provided a labeling amendment on February 22, 2012 that provides the immediate container as well as carton labels for Topicort (desoximetasone) Topical Spray, 0.25%.

A: IMMEDIATE CONTAINER LABELS **ACCEPTABLE**

(b) (4)

(b) (4)

5 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAMID R SHAFIEI
03/21/2013

MOO JHONG RHEE
03/21/2013
Chief, Branch IV

NDA 204141

TRADENAME (desoximetasone) Topical Spray, 0.25%

Taro Pharmaceutical USA, Inc.

Hamid R. Shafiei, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of New Drug Quality Assessment II
Branch IV

CMC REVIEW
For the Division of Dermatology and Dental Products

Table of Contents

CMC Review Data Sheet

1. NDA 204141

2. REVIEW #: 1

3. REVIEW DATE: 1/23/2013

4. REVIEWER: Hamid R. Shafiei, Ph.D.

5. PREVIOUS DOCUMENTS:

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Submission	06/12/2012
Correspondence (C)	
Amendment (BC)	07/16/2012
Amendment (BC)	

7. NAME & ADDRESS OF APPLICANT:

Name:	Taro Pharmaceutical USA, Inc.
Address:	3 Skyline Drive, Howthorne, NY 10532
Representative:	Kavita Sirvastava
Telephone:	(914) 345-9001 Ext. 6160

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Topicort®(pending)
b) Non-Proprietary Name: Desoximetasone
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: [redacted] plaque psoriasis in patients 18 year of age or older

CMC Review Data Sheet

11. DOSAGE FORM: Topical Spray

12. STRENGTH/POTENCY: 0.25%

13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: __√__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

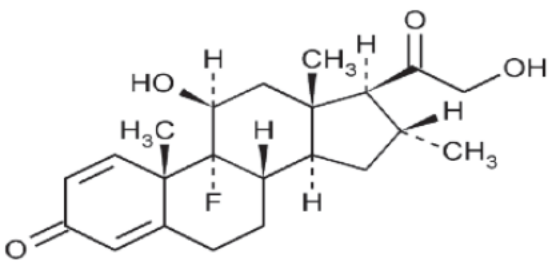
__√___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Desoximetasone: 9-Fluoro-11β,21-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione

OR

Pregna-1,4-diene-3,20-dione,9-fluoro-11,21-dihydroxy-16-methyl-,(11β, 16α)-



USAN Name:	Desoximetasone
INN Name:	Desoximetasone
Molecular Formula:	$C_{22}H_{29}FO_4$
Molecular Mass:	376.46
CAS Number:	382-67-2

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
13861	II	Taro Pharmaceuticals Industries, LTD	Drug Substance	3*	Adequate	09/13/2005 01/22/2013	Liang Huang Hamid Shafiei
10666	III	[redacted] (b) (4)		4			
8941	III			4			
12506	III			4			
6350	III			4			

* DMF 13861 has been previously reviewed in 2005 and found to be adequate to support ANDA 73193/S024, ANDA 73210/S019, and ANDA 74286/S010 The reviewer of this NDA has reviewed all amendments and annual reports submitted to this DMF since 2005 on 01/22/2013 and found this DMF still adequate to support this NDA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	N/A	
NDA	N/A	

CMC Review Data Sheet

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	Acceptable	10/25/12	Duan Renqin, Ph.D.
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A, according to the current ONDQA policy		
DMEPA	N/A		
EA	Categorical exclusion is granted (see review)	1/3/13	Bloom Raanan, Ph.D.
Microbiology	Acceptable	11/5/12	Bryan Riley, Ph.D.

The CMC Review for NDA 204-141

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has provided sufficient information to assure identity, strength, purity, and quality of the drug product, TRADENAME (desoximetasone) Spray 0.25%.

However, the Office of Compliance has ***not*** made an overall "Acceptable" recommendation regarding the facilities involved in this NDA.

Also label/labeling issues identified have ***not*** been satisfactorily resolved.

Therefore, from the ONDQA perspective, this NDA is ***not*** recommended for approval in its present form, per 21 CFR 314.125(b)(6) & (13).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

Not applicable.

II. Summary of CMC Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The drug substance, [redacted] USP is a synthetic corticosteroid. This drug substance is a compendial active ingredient that has been used in multiple approved topical products such as gel, cream, and ointment since 1977. The topical corticosteroids constitute a class of primarily synthetic steroids used as anti-inflammatory and antipruritic agents. The drug substance intended for use as the active ingredient in the formulation of TRRADENAME (desoximetasone) Spray 0.25% is manufactured and supplied by [redacted] The information regarding the manufacturing process, process controls, release and stability testing, and packing of this drug substance is provided in Taro's DMF 13861. Desoximetasone is a [redacted] This drug substance has [redacted] The stereochemistry of this API is confirmed by IR identification testing against an official USP standard and [redacted]

This API is insoluble in water but freely soluble in alcohol, acetone, and chloroform. Since this molecule is a neutral molecule, its water solubility does not change as a function of pH. [redacted] There are no known polymorphs for this API. Since the drug product manufactured from this active ingredient is formulated as a solution, no API particle size determination has been performed.

The proposed drug substance specification includes testing and acceptance criteria for description, identification, melting range, specific rotation, assay, related substance, loss on drying, heavy metals, residue on ignition, and residual solvents. The proposed specification is consistent with USP compendial requirement and current ICH guidelines. The proposed specification for release and stability testing of the drug substance is considered adequate.

The stress testing of this API have shown indication that this drug substance may be [redacted] The force degradation results have also shown that this drug substance is [redacted] The long-term (25ºC / 60% RH) stability of this drug substance packaged in the proposed container closure has been examined for 60 months. The stability results from 60-month long-term stability testing of 3 lots of drug substance manufactured by [redacted] indicates that this API is stable for 60 months when stored at 25ºC / 60% RH in the proposed container closure. The long-term stability data also illustrates that the proposed container closure is acceptable and provides adequate protection [redacted] Based on the stability results, a re-test period of [redacted] and an expiration dating period of 5 years is assigned to the drug substance packaged in the proposed container closure and stored at 20 - 25ºC. Both proposed re-test and expiration dating periods are adequate. Based on the information provided in this application as well as DMF 1386, it is concluded that the drug substance intended for use in the manufacture of TRADENAME (desoximetasone) Spray, 0.25% is Satisfactory.

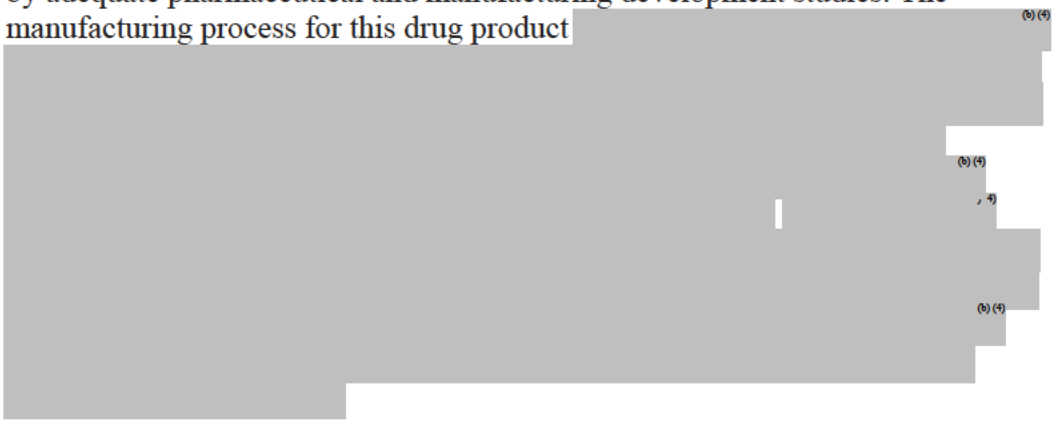
(2) Drug Product

TRADENAME (desoximetasone) Spray, 0.25% for topical administration contains a synthetic high potency corticosteroid, desoximetasone as the active ingredient. The drug product is intended for treatment of [redacted] plaque psoriasis in patient 18 years of age or older.

The product is a clear, colorless liquid presented [redacted] (containing 6mL of drug product as the physician samples), 30-mL, 50-mL, and 100-mL white high-density polyethylene (HDPE) bottles with white [redacted] screw cap closures accompanied with a [redacted] manual spray pump with screw type closure. The spray pump is to be installed by the pharmacist prior to patients use. Each gram [redacted] of TRADENAME (desoximetasone) Spray, 0.25% contains 2.5 mg of desoximetasone as the active ingredient and glyceryl oleate,

isopropyl alcohol (23.4%), isopropyl myristate, L-menthol, and mineral oil as excipients.

The manufacturing process for this drug product is well controlled and supported by adequate pharmaceutical and manufacturing development studies. The manufacturing process for this drug product



The specification for the drug product release includes testing and acceptance criteria for description, identification, desoximetasone assay, isopropyl alcohol assay, degradation products (impurities), residual solvents, and minimum fill. The product specification dose not include testing and acceptance criteria for bioburden. Since this drug product is a non-aqueous product that contains 23.4% isopropyl alcohol and (b) (4) mineral oil, it is suggested that this drug product does not promote microbial growth and therefore, bioburden testing is not necessary. In support of the proposed omission of the bioburden testing from the drug product specification, the applicant has tested various lots of desoximetasone spray 0.25% for total yeasts & molds, total aerobic microbial count, p.aurogenosa and s.aureus (USP <61>, <62>) during product release, stability and through the product's proposed shelf-life as a part of pharmaceutical development. To date no microbial growth has been observed in any of batches tested. Therefore, the proposed drug product specification is deemed acceptable.

In-use stability and pump performance testing for desoximetasone spray 0.25% were performed. The pump performance was examined by measuring the weight of each actuation and the amount of active delivered. The in-use stability involved testing for the spray delivery amount and the delivered product quality. This was performed by determining the amount of product delivered by each spray actuation and by monitoring the product quality attributes such as desoximetasone assay and degradation products throughout the intended duration of patient use (28 days). The in-use stability data submitted indicates that the pump is able to consistently deliver the required amount of the active with an acceptable quality over the period of patient's use. Container closure compatibility with the drug product was determined using a risk-based approach. The risk-based assessment was derived from the maximum potential leachables / extractables that could be introduced to drug product from the materials and additives used in the

construction of each component of the container closures including the spray pump. The results indicated that the total maximum possible amount of leachables / extractables that could be introduced into the drug product from the proposed container closures are below the levels of any toxicological concern.

The 6-month accelerated (40ºC / 75% RH) and 24-month long-term (25ºC / 60% RH) stability results from multiple lots of drug product packaged in all packaging configurations indicated this drug product is stable for 24 month when stored at 20 - 25ºC. Additionally the stability data indicated that the proposed container closures and packaging configurations provide adequate protection from light. Based on the stability results, the applicant has proposed an expiration dating period of 24 months and storage condition of 20 – 25ºC with excursion permitted to 15 – 30ºC for the drug product packaged in the proposed container closures. The proposed expiration dating period and storage condition are considered acceptable.

B. Description of How the Drug Product is Intended to be Used

TRADENAME (desoximetasone) Spray 0.25% for topical administration is a clear, colorless liquid presented in (b) (4) (containing 6mL of drug product as the physician samples), 30-mL, 50-mL, and 100-mL white high-density polyethylene (HDPE) bottles with white (b) (4) screw closures co-packaged with a (b) (4) manual spray pump with screw type closure. The Spray pump is to be installed by the pharmacist prior to patients use. The spray pump is used to deliver a thin film of the drug product to the affected skin area twice daily. This product is indicated for the treatment of moderate to severe plaque psoriasis in patient 18 years of age or older.

C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125 (b)(13)

- The final recommendation from the Office of Compliance is still "Pending".

21 CFR 314.125 (b)(6)

- Label/labeling issues has not been resolved.

(see the **List of Deficiencies** on p.85)

III. Administrative

A. Reviewer's Signature:

(See appended electronic signature page)

Hamid R. Shafiei, Ph.D.

B. Endorsement Block:

(See appended electronic signature page)

Moo-Jhong Rhee, Ph.D. Branch Chief, Branch IV, Division II, ONDQA

C. CC Block: entered electronically in DFS

87 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAMID R SHAFIEI
01/23/2013

MOO JHONG RHEE
01/23/2013
Chief, Branch IV

Initial Quality Assessment
Branch IV
Division of New Drug Quality Assessment II

OND Division:	Division of Dermatology and Dental Products
NDA:	204-141
Applicant:	Taro Pharmaceuticals USA, Inc.
Stamp Date:	June 12, 2012
PDUFA Date	April 12, 2013
Trademark:	Topicort®
Established Name:	Desoximetasone
Dosage Form:	Spray
Route of Administration:	Topical
Indication:	Relief of (b) (4) plaque psoriasis in patients 18 years of age or older
CMC Lead:	Shulin Ding

	YES	NO
ONDQA Fileability:	☒	☐
Comments for 74-Day Letter	☒	☐

Summary and Critical Issues:

A. Summary

Taro Pharmaceuticals has submitted a 505(b)(1) New Drug Application (NDA) for the prescription use of Topicort® (desoximetasone) spray, 0.25% for the topical treatment of plaque psoriasis in patients 18 years of age or older.

The applicant references DMF 13861 held by Taro Israel for the CMC information of the proposed drug substance. A letter of authorization from Taro Israel is provided. The proposed drug substance manufacturing site is (b) (4) The last CMC review on the DMF was filed on 9/13/2005, and the DMF was deemed adequate to support topical products. Submissions to the DMF subsequent to the last CMC review have not been reviewed.

The proposed drug product is a clear, colorless, non-aqueous liquid packaged in white high-density-polyethylene (HDPE) round bottles with white (b) (4) screw closures. It is co-packaged with a spray pump which is to be inserted into the bottle and fastened by turning clockwise by a pharmacist at time of dispensing.

The proposed trade sizes are 100 mL, 50 mL, and 30 mL. The physician sample size is 6 mL. In addition to the active ingredient, the formulation also contains the following excipients: mineral oil, USP; L-menthol, USP; isopropyl myristate, NF; isopropyl alcohol, USP; and glyceryl oleate. The quality of glyceryl oleate proposed for this NDA conforms to Taro's internal standard rather than to the standard prescribed by NF monograph. There are no novel excipients present in the formulation. Neither do any excipients originate from animal source.

The formulation of the proposed product is prepared [redacted]

The to-be-marketed formulation [redacted] Stability data provided in the initial submission to support an expiration dating period of 24 months at 20°-25°C (excursions permitted to 15°-30°C) include the following:

Lot #	Batch size	Fill size	Long Term (25°C/60%RH)	Accelerated (40°C/75%RH)
L163-58859	[redacted]	100 mL 50 mL 30 mL 6 mL	24 months	6 months
L-163-59328		100 mL	18 months	6 months
L163-60467		100 mL 50 mL 30 mL 6 mL	3 months	3 months
L-163-60468		100 mL 50 mL 30 mL 6 mL	3 months	3 months

Special stability studies such as in-use stability, thermal cycling [redacted] weight loss, and pump performance are also provided to support storage/handling of the drug product. The proposed "in-use expiration dating period" is [redacted]

B. Critical issues for review

1. Environmental Assessment
   The applicant cites 21CFR 25.30 and 25.31(a) (no increase in the use of the active moiety) as the basis to support its categorical exclusion claim from the preparation of Environmental Assessment. The citations are unacceptable because the use of the active moiety will increase upon the approval of this NDA. To support the categorical exclusion claim, the applicant should provide annual production forecast for 5 years, and the calculation of the estimated concentration of the substance at the point of entry into the aquatic environment.

2. Establishment Information
   An IR letter was sent on July 7, 2012 to request clarification for some facilities. The applicant's response (amendment received on July 16, 2012) is adequate.

3. Letter of Authorization
   The letter of authorization provided in the initial submission for DMF [redacted] is not appropriate. Specifically, the letter does not contain language that

authorizes FDA to access the DMF in connection with the review of NDAs submitted by Taro Pharmaceuticals. A request should be made to the applicant to re-submit the letter of authorization with appropriate language.

4. [redacted] Change in the Registration Stability Studies of Drug Product
The older two registration lots (L-163-5889 and 59328) [redacted] These two lots [redacted]. The cap supplier remains the same. [redacted] is not discussed in Module 3, and will need a critical review.

5. In-Use Stability Studies
   - The in-use stability studies did not include an investigation on the 6 ml physician sample size. Therefore, the "in-use expiration dating period" of the 6 ml size is not supported.

   - The in-use stability studies did not analyze the discharged formulation for the potential impact of the pump on the quality of the formulation (e.g. potential drug uptake by the pump, leachables from the pump, etc.). As a result, the strength, purity, and quality of the product can not be assured.

   - The in-use stability studies did not evaluate the following attributes: weight loss, package integrity, and pump performance.

6. Extractables/Leachables Studies
The study design is highly deficient. The most critical deficiency is that the studies were not conducted using appropriate analytical technologies. Extracts were analyzed using only the proposed regulatory assay method. This method [redacted]. Therefore, extractables/leachables that do not have [redacted] can be easily missed.

The interaction of the formulation with packaging components [redacted]

7. Conformance to USP<661>
Data showing the conformance of packaging components to USP<661> can not be found in the NDA. The data may exist in the DMFs. The reviewer should look for this information when reviewing Type III DMFs.

8. Excipient Function
The following functions are assigned in Section 3.2.P.1 to formulation excipients:

Glyceryl oleate [redacted]
Isopropyl myristate [redacted]
L-Menthol [redacted]
Mineral oil [redacted]

These assigned functions can not be substantiated using physicochemical properties of the excipients alone; therefore, they should be deleted from Module 3 unless the applicant can provide justification that is acceptable to the clinical review team.

9. Control over Glyceryl Oleate
   The proposed specification for glyceryl oleate is Taro's in-house standard which is inferior to that prescribed by NF monograph. The quality of a formulation excipient which is monographed in USP/NF should be equal to or better than the compendical standard.

10. Bulk Hold Time
    Stability data are not provided to support the proposed (b) (4) hold time.

11. Total Deliverable
    This attribute was requested in the Pre-NDA meeting. Although it is included in the pump performance study report, no definite value in gram or mL with a proposed variation range is given by the applicant for each fill size.

12. Drug Product Specification
    The following tests are omitted from the proposed drug product specification: package integrity, weight loss, microbial limit, pump performance. The sponsor provides a justification to support the omission of the last three but not the test on package integrity.

C. Comments for 74-Day Letter:

1. Submit representative drug product samples for each proposed configuration for confirmation of dosage form and packaging design.

2. Provide annual production forecast for 5 years, and the calculation of the estimated concentration of the substance at the point of entry into the aquatic environment.

3. The letter of authorization provided in the initial submission for DMF (b) (4) does not contain language that authorizes FDA to access the DMF in connection with the review of NDAs submitted by Taro Pharmaceuticals. Re-submit the letter of authorization issued by the DMF holder with appropriate language for DMF (b) (4)

4. The in-use stability studies provided in the initial submission are highly inadequate. Provide in-use stability data for all proposed configurations (including the physician sample size). The data should be generated from the discharged (i.e. pumped out) formulation and cover multiple time points over the proposed "in-use expiration dating period." The discharged formulation should be tested minimally for the following parameters: assay of desoximetasone, related substances, assay of isopropyl alcohol, and leachables. Additionally, you should evaluate weight loss, package integrity (both interior and exterior for all formulation-contacting parts), and pump performance at multiple time points over the course of in-use stability studies.

5. The extractables/leachables studies provided in the initial submission are highly inadequate. Because the extracts were analyzed using only an HPLC method [redacted] it is very possible that extractables/leachables [redacted] were missed. We recommend that you first screen each [redacted] and extracts be analyzed using GC/mass and/or LC/mass. Identify potential leachables from the extractables found in the extracts, and then check these potential leachables in the registration stability and in-use stability study samples. Any leachables once confirmed to be present in the stability samples at a level above ICH Q3B reporting/identification/qualification threshold, you should report/identity/qualify them accordingly.

6. Provide bulk stability data to support the proposed bulk hold time.

7. Provide the section on filling operation for Master Batch Record and Executed Batch Records. The section should include the proposed in-process control over fill volume (or fill weight).

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA are [redacted] change, pump performance studies, in-use stability studies, extractables/leachables studies, bulk hold time, and drug product specification.

Drug substance manufacturing site is located in [redacted] Drug product manufacturing site is located in [redacted] GMP inspection requests have been submitted.

Shulin Ding, Ph.D.
CMC Lead

Moo-Jhong Rhee, Ph.D.
Chief, Branch IV

NDA Number:	Supplement Number and Type:	Established/Proper Name:
204141	0000	Desoximetasone spray, 0.25%
Applicant: Taro	Letter Date: June 11, 2012	Stamp Date: June 12, 2012

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	**Yes**	**No**	**Comment**
1.	Is the CMC section organized adequately?	x		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	x		
3.	Are all the pages in the CMC section legible?	x		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	x		

B. FACILITIES*				
	Parameter	**Yes**	**No**	**Comment**
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	x		
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? **This question is not applicable for synthesized API.**			n/a

7.	Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Complete and accurate information is in the amendment received on July 16, 2012.
8.	Are drug product manufacturing sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Complete and accurate information is in the amendment received on July 16, 2012.

9.	Are additional manufacturing, packaging and control/testing laboratory sites are identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable)	x		Complete and accurate information is in the amendment received on July 16, 2012.
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Provided in Module 1 of the initial submission for the facilities listed in the attachment to Form 356h. The statement is provided in the amendment received on July 16, 2012 for the contract analytical laboratories.

* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a *potential* filing issue or a *potential* review issue.

C. ENVIRONMENTAL ASSESMENT				
	Parameter	**Yes**	**No**	**Comment**
11.	Has an environmental assessment report or categorical exclusion been provided?	x		Categorically exclusion is claimed but the claim basis is inappropriate.

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	**Yes**	**No**	**Comment**
12.	Does the section contain a description of the DS manufacturing process?	x		Also referenced to DMF 13861 for details.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF 13861.
14.	Does the section contain information regarding the characterization of the DS?	x		Also referenced to DMF 13861 for details.
15.	Does the section contain controls for the DS?	x		
16.	Has stability data and analysis been provided for the drug substance?	x		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		x	n/a
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		x	n/a

E. DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	x		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	x		
21.	Is there a batch production record and a proposed master batch record?	x		Missing filling records.
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	x		
23.	Have any biowaivers been requested?		x	n/a
24.	Does the section contain description of to-be-marketed container/closure system and presentations)?	x		
25.	Does the section contain controls of the final drug product?	x		
26.	Has stability data and analysis been provided to support the requested expiration date?	x		
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		x	n/a
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		x	n/a

F. METHODS VALIDATION (MV)				
	Parameter	**Yes**	**No**	**Comment**
29.	Is there a methods validation package?	x		

G. MICROBIOLOGY				
	Parameter	**Yes**	**No**	**Comment**
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product?		x	This is not a sterile product.

H. MASTER FILES (DMF/MAF)				
	Parameter	**Yes**	**No**	**Comment**
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	x		LOA for DMF (b) (4) provided in the initial submission is not appropriate. Specifically, the letter does not contains language that authorizes FDA to access the DMF in connection with the review of NDAs submitted by Taro Pharmaceuticals.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
13861	II	Taro Isarel	Desoximetasone USP	10/13/2010	
(b) (4)	III	(b) (4)	(b) (4)	7/20/2010	
	III			1/3/2011	
	III			11/24/2008	
	III			6/14/2010	

I. LABELING				
	Parameter	**Yes**	**No**	**Comment**
32.	Has the draft package insert been provided?	x		
33.	Have the immediate container and carton labels been provided?	x		

J. FILING CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
34.	**IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE?**	x		
35.	If the NDA is not fileable from the product quality perspective, state the reasons and provide **filing** comments to be sent to the Applicant.			n/a
36.	Are there any **potential review** issues to be forwarded to the Applicant for the 74-day letter?	x		See pages 3 and 4.

{See appended electronic signature page}

Shulin Ding, Ph.D.
CMC Lead
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

{See appended electronic signature page}

Moo-Jhong Rhee, Ph.D.
Branch Chief
Division of New Drug Quality Assessment II
Office of New Drug Quality Assessment

Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SHULIN DING
07/20/2012

MOO JHONG RHEE
07/20/2012
Chief, Branch IV