

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

203567Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 27-May-2014
To: CMC Review #2 for NDA 203567
From: Bogdan Kurtyka, Ph.D.
CMC Reviewer, ONDQA Division II
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV ONDQA Division II
CC: Shulin Ding, Ph.D.
CMC Lead, ONDQA Division II
Subject: **Final CMC Recommendation**

Previous CMC Review #2 dated 08-May-2014 and entered into DARRTS system on 09-May-2014 noted the following deficiencies which resulted in the recommendation of “Non Approval” action.

1. The Office of Compliance has *not* issued an overall “Acceptable” recommendation.
2. Unresolved label/labeling issues

Regarding Item #1:

On 27-May-2014 the Office of Compliance issued an overall “Acceptable” recommendation for establishments (see the **Attachment 1**).

Regarding Item #2,

On 16-May-2014 and 23-May-2014, the applicant submitted finalized label/labeling which are satisfactory from the ONDQA’s perspective (see the **Attachment 2**).

Recommendation:

Because these issues were resolved satisfactorily, from the ONDQA perspective, this NDA is now recommended for **Approval** with expiration dating period of 36-month for all container/closure configurations.

Attachment 1: EES Summary Report

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 203567/000 Org. Code: 540 Priority: 1 Stamp Date: 26-JUL-2012 PDUFA Date: 20-JUN-2014 Action Goal: District Goal: 21-APR-2014	Sponsor: DOW PHARM 1330 REDWOOD WAY PETALUMA, CA 94954 Brand Name: JUBLIA (EFINACONAZOLE) TOPICAL SOLUTION, Estab. Name: (EFINACONAZOLE) TOPICAL SOLUTION, 10% Generic Name: Product Number; Dosage Form; Ingredient; Strengths 001; SOLUTION; EFINACONAZOLE; 10%
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FDA Contacts:	B. KURTYKA	Prod Qual Reviewer	3017961431
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800) 3017963877
	S. DIXON	Regulatory Project Mgr	(HFD-540) 3017961015
	S. DING	Team Leader	3017961349

Overall Recommendation:	ACCEPTABLE	on 27-MAY-2014	by T. WILSON	()	2404024226
	PENDING	on 23-JAN-2014	by EES_PROD		
	PENDING	on 06-JAN-2014	by EES_PROD		
	ACCEPTABLE	on 06-JAN-2014	by T. SHARP	()	3017963208
	PENDING	on 31-DEC-2013	by EES_PROD		
	ACCEPTABLE	on 09-MAY-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 10-AUG-2012	by EES_PROD		
	PENDING	on 03-AUG-2012	by EES_PROD		
	PENDING	on 03-AUG-2012	by EES_PROD		

Establishment:	CFN: 2950819	FEI: 1000135370	
	DOW PHARMACEUTICAL SCIENCES		
	PETALUMA, , UNITED STATES 949547122		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER FINISHED DOSAGE RELEASE TESTER FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment: CFN: 9612799 FEI: 3002807376
KAKEN PHARMACEUTICAL CO., LTD.
301 GENSUKE FUJIEDA SHI 426
FUJIEDA-SHI, SHIZUOKA-KEN, JAPAN
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE RELEASE TESTER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE RELEASE TESTER
Profile: (b) (4) LIQUID (OTHER THAN SUSP & OAI Status: NONE
EMULSIONS)
Last Milestone: OC RECOMMENDATION
Milestone Date: 27-MAY-2014
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 06-JAN-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE OTHER TESTER
Profile: CONTROL TESTING LABORATORY OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-APR-2014
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CFN: (b) (4) FEI: (b) (4)
(b) (4)
DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER
Profile: (b) (4) API BY CHEMICAL SYNTHESIS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-MAY-2013
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Attachment 2: Finalized labeling and labels

1. Package Insert

(a) “Highlights” Section

JUBLIA[®] (efinaconazole) topical solution, 10%
For topical use
Initial U.S. Approval: 2014

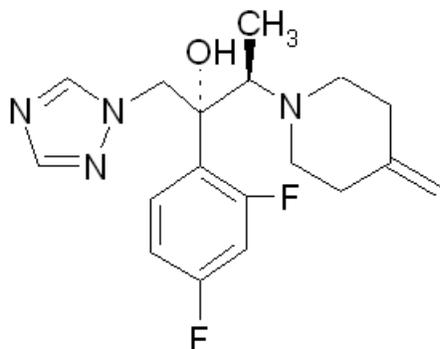
(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths

JUBLIA (efinaconazole) topical solution, 10% contains 100 mg of efinaconazole in each gram of clear, colorless to pale yellow solution.

#11: Description

JUBLIA contains 100 mg of efinaconazole. Efinaconazole is an azole antifungal with a chemical name of ((2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1-(1H-1,2,4-triazol-1-yl) butan-2-ol). The structural formula for efinaconazole is represented below:



Molecular Formula: C₁₈H₂₂F₂N₄O Molecular Weight: 348.39

JUBLIA contains the following inactive ingredients: alcohol, anhydrous citric acid, butylated hydroxytoluene, C12-15 alkyl lactate, cyclomethicone, diisopropyl adipate, disodium edetate, and purified water.

#16: How Supplied/Storage and Handling

JUBLIA (efinaconazole) topical solution, 10% is a clear, colorless to pale yellow solution supplied in a white plastic bottle with an integrated flow-through brush applicator as follows:

4 mL (NDC 0187-5400-04)

8 mL (NDC 0187-5400-08) Storage and Handling Conditions:

Store at 20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature].

- Solution is flammable; keep away from heat or flame
- Protect from freezing
- Keep out of the reach of children
- Keep bottle tightly closed
- Store in upright position

2. Immediate container labels

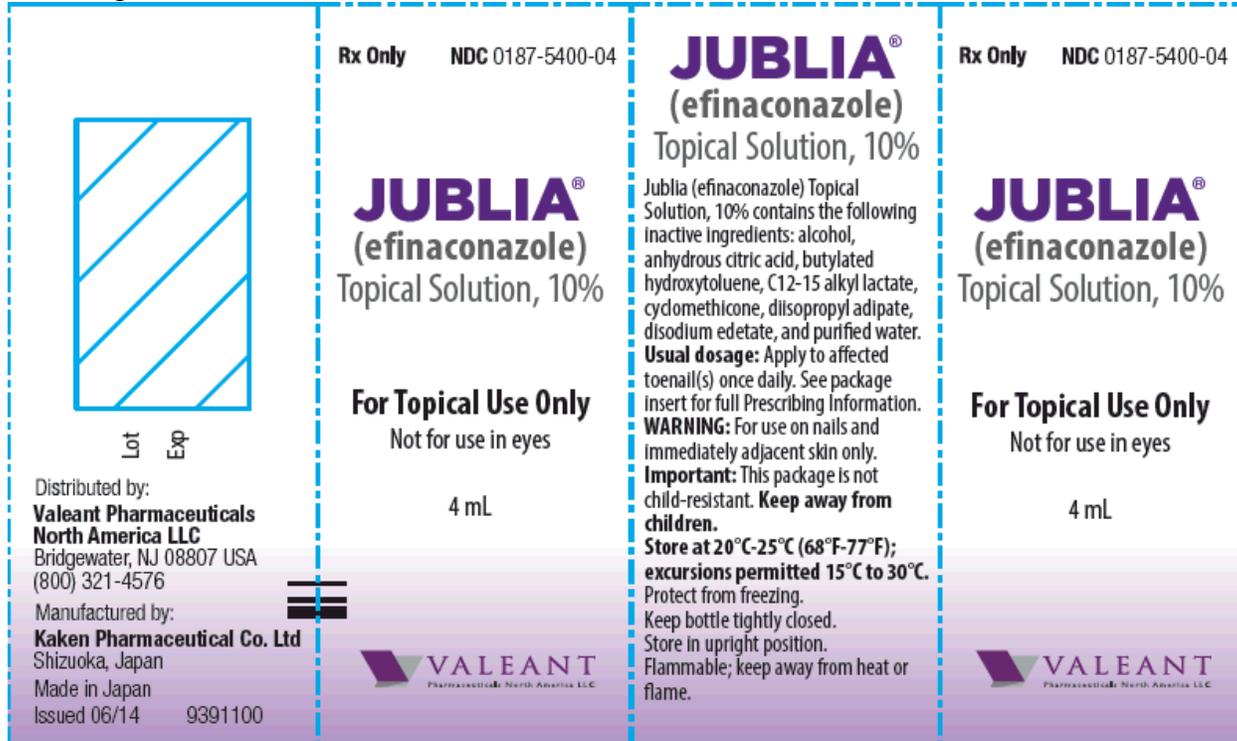
The image of the label for 4 mL bottle is shown below:



Labels for 8 mL bottle and physician sample have the same information, (b) (4)

3. Carton labeling

The image of the label for 4 mL bottle is shown below:



Cartons for 8 mL bottle and physician sample have the same information, (b) (4)

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/s/

BOGDAN KURTYKA
05/29/2014

MOO JHONG RHEE
05/29/2014
Chief, Branch IV

NDA 203567

**Jublia (efinaconazole) topical solution
10%**

Dow Pharmaceutical Sciences

Bogdan Kurtyka, Ph.D.
Review Chemist

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

**CMC REVIEW OF NDA 203567
For the Division of Dermatological and Dental Products (HFD-540)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203567
2. REVIEW #: 2
3. REVIEW DATE: 8-May-2014
4. REVIEWER: Bogdan Kurtyka, Ph.D.
5. PREVIOUS DOCUMENTS: CMC Review #1 with 3 addenda

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Resubmission	20-Dec-2013
Labeling amendment	16-Jan-2014

7. NAME & ADDRESS OF SPONSOR:

Name: Dow Pharmaceutical Sciences
Address: Pentaluma, CA 94954, USA
Telephone: 707-796-7222
Fax: 707-793-0145

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Jublia
- b) Non-Proprietary Name (USAN): Efinaconazole
- c) Code Name/# (ONDQA only): IDP-108
- d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: 1
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Azole antifungal agent

11. DOSAGE FORM: Solution CODE: 138

12. STRENGTH/POTENCY: 10%

13. ROUTE OF ADMINISTRATION: Topical CODE: 011

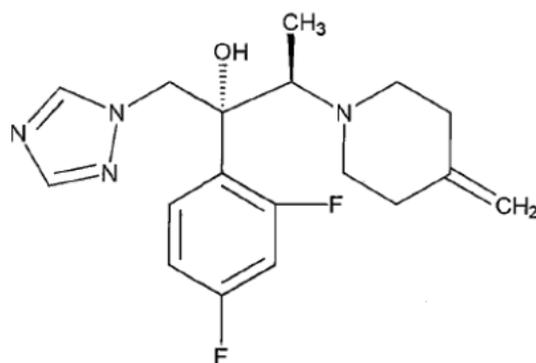
CMC Review Data Sheet

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:

Chemical Name: (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-3-hydroxypropyl-1*H*-imidazole
 USAN Name: Efinaconazole
 CAS Number: 164650-44-6
 Structural Formula:



Molecular Formula: C₁₈H₂₂F₂N₄O
 Molecular Weight: 348.39

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
21870	II	Kaken Pharmaceutical	Efinaconazole	1	Adequate	13-Jan-2014, checked into DARRTS on 14-Jan-2014	Reviewed by Dr. Bogdan Kurtyka
(b) (4)	III		(b) (4)	4	N/A	N/A	

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

CMC Review Data Sheet

be reviewed)

B. Other Documents: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	N/A		
DMEPA	N/A		
EA	Categorical exclusion granted (see Review #1)	22-Jan-2013	Bogdan Kurtyka, Ph.D.
Microbiology	Approval	13-Jan-2014	Bryan S. Riley, Ph.D.

Executive Summary Section

The CMC Review for NDA 203567

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has resubmitted to address the deficiencies listed in the Complete Response letter dated May 13, 2013, and now deemed to have provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The office of Compliance has *not* issued yet an overall “Acceptable” recommendation for this resubmission .

Issues on the new label/labeling are *not* resolved as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is *not* ready for approval per 21CFR 314.125(b)(6),(13) in its present form until the above issues delineated in the “List of Deficiencies” (p. 32) are satisfactorily resolved.

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

II. Summary of CMC Assessments

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

(1) Drug Substance

The sponsor references DMF 21870 (Kaken Pharmaceuticals) for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the proposed drug substance, (b) (4) A letter of authorization to cross reference the DMF is provided in the application. The DMF 21870 has been reviewed and found adequate to support this application.

(2) Drug Product

Efinaconazole solution 10% is indicated for treatment of onychomycosis. It is a clear, colorless to pale yellow solution. The inactive ingredients of the formulation are commonly used in topical drug products. All except one (C12-15 alkyl lactate) excipients are listed in the Inactive Ingredients Database and the proposed amounts do not exceed previously approved levels. The drug product is manufactured by (b) (4)

Executive Summary Section

(b) (4). The sponsor proposed Kaken Pharmaceutical (Japan) as the manufacturing site.

The drug product specification includes: appearance, package integrity, identification, assay of drug substance, impurities, assays of (b) (4) and microbial testing. The specification attributes and their analytical methods are deemed satisfactory for assuring the identity, strength, purity, and quality.

Efinaconazole solution is packaged in a 10 mL HDPE bottle with a brush applicator in a (b) (4) cap. The information included in the application demonstrates that the proposed container/closure system meets all recommendations of relevant USP monographs and the Agency's guidance. The new container closure system and control of filling operation satisfactorily addresses all deficiencies listed in the Action Letter.

The sponsor provided the results of 24 months long-term stability studies, and proposed an 36-month expiration dating period under the controlled room conditions. The proposed expiration dating period is supported by the submitted data.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(b).

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

The drug product should be applied once daily using the built-in flow-through brush applicator. During application the nail, the nail folds, nail bed, hyponychium, and the undersurface of the nail plate, should be completely covered by the formulation.

C. Basis for Not-Approval Recommendation**21CFR 314.125(b)(6)**

- Various sections of Package Insert including Highlights, Sections 3, 11 and 16 are inadequate.
- The carton/container labels are inadequate.

21CFR 314.125(b)(13)

- The Office of Compliance did not issue an overall "Acceptable" recommendation for the manufacturing establishments.

(see the "List of Deficiencies" on p.32).

III. Administrative

Executive Summary Section

- A. Reviewer's Signature:** *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA
- 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 DARRTS

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/s/

SHULIN DING
05/09/2014

MOO JHONG RHEE
05/09/2014
Chief, Branch IV

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

OND Division: Division of Dermatology and Dental Products
NDA: 203-567
Category: Class 2 Resubmission
Applicant: Dow Pharmaceutical Sciences.
Stamp Date: Dec. 20, 2013
PDUFA Date: June 20, 2014
Trademark: Jublia®
Established Name: Efinaconazole
Dosage Form: Solution
Route of Administration: Topical
Indication: Onychomycosis

CMC Lead: Shulin Ding

ONDQA Resubmission Completeness: YES NO

Summary and Critical Issues:

A. Summary

This review is the Initial Quality Assessment for the resubmission of NDA 203567 Jublia® (efinaconazole) topical Solution, 10%. NDA 203567 is a Type 1 505(b)(1) NDA originally submitted to the FDA on July 26, 2012. It received a Complete Response action on May 13, 2013 due to CMC deficiencies related to excessive product leakage. The applicant states in the cover letter of the resubmission that to address the deficiencies outlined in the CR action letter the originally proposed flow-thru brush applicator has been replaced with another applicator which is not prone to leaks. The new flow-thru brush applicator is supplied by (b) (4). Its design (b) (4).

The applicant further states that the formulation, method of bulk manufacturing of finished product, as well as the specifications and analytical methods for the drug substance, excipients, and finished product remain the same as before in the original submission. Only the container/closure system, packaging operation and the drug product manufacturer are new. Additionally, there is one new testing lab (b) (4) added to this NDA as a testing facility for the drug substance.

To support the proposed product packaged in the improved applicator, the applicant provided the following information in the resubmission:

CMC Information Submitted in Resubmission

	CMC Information Provided	Comments
1	Reference to Type III DMF (b) (4) for the (b) (4) with a LOA	New DMF. No review has been conducted.
2	Updated Section P. 3 Manufacturing for the	Two fill sizes, 4 mL fill in 10 mL bottle and

	<p>following:</p> <p>(a) (b) (4)</p> <p>(b) New fill sizes are proposed.</p> <p>(c) A new DP manufacturer (Kaken Pharmaceutical) is proposed, replacing the originally proposed (b) (4).</p> <p>(d) A new commercial scale batch size, (b) (4), is proposed.</p>	<p>8 mL fill in 10 mL bottle, are proposed. The 4 mL fill in 10 mL bottle is also the physician sample size.</p>
3	<p>Updated Section P. 2.4 and P.7 Container/Closure for the proposed applicator. The following information is provided:</p> <p>(a) Description</p> <p>(b) Specifications</p> <p>(c) Results of extractables studies per USP<661> and USP<671></p> <p>(d) Comparison between the improved applicator and the original one including drop size and dosing amount in a simulated in-use study</p>	<p>The comparison tables are reproduced and presented on the following page.</p>
4	Updated Section P.5 Drug Product Specification	
5	Batch analysis for 6 Kaken (b) (4) batches packaged in the improved applicator (b) (4)	Batch size: (b) (4)
6	24 months of registration stability data from three Kaken (b) (4) batches packaged in the improved applicator (accelerated, and long term) for each fill size. Both upright and horizontal orientations were investigated.	Proposed expiration dating period is 36 month at USP controlled room temperature
7	In-use stability studies 1.5 months, 10 units of 8 mL size. A total of (b) (4) applications (b) (4) were dispensed through the brush. Each drop weight was measured.	Package integrity and weight loss were included in the protocol in addition to assay of drug, ethanol, and related substances.
8	Photostability and freeze/thaw cycling studies	
9	Post approval stability commitment	
10	Label/labeling	
11	Executed packaging records and Master Batch Record	

Comparison of To-Be-Marketed Container with the Original Container

	To-be-marketed Container Closure	Original NDA Container Closure	
Formulation (Qualitative and Quantitative)			
Efinaconazole	10%	(b) (4)	
Excipients	Same		
Package			
Image			
Bottle	Round White, HDPE 10 mL capacity		
Brush/Cap	Flow Thru Design with Brush Applicator Inside Plug – (b) (4) Brush – (b) (4) Cap – (b) (4)		
Fill Size	(b) (4)		
Average volume of a drop	(b) (4)		
Application	Apply product to the nail and use brush to spread solution		
Manufacturing			
Location	(b) (4) US FDA Registered Facility		

Dose Comparison of To-Be-Marketed Container with the Original Container

Container	Daily Dose (µL) Average ± SD (minimum-maximum)	Cumulative use for 28 days (µL) Average ± SD (minimum-maximum)	Percent use against P3 container Average (minimum-maximum)
To-be-marketed	(b) (4)		
Original NDA			

**Formulation Composition for the Proposed To-Be-Marketed Formulation
(no change in formulation composition)**

Ingredient	Grade	Function	Concentration (%w/w)	Total Weight in 4-mL Fill Size (g)	Total Weight in 8-mL Fill Size (g)
Efinaconazole	N/A	Active	10.0	(b) (4)	(b) (4)
Cyclomethicone	NF				
Diisopropyl Adipate	Cosmetic				
C12-15 Alkyl Lactate	Cosmetic				
Butylated Hydroxytoluene	NF				
Citric Acid, Anhydrous	USP				
Edetate Disodium	USP				
Purified Water	USP				
Alcohol	USP				

B. Critical issues for review

1. Reviewer should look into the adequacy of in-process controls and drug product specification to support this product especially regarding leakage issue..
2. Reviewer should assess whether the manufacturing process (especially the (b) (4)/plugging/capping operation) used by the registration stability batches is representative of the commercial process (i.e. compare executed batch records with Master Batch Record).

C. Consults:

CONSULT	YES	NO	COMMENTS
Establishment Evaluation Request (EER)	x		Submitted on Jan. 6, 2014
Pharmacology/Toxicology		x	
Methods Validation		x	NME. Method validation request was sent in the first cycle review, and the review was filed in DARRTS on Feb. 22, 2013.
Environmental Assessment		x	Categorical exclusion claimed was granted in the first cycle review.
Other	x		Product quality microbiology reviewer assignment was requested but not made. Email received from CDER OPS IO MICRO indicated that the submission is acceptable from a product microbiology standpoint, and will be recommended for approval. A review memo describing the assessment of the microbial controls for the drug product will be entered into DARRTS.

D. Comments/Recommendation:

The submission has addressed the deficiencies outlined in the CR action letter dated May 13, 2013 in completeness. Therefore, a substantial review can be performed from the CMC perspective.

Both drug substance and drug product manufacturing sites are located in Japan. GMP inspection requests have been submitted.

The assigned CMC reviewer to this NDA is Dr. Bogdan Kurtyka. Biopharm review is not needed since this is a solution product. Product quality microbiology review was performed by Vera Viehmann.

{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

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/s/

SHULIN DING
01/10/2014

MOO JHONG RHEE
01/10/2014
Chief, Branch IV

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 10-May-2013
To: CMC Review #1 for NDA 203567
From: Bogdan Kurtyka, Ph.D.
CMC Reviewer, ONDQA Division II
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV ONDQA Division II
CC: Shulin Ding, Ph.D.
CMC Lead, ONDQA Division II
Subject: **Update on Facility Inspection**

CMC Review #1 dated 07-Feb-2013 and Addenda dated 1-Mar-2013 and 11-Apr-2013 noted multiple deficiencies which mostly originated from a leakage problem in the container/closure system, and two other unresolved issues (inadequate information regarding manufacturing process and process controls, and labeling). In addition, cGMP compliance evaluation of the facilities involved in this application was not yet completed.

On 09-May-2013 the Office of Compliance issued an overall “Acceptable” recommendation for facilities listed in the application (see the Appendix). Nevertheless, the NDA continues to be inadequate for approval because the aforementioned CMC and labeling deficiencies remain unresolved.

The information needed to resolve the deficiencies remains the same as in the Addendum dated 11-Apr-2013, with the exception of Item #5 on GMP compliance, which has been resolved.

Appendix:

FDA CDER EES ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application:	NDA 203567/000	Sponsor:	DOW PHARM
Org. Code:	540		1330 REDWOOD WAY
Priority:	1		PETALUMA, CA 94954
Stamp Date:	26-JUL-2012	Brand Name:	Efinaconazole (Topical)
PDUFA Date:	26-MAY-2013	Estab. Name:	
Action Goal:		Generic Name:	Efinaconazole (Topical)
District Goal:	27-MAR-2013	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION; EFINACONAZOLE; 10%

FDA Contacts:	B. KURTYKA	Prod Qual Reviewer	3017961431
	C. TRAN-ZWANETZ	Product Quality PM	(HFD-800) 3017963877
	S. DIXON	Regulatory Project Mgr	(HFD-540) 3017961015

Overall Recommendation:	ACCEPTABLE	on 09-MAY-2013	by J. WILLIAMS	()	3017964196
	PENDING	on 10-AUG-2012	by EES_PROD		
	PENDING	on 03-AUG-2012	by EES_PROD		
	PENDING	on 03-AUG-2012	by EES_PROD		

Establishment:	CFN: 2950819	FEI: 1000135370
	DOW PHARMACEUTICAL SCIENCES	

DMF No:	PETALUMA, , UNITED STATES 949547122	AADA:	
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Responsibilities:	DRUG SUBSTANCE RELEASE TESTER
	FINISHED DOSAGE RELEASE TESTER
	FINISHED DOSAGE STABILITY TESTER

Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
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Last Milestone:	OC RECOMMENDATION
------------------------	-------------------

Milestone Date:	25-JAN-2013
------------------------	-------------

Decision:	ACCEPTABLE
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Reason:	DISTRICT RECOMMENDATION
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**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

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

DMF No: AADA:

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

Profile: (b) (4) LIQUID (OTHER THAN SUSP & OAI Status: NONE
EMULSIONS)

Last Milestone: OC RECOMMENDATION

Milestone Date: 11-OCT-2012

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CONTROL TESTING LABORATORY OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 06-AUG-2012

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

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

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE STABILITY TESTER

Profile: (b) (4) API BY CHEMICAL SYNTHESIS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 09-MAY-2013

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

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/s/

BOGDAN KURTYKA
05/10/2013

MARIE KOWBLANSKY on behalf of MOO JHONG RHEE
05/10/2013

MEMORANDUM

Date: April 12, 2013

To: NDA 203-567

From: Terrance Ocheltree, Ph.D., R.Ph.
Director
Division of New Drug Quality Assessment II
ONDQA

Subject: Tertiary review of ONDQA recommendation for NDA 203-567, (b) (4) (efinaconazole) Topical Solution, 10%. Efinaconazole is a new molecular entity (NME).

I have assessed the ONDQA review of NDA 203-567 by Bogdan Kurtyka, Ph.D. The initial ONDQA CMC review was entered into DARRTS on February 8, 2013, with a recommendation for a Complete Response due to a lack of sufficient information to assure the identity, strength, purity, and quality of the drug product; an absence of a recommendation from the Office of Compliance on the manufacturing and testing sites; and pending labeling issues. The ONDQA review was amended in DARRTS on March 1, 2013 by Dr. Kurtyka to generate a Discipline Review (DR) Letter. The DR Letter was sent to the applicant on March 8, 2013. A teleconference was held with the applicant on March 12, 2013 and the applicant submitted an information amendment on March 19, 2013. A subsequent teleconference was held with the applicant on March 20, 2013 to provide further clarifications for the deficiencies outlined in the DR Letter. A second amendment to the ONDQA CMC review was entered into DARRTS on April 11, 2013, restating the deficiencies regarding the drug product, manufacturing process, labeling, and manufacturing and testing sites overall recommendation. The Overall Recommendation for site acceptability is still pending from the Office of Compliance.

An ONDQA Biopharmaceutics review was not performed since the product is a topical solution. Therefore, bioavailability and biopharmaceutics are not an issue.

A Method Validation Consult Request was generated to evaluate the test methods for Assay and Impurities for drug substance and drug product. The Method Validation Report Summary was entered into DARRTS on February 22, 2013, stating the methods are acceptable for quality control and regulatory purposes.

(b) (4) contains efinaconazole manufactured and tested by Kaken Pharmaceutical Co., Ltd. The drug substance is referenced by appropriate Letter of Authorization (LOA) to a Drug Master File (DMF), DMF 21870. The DMF was reviewed and found to be adequate to support this NDA. The review was entered into DARRTS on December 12, 2012.

(b) (4) is packaged in a 10 mL HDPE bottle with a brush applicator

I concur with the determination that the information as provided in the NDA is not adequate to assure the identity, strength, purity, and quality of the drug product, and the overall Quality recommendation of Complete Response.

Secondary review of the CMC reviews was performed by Moo-Jhong Rhee, Ph.D.

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/s/

TERRANCE W OCHELTREE
04/12/2013

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 11-Apr-2013
To: CMC Review #1 for NDA 203567
From: Bogdan Kurtyka, Ph.D.
CMC Reviewer, ONDQA Division II
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV ONDQA Division II
CC: Shulin Ding, Ph.D.
CMC Lead, ONDQA Division II
Subject: **Final CMC Recommendation and the Proposed Complete Response letter**

CMC Review #1 dated 07-Feb-2013 and Addendum dated 1-Mar-2013 noted multiple deficiencies which mostly originated from the leakage problem of the container/closure system, and two other unresolved issues. Because of these deficiencies, in the last Addendum, “Non Approval” action was recommended.

After the 1-Mar-2013 Addendum was signed off and filed, a CMC discipline review letter was sent to the sponsor on 8-Mar-2013, and a teleconference was held on 12-Mar-2013 to inform the applicant of CMC review conclusion. Subsequently, the sponsor submitted an information amendment on 19-Mar-2013, and a teleconference with the sponsor was held on 20-Mar-2013 to provide further clarifications for the deficiencies outlined in the discipline review letter.

The purpose of this addendum is to affirm the previous CMC recommendation of “Non Approval” and, due to the complexity of the issues, to further elaborate the deficiencies delineated in the 1-Mar-2013 addendum in order to communicate more clearly to the applicant via a CR action letter.

The following is the revised language recommended for the CR action letter:

DEFICIENCIES

The quality of the product can not be assured due to:

- 1. Inadequate manufacturing process and control information of the filling/capping (b) (4) operation**

Per 21 CFR 314.50 (d)(1)(ii)(c), the application shall contain the proposed or actual master production record, including a description of the equipment, to be used for the manufacture of a commercial lot of the drug product or a comparably detailed description of the production process for a representative batch of the drug product. The description is expected to be included in Section 3.2.P.3 of the application.

However, the application did not describe the filling/capping (b) (4) process in the Section P.3 as well as in the Master Batch Record with sufficient details and specifics to ensure the process is robust and can produce batches with acceptable leakage rate.

Report 129 in the Developmental Section concluded with recommendations on processes improvement, stating that additional enhancements are necessary as follows:

- (b) (4)
- (b) (4)
- (b) (4)

But none of the recommendations of the Report 129 on the process improvement are officially implemented in the Section P3 (manufacturing process) and in Master Batch Record. (Note that Report 129, included in Section 3.2.P.2, is not considered a binding agreement with the Agency.)

2. Inadequate specification for the drug product

Stability study results on weight loss for the (b) (4)mL fill stored at 25°C confirms a significant loss of formulation ingredient(s) in multiple units (referred to as true leakers in this letter) which eventually showed residues on the outside of the bottles. Table 1 below summarizes the weigh loss data of all five true leakers found in the weight loss study on the (b) (4)mL fill bottles. For comparison, the mean values of all non-leaking units (55 units) are shown in the last column.

The weight loss study consisted of 10 units for each orientation per batch. Therefore, the total number of units set aside for the weigh loss evaluation of the (b) (4)mL configuration was 60 units (3 batches, 2 orientations per batch). Note that all three stability batches were 100% visually inspected prior to release for clinical/stability studies, and any bottles found with residues on the exterior surface were rejected (approximately 5% rejection for the (b) (4)mL fill size per batch, see p.28 of Report 129). Therefore, these 60 units set aside for weight loss evaluation were considered to be “non-leaking” initially. Five true leakers were identified among the 60 units by examining the weight loss rate. The residues found at later time points on the exterior surface of these five units are believed to be due to leaks (not due to (b) (4) dripping).

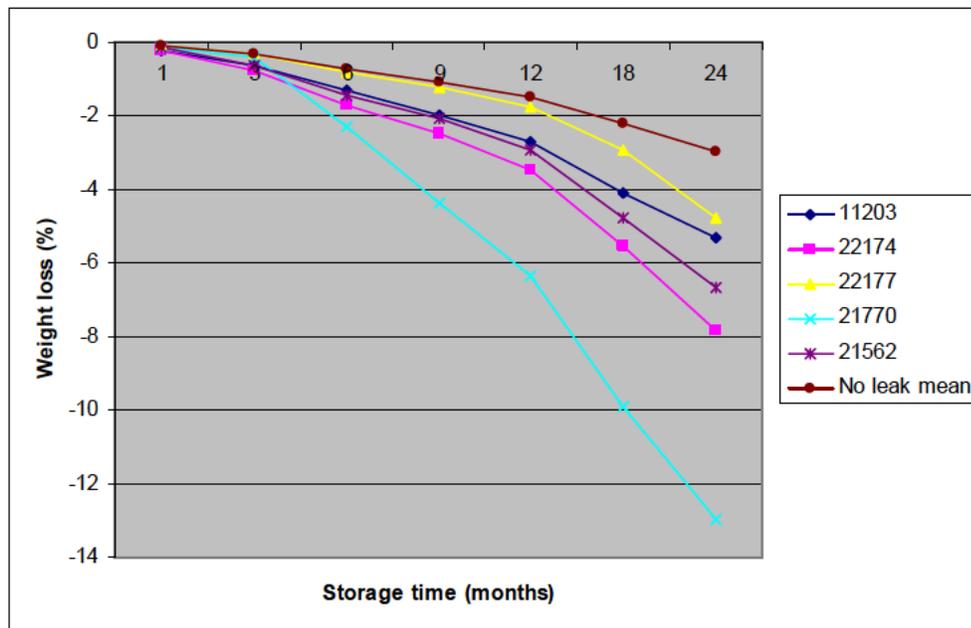
Table 1. Weight Loss Data (% Weight Change) for Units with Unusually High Weight Loss Rate

Month	Batch DP1453F2 Sample # 00011203 upright	Batch DP1473F1 Sample # 00022174 horizontal	Batch DP1473F1, Sample # 00022177 horizontal	Batch DP1474F4 Sample # 00021770 horizontal	Batch DP1474F4 Sample # 00021562 upright	Mean of non-leaking units (n=55)
1	-0.2140	-0.2298	-0.1123	-0.1211	-0.1439	-0.1048
3	-0.6158	-0.7544	-0.3298	-0.4018	-0.6105	-0.3248
6	-1.3035*	-1.7000	-0.7982	-2.2912*	-1.4404	-0.6982
9	-1.9877*	-2.4930	-1.2070	-4.3684*	-2.0789	-1.0343
12	-2.7070*	-3.4561	-1.7596	-6.3263*	-2.9474	-1.4428
18	-4.0789*	-5.5158*	-2.9281	-9.8860*	-4.7842	-2.1362
24	-5.3035*	-7.8439*	-4.7825*	-12.9842*	-6.6719*	-2.9088

*Observation of residue on the container was noted in the stability data tables of Section 3.2.P.8.

The graphic presentation of Table 1 is shown on the following page:

Graph 1. Units with Unusually High Weight Loss Rate



As shown in Table 1, the % weight change of the true leakers ranges from 5% to 13% at 24 month time point. The mean weight change of the non-leaky bottles at 24 month is 2.9% with a range from 2.5% to 3.3% (range data not shown in Table 1).

The manifestation of a leak is typically gradual, and some units did not show clear, unusual higher weight loss rate until Month 9 or 12 (e.g., Sample # 00022177, the second line from the top). Furthermore, true leakers may not have residues on the exterior surface of the bottle, as evidenced in Sample # 00022174 (5th line from the top). Residue was not detected on the exterior surface of this sample until Month 18 despite a

significantly higher weight loss at every time point (Table 1), indicating that visual detection of residue may not be a reliable indicator for leakage.

The presence of latent leakers is supported by the package integrity test results submitted in Section 3.2.P.8. The test is a visual examination of the bottle. Table 2 is a summary the results of three stability batches manufactured according to the process described in the Section P.3. All three batches show more and more incidence of failure as time goes by despite being visually inspected and found no leaking or exterior residue initially.

Table 2 Package Integrity Test Results Reported in Section P.8 for Stability Batches DP1453F2, DP1473F1, and DP1474F4 with a fill volume of (b) (4) mL

Batch	Position	Time point (months)							
		0	1	3	6	9	12	18	24
DP1453F2	horizontal	Pass	Pass	Pass	Fail*	Pass	Fail*	Fail*	Fail*
	upright	Pass	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*
DP1473F1	horizontal	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*	Fail*
	upright	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*	Fail*
DP1474F4	horizontal	Pass	Pass	Pass	Fail*	Fail*	Fail*	Fail*	Fail*
	upright	Pass	Pass	Pass	Pass	Pass	Pass	Fail*	Fail*

*Failure due to observed evidence of residue or leakage. Only one unit was pulled for package integrity per time point

The observations discussed above clearly indicate that the current method ((b) (4) examination) for assessing container integrity is **not specific and sensitive enough to support the proposed product**. It is not sensitive because it can not timely detect subtle leaks which, given time, may develop into a significant leak. It is not specific because it can not detect leaks that do not produce residues, and for those residue-producing leaks, it can not reliably discern the cause of the residues (i.e., filling dripping or a true leak).

For a product with a volatile organic formulation and a known history of leakage, the use of a sensitive and specific method for leak detection is critical to ensure the quality of the product. Multiple technologies with different leak-detection principles such as pressure or voltage differentiation are available for evaluation.

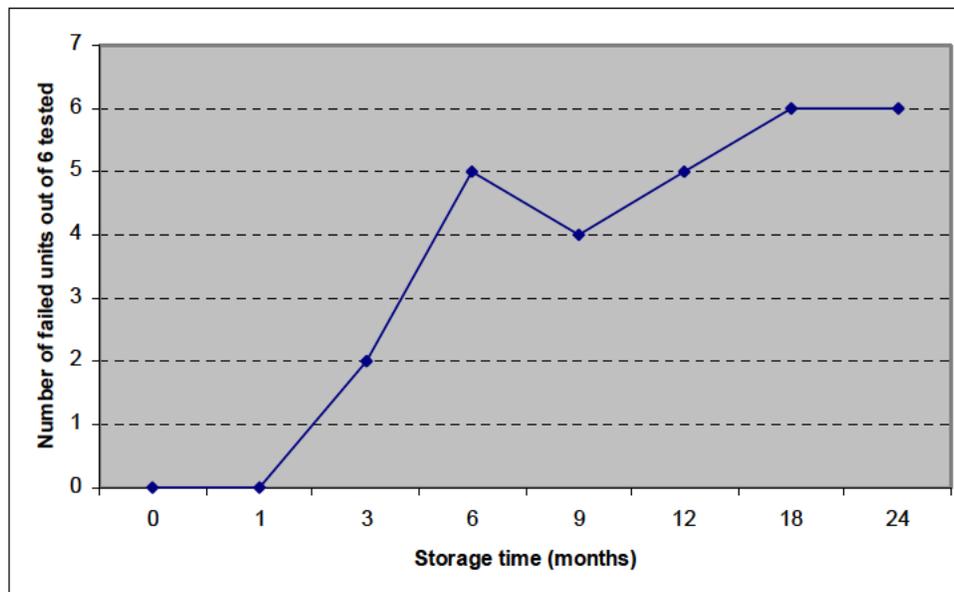
3. Inadequate integrity of the container closure system

Batch release and stability data submitted in the application show unacceptable number of failure incidences for package integrity. Additionally, the presence of a significant number of true leakers has been confirmed through the weight loss study. These observations indicate that the proposed container closure system does not provide adequate protection for the drug product.

In the teleconference on 20-Mar-2013 and in the information submitted before the teleconference on 19-Mar-2013, the number of bottles with residue on the exterior surface (also referred to as “leakers”) was claimed to be lower than (b) (4) % for batches made using (b) (4). The estimate of (b) (4) % was calculated based on package integrity test results collected from Batches (b) (4) 1460 and (b) (4) 1461 over a period of 3-4 months (pages 36-37 of Report 129).

However, short term data alone are not indicative of overall package integrity failure rate for a product with a history of latent leaks as shown in Tables 1 and 2 as well as Graph 1. The data submitted to the stability section of the application indicate that leakage is more likely to be detected after 3 months of storage of drug product. Graph 2 is the presentation of the pooled data from Table 2, showing total number of failure incidence for package integrity from the initial time point through 24 months. At Time Zero and one month, no failure was noted, but after 18 months all containers tested for package integrity failed the test. Therefore, the estimated (b) (4) % leaking rate based on 3-4 months of data may likely underestimate the true leak rate for the proposed expiration dating period of (b) (4) months.

Graph 2. Package Integrity Failure Incidences Observed in Stability Batches



In the teleconference on 20-Mar-2013 you stated that the leakage issue had been fully resolved by (b) (4)

(b) (4) We have reached conclusion and deemed that your statements are not supported by the information/data submitted to the NDA to-date based on the following reasons:

- True leakers and latent leakers have been detected for multiple batches in the weight loss study.
- The greater failure incidence in package integrity test for later time points indicates that (b) (4) is not the only cause responsible for the failure.
- The non-specific visual method employed for leakage detection can not discern the cause of exterior residue (i.e. filling line dripping/vibration or true leakage), and can not detect non-residue-producing leaks.

You asserted in the 19-Mar-2013 amendment that (b) (4)

We have concluded that your argument is not valid because stability samples are randomly withdrawn from the overall pool and considered a statistical representation of the stability batch at a given time point.

4. Inadequate stability data to assure the expiration dating period

The stability data presented in Section 3.2.P.8 (stability) of the application were generated from batches manufactured using a manufacturing process which is not representative of commercial production process. As stated in Report 129, additional process improvements would need to be made in filling/capping (b) (4) operation for commercial production. Therefore, the provided data to-date in Section P.8 are not considered to be representative of stability characteristics of commercial batches which are to be produced using an improved process.

The two (b) (4) batches ((b) (4) 1460 and (b) (4) 1461) presented in Section 3.2.P.2 Pharmaceutical Development (Report 129 pages 36-38) are not considered to be registration or supportive registration stability batches by the Agency. To qualify as a registration stability batch, the batch must have a full testing panel and acceptable testing intervals in addition to no smaller than one tenth of production batch size and a manufacturing process representative of commercial process. According to Section 3.2.P.2 of the application, these two (b) (4) batches were tested for one attribute only (package integrity by (b) (4) inspection), and (b) (4) 1460 is a vehicle batch (not the to-be-marketed formulation).

5. Pending cGMP compliance evaluation of the facilities involved in this application.

6. Pending label/labeling evaluation.

INFORMATION NEEDED TO RESOLVE DEFICIENCIES

1. Regarding manufacturing process and control information
 - Update Section P.3 and Master Batch Record with description for the optimized commercial process, including details of the filling/capping (b) (4) operation with all in-process controls and operation ranges of process parameters.
 - Produce three production batches using the optimized processes, and submit minimum of 12 months of long-term and 6 months of accelerated stability data, including failure rate due to leakage, for both upright as well as horizontal orientations.
 - Two of the batches should be at least pilot scale batches. The process must be the one to be validated for routine production, and the batches must be manufactured using the to-be-marketed container/closure system.
 - Assay results should be generated for leaking units whenever feasible.

2. Regarding the specification for the drug product
 - Update specification for the drug product to include a specific and sensitive leakage test method and its acceptance criterion.
 - The leakage test method must be validated and should not rely on (b) (4) (b) (4) to detect leaks. Validation data for the method must be provided.
3. Regarding integrity of the container closure system
 - Establish a control strategy to ensure the integrity of container closure system without leakage
 - Provide complete description of the to-be-marketed container/closure system and any modifications to the system since the initial submission of the NDA
 - Provide representative samples (three units) of the to-be-marketed product.
4. Regarding stability data
 - In addition to the data described in the Item 1 above, provide in-use stability data for the drug product packaged in the to-be-marketed container/closure system.
5. **Regarding cGMP compliance**
 - Satisfactory recommendation from the Office of Compliance is needed.
6. **Regarding label/labeling**
 - Satisfactory resolution of all label/labeling issues.

ADDITIONAL COMMENTS

The following comments are provided to enhance the Agency's understanding of the quality of clinical batches. They are not approvability issues. However, the requested information should be included in your resubmission.

- Appendix II of the Report 129 states that all bottles from batch DP1444 were weighed, with the acceptance criteria to be specified in the batch record. Please provide:
 - the acceptance criteria,
 - weight results (summarized in table format)
 - full accountability of all bottles; and the fate of bottles that failed the check.
- Report 129 states that leaking bottles from batch DP1453 were stored for further (b) (4) evaluation. Please provide:
 - results of (b) (4) evaluation (e.g., assay, weigh loss, etc.)
 - full accountability of all bottles sent to (b) (4), including those bottles sent to clinical studies experimental details

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/s/

BOGDAN KURTYKA
04/11/2013

MOO JHONG RHEE
04/11/2013
Chief, Branch IV

Memorandum

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: 1-Mar-2013
To: CMC Review #1 for NDA 203567
From: Bogdan Kurtyka, Ph.D.
CMC Reviewer, ONDQA Division II
Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV ONDQA Division II
CC: Shulin Ding, Ph.D.
CMC Lead, ONDQA Division II
Subject: **Final CMC Recommendation**

Previous CMC Review #1 dated 07-Feb-2013 noted multiple deficiencies which mostly originated from the leakage problem of the container/closure system. These and two other unresolved issues resulted in the recommendation of "Non Approval" action.

To sum up, the following is the list of deficiencies which should be resolved to meet the regulatory requirements for the approval of this application:

- Inadequate manufacturing process and control information
- Inadequate specification for the drug product
- Inadequate integrity of the container closure system
- Inadequate stability data to assure the expiration dating period.

Additional deficiencies were as follows:

- No final recommendation from the office of Compliance for the facilities
- Unresolved label/labeling issues

These are still pending.

Recommendation:

Because of these unresolved issues, from the ONDQA perspective, this NDA is not recommended for approval in its present form per 21 CFR 314.125(b)(1), (6), and (13).

To resolve these issues, the following information is needed:

1. Regarding manufacturing process and control information

- Description for the optimized commercial process, including details of the filling/capping (b) (4) operation with all in-process controls and operation ranges of process parameters.
- Additional process development information for the optimized commercial process, and refinements in container/closure in order to achieve acceptable container/closure integrity.
- Master Batch Records for the optimized commercial manufacturing process.

2. Regarding the specification for the drug product

- Updated specification including leakage test method and its acceptance criterion. The leakage test method must be a validated one and not rely on (b) (4) (b) (4) to detect the leak. Method validation data must be provided.

3. Regarding integrity of the container closure system

- Proposed control strategies for preventing the leakage
- Complete description of the to-be-marketed container/closure system and any modifications to the system since the initial submission of the NDA.

4. Regarding stability data

- Stability data from 3 batches manufactured using the optimized commercial process according to ICH Q1A. The process must be the one to be validated for routine production, and the batches must be manufactured using the to-be-marketed container/closure system.
- In-use stability data for the drug product packaged in the to-be-marketed container/closure system

5. Final “Acceptable” recommendation from the Office of Compliance.

6. Finalized label/labeling

In addition, to further understanding of the quality of clinical batches, the following information is needed:

- Appendix II of the Report 129 states that all bottles from batch DP14444 were weighted, with the acceptance criteria to be specified in the batch record. The sponsor needs to provide:
 - the acceptance criteria,
 - weighing results (summarized in table format)
 - full accountability of all bottles; and the fate of bottles that failed the check.
- Report 129 states that leaking bottles from batch DP1443 were stored for further (b) (4) evaluation. The sponsor needs to provide:
 - results of (b) (4) evaluation (e.g. assay, weigh loss, etc.)
 - full accountability of all bottles sent to (b) (4) including those bottles sent to clinical studies
 - experimental details

Attachments:

Attachment-1: Review Notes

1. Some clarification on the following statement made in the Review #1:

“Leakage of a significant fraction of containers has been observed and is not acceptable as discussed in the Pharmaceutical Development and Stability sections of this review. Although the analytical data obtained from the leaked bottles presented in Report 129 suggest that the *loss of strength* may not be significant, whether the clinical data generated from the clinical batches containing a significant number of leakage products are seriously compromised or not, is beyond the CMC purview”.

The expression “loss of strength” in the Review #1 was initially based on the premise that leakage is meant to be the leak of the drug product from the container that might cause loss of strength. The applicant acknowledged that (b) (4) was not robust and that caused to make the drug product to appear leaked, and this was corrected.

However, further examination indicates that ethanol evaporation from the bottle could be another source for making the drug product to appear leaked, and this could be one of the major factors in the change of assay values of the samples tested. In this case, the actual observed change in the assay value is in the direction of increase.

As stated in the Review #1, the submitted data are not sufficient to allow to state with certainty that the assay values of the clinical samples were within the acceptance criterion range ((b) (4) % LC) throughout duration of the clinical studies. However, based on the submitted data, it is possible to state with high confidence that assay values of the clinical batches were not higher than (b) (4) % LC (in the worst case).

This conclusion is based on following reasoning:

- In the worst case, non-leaking bottles may show increased assay values of up to (b) (4) % on storage for about 24 months (probably due to evaporation of ethanol as indicated by stability study)
- Once opened, due to, again, the evaporation of ethanol, the assay value of a bottle may increase another (b) (4) % (as indicated by in-used study)
- It is estimated that leakage may contribute to maximum of (b) (4) % increase of assay. This estimation is based on the observation that physician’s samples (b) (4) show assay increase of (b) (4) % in 12 months. Therefore low level of formulation in container promotes assay increase through evaporation of ethanol. However, container weigh decrease measured during stability studies showed that leakages were never as extensive as loss of (b) (4) % of formulation. Very few samples from batch DP1473F1 showed high leakage of up to (b) (4) % (indicated by weight change), however, majority of leaking bottles lost much less weight (up to several percent) and this leads to a conclusion that the additional (b) (4) % increase of assay due to the leakage is a reasonable upper limit estimate.

2. Method Validation package

The method validation for NDA 203567 requested from Division of Pharmaceutical Analysis in St. Louis has been completed. The following methods were evaluated and found acceptable for quality control and regulatory purposes:

- Determination of drug substance assay by reverse-phase HPLC (STM 04-360)
- Determination of impurities in drug substance by reverse-phase HPLC (STM 04-361)

- Quantitation of drug substance, (b) (4), and degradation products in drug product formulation by reverse-phase -HPLC with UV detection (STM 04-290)

The Method Validation Report Summary was entered in to DARRTS on 22-Feb-2013.

Attachment-2: EES Report

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Application:	NDA 203567/000	Sponsor:	DOW PHARM
Org. Code:	540		1330 REDWOOD WAY
Priority:	1		PETALUMA, CA 94954
Stamp Date:	26-JUL-2012	Brand Name:	Efinaconazole (Topical)
PDUFA Date:	26-MAY-2013	Estab. Name:	
Action Goal:		Generic Name:	Efinaconazole (Topical)
District Goal:	27-MAR-2013	Product Number; Dosage Form; Ingredient; Strengths	001; SOLUTION; EFINACONAZOLE; 10%
FDA Contacts:	K. JENNINGS	Project Manager	3017962919
	B. KURTYKA	Review Chemist	3017961431

Overall Recommendation:	PENDING	on 10-AUG-2012	by EES_PROD
	PENDING	on 03-AUG-2012	by EES_PROD
	PENDING	on 03-AUG-2012	by EES_PROD

Establishment:	CFN: 2950819	FEI: 1000135370	
	DOW PHARMACEUTICAL SCIENCES		
	PETALUMA, , UNITED STATES 94954		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE RELEASE TESTER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-JAN-2013		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

**FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT**

Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER FINISHED DOSAGE MANUFACTURER FINISHED DOSAGE STABILITY TESTER		
Profile:	(b) (4) LIQUID (OTHER THAN SUSP & EMULSIONS)	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	11-OCT-2012		
Declason:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		
<hr/>			
Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	FINISHED DOSAGE RELEASE TESTER		
Profile:	CONTROL TESTING LABORATORY	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	06-AUG-2012		
Declason:	ACCEPTABLE		
Reason:	BASED ON PROFILE		
<hr/>			
Establishment:	CFN: (b) (4)	FEI: (b) (4)	
	(b) (4)		
DMF No:		AADA:	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER DRUG SUBSTANCE STABILITY TESTER		
Profile:	(b) (4) API BY CHEMICAL SYNTHESIS	OAI Status:	NONE
Last Milestone:	INSPECTION SCHEDULED		
Milestone Date:	06-FEB-2013		

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/s/

BOGDAN KURTYKA
03/04/2013

MOO JHONG RHEE
03/04/2013
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION REPORT SUMMARY

TO: Bogdan Kurtyka, Ph.D., CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: bogdan.kurtyka@fda.hhs.gov
Phone: (301) 796-1431
Fax: (301) 796-9745

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
Suite 1002
1114 Market Street
St. Louis, MO 63101
Phone: (314) 539-3815

Through: John Kauffman, Acting Deputy Director
Phone: (314) 539-2168

SUBJECT: Methods Validation Report Summary

Application Number: 203567

Name of Product: (b) (4) (efinaconazole) Topical Solution, 10%

Applicant: Dow Pharmaceutical Sciences

Applicant's Contact Person: Charity Abelardo, Acting Sr. Director Regulatory Affairs

Address: 1330 Redwood Way, Petaluma, CA 94954

Telephone: (707) 793-2600 Fax: Not available

Date Methods Validation Consult Request Form Received by DPA: 9/28/12

Date Methods Validation Package Received by DPA: 9/28/12

Date Samples Received by DPA: 10/17/12

Date Analytical Completed by DPA: 2/21/13

Laboratory Classification: 1. Methods are acceptable for control and regulatory purposes.
2. Methods are acceptable with modifications (as stated in accompanying report).
3. Methods are unacceptable for regulatory purposes.

Comments: See attached memo for comments and data summary.



Date: February 22, 2013

To: Bogdan Kurtyka Ph. D, CMC Reviewer, Office of New Drug Quality Assessment

Through: John Kauffman, Acting Deputy Director, Division of Pharmaceutical Analysis

From: Anjanette Smith, Chemist, Division of Pharmaceutical Analysis

Subject: Method Validation for NDA 203567
(b) (4) (efinaconazole) topical solution, 10%
Dow Pharmaceutical Sciences

The following methods were evaluated and are acceptable for quality control and regulatory purposes:

- Determination of IDP-108 content in IDP-108 drug substance by reverse-phase HPLC (STM 04-360)
- Determination of IDP-108 impurities in IDP-108 drug substance by reverse-phase HPLC (STM 04-361)
- Quantitation of IDP-108, (b) (4), and degradation products in IDP-108 formulations by RP-HPLC with UV detection (STM 04-290)

Summary of results attached.

Data package available at <http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880403517>

Determination of IDP-108 content in IDP-108 drug substance by reverse-phase HPLC

	Identification of IDP-108	Amount of IDP-108, %w/w
	sample 1: (b) (4) sample 2: (b) (4)	sample 1: (b) (4) sample 2: (b) (4) avg(2): (b) (4)
Specification	(b) (4)	(b) (4)
Result	Pass	

UV spectra of IDP-108 in sample matched that in standard.

Determination of IDP-108 impurities in IDP-108 drug substance by reverse-phase HPLC

Amount of known and unknown IDP-108 impurities

	RT	RRT	Sample 1 %w/w	Sample 2 %w/w	Avg %w/w	Specification
					(b) (4)	(b) (4)
						NMT
						NMT
						NMT
Total					(b) (4)	NMT (b) (4)
Result					Pass	

(b) (4) impurity was not detected in the samples.

Quantitation of IDP-108, (b) (4), and degradation products in IDP-108 formulations by RP-HPLC with UV detection

	ID of IDP-108	ID of (b) (4)	IDP-108 content		(b) (4) content	
			%w/w	%LC	%w/w	%LC
sample 1						(b) (4)
sample 2						
avg(2)						
Specification						
Result						Pass

LC = label claim

UV spectra of IDP-108 in sample matched that in standard.

Degradation product content

	RT, min.	RRT	%w/w	%LC
sample 1				(b) (4)
sample 2				
avg(2)				
Specification				NMT (b) (4)
Result				Pass

No known degradation products were detected.

Specification: NMT (b) (4) LC for each (b) (4) degradation product
 NMT (b) (4) LC each additional degradation product
 NMT (b) (4) LC total degradation products

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/s/

MICHAEL L TREHY
02/22/2013

JOHN F KAUFFMAN
02/22/2013

NDA 203567

(b) (4)

**(efinaconazole) solution
10%**

Dow Pharmaceutical Sciences

Bogdan Kurtyka, Ph.D.
Review Chemist

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

**CMC REVIEW OF NDA 203567
For the Division of Dermatological and Dental Products (HFD-540)**

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CMC Review Data Sheet

CMC Review Data Sheet

1. NDA 203567

2. REVIEW #: 1

3. REVIEW DATE: 07-Feb-2013

4. REVIEWER: Bogdan Kurtyka, Ph.D.

5. PREVIOUS DOCUMENTS: N/A

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original Submission	26-Jul-2012
Stability update	07-Dec-2012
Container/closure update	07-Dec-2012
Amendment	17-Dec-2012
Amendment	09-Jan-2013

7. NAME & ADDRESS OF SPONSOR:

Name: Dow Pharmaceutical Sciences
Address: Pentaluma, CA 94954
USA
Telephone: 707-793-2600
Fax: 707-665-4680

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: (b) (4)
b) Non-Proprietary Name (USAN): Efinaconazole
c) Code Name/# (ONDQA only): IDP-108
d) Chem. Type/Submission Priority (ONDQA only):
 - Chem. Type: I
 - Submission Priority: S

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

10. PHARMACOL. CATEGORY: Triazole antifungal agent

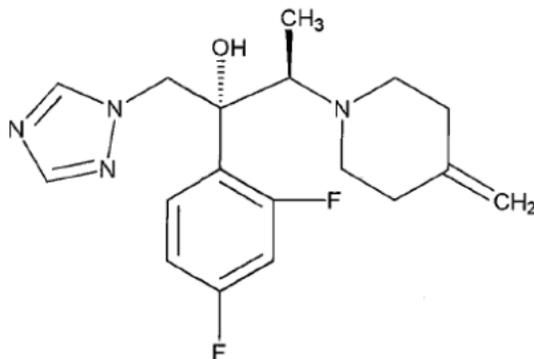
11. DOSAGE FORM: Solution CODE: 138

CMC Review Data Sheet

12. STRENGTH/POTENCY: 10 %
13. ROUTE OF ADMINISTRATION: Topical CODE: 011
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:

Chemical Name: (2R,3R)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidin-1-yl)-1H-imidazole
 USAN Name: Eficconazole
 CAS Number: 164650-44-6
 Structural Formula:



Molecular Formula: C₁₈H₂₂F₂N₄O
 Molecular Weight: 348.39

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
21870	II	Kaken Pharmaceutical	Efinaconazole	1	Adequate	15-Dec-2010, checked into DARRTS on 15-Mar-2011	Reviewed by Dr. Bogdan Kurtyka
(b) (4)	III		(b) (4)	4	N/A	N/A	
	III			4	N/A	N/A	

CMC Review Data Sheet

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: N/A

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Pending		
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	Pending		
DMEPA	N/A		
EA	Categorical exclusion granted (see review)	22-Jan-2013	Bogdan Kurtyka, Ph.D.
Microbiology	N/A		

Executive Summary Section

The CMC Review for NDA 203567

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant of this NDA has *not* provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The office of Compliance has *not* issued yet an overall recommendation for the facilities involved in this application.

Issues on the label/labeling are still pending as of the date of this review.

Therefore, from the ONDQA perspective, this NDA is *not* recommended for approval per 21CFR 314.125(b)(1),(6), and (13) in its present form until the above issues delineated in the “**List of Deficiencies**” (p. 50) are satisfactorily resolved.

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

II. Summary of CMC Assessments

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

(1) Drug Substance

The sponsor references DMF 21870 (Kaken Pharmaceuticals) for details on the description, characterization, manufacture, packaging, specification for quality control testing, and stability of the proposed drug substance, (b) (4). A letter of authorization to cross reference the DMF is provided in the application. The DMF (b) (4) has been reviewed and found adequate to support this application.

(2) Drug Product

Efinaconazole solution 10% is indicated for treatment of onychomycosis. It is a clear, colorless to pale yellow solution. The inactive ingredients of the formulation are commonly used in topical drug products. All except one (C12-15 alkyl lactate) excipients are listed in the Inactive Ingredients Database and the proposed amounts do not exceed previously approved levels. The drug product is manufactured by (b) (4)

(b) (4)
The sponsor proposed (b) (4)
as the manufacturing site.

Executive Summary Section

The drug product specification includes: appearance, package integrity, identification, assay of drug substance, impurities, assays of (b) (4), and microbial testing. The specification attributes and their analytical methods are deemed satisfactory for assuring the identity, strength, purity, and quality. However, the acceptance criterion for total impurities is considered too high to assure the drug product purity.

Efinaconazole solution is packaged in a 10 mL HDPE bottle with a brush applicator in a (b) (4) cap. The information included in the application DOES NOT demonstrate that the proposed container/closure system meets all recommendations of relevant USP monographs and the Agency's guidance.

The sponsor provided the results of 30 months long-term stability studies for one batch and 24 months for two batches of drug product, and proposed an (b) (4) month expiration dating period under the controlled room conditions. However, based on the submitted stability data, the proposed expiration dating period cannot be granted. Multiple failures of container integrity attribute during stability studies indicate that the drug product quality cannot be assured with the manufacturing process and controls described in the application.

The applicant claimed categorical exclusion from the Environmental Assessment based on 21CFR 25.31(b).

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

The drug product should be applied once daily using the built-in flow-through brush applicator. During application the nail, the nail folds, nail bed, hyponychium, and the undersurface of the nail plate, should be completely covered by the formulation.

C. Basis for Not-Approval Recommendation

21CFR 314.125(b)(1)

- The description of the filling operation of the drug product manufacturing process does not include all required information including ranges for in-process controls.
- The proposed container/closure does not provide adequate protection of the drug product.
- Due to container integrity issue the currently submitted stability data are not adequate to assure the product quality and do not support the proposed (b) (4) months expiration dating period.

21CFR 314.125(b)(6)

- Section 11 (Description) of package insert does not list inactive ingredients in the alphabetical order. In addition, the name (b) (4) is not a

Executive Summary Section

compendial name. The compendial name for this excipient is “anhydrous citric acid”.

- Section 16 (How Supplied/Storage and Handling) of package insert lists incomplete conditions for USP controlled room temperature. It should read “Store at 20-25°C (68-77°F)”.
- The carton label is not adequate. The conditions for USP controlled room temperature are incomplete and should read “Store at 20-25°C (68-77°F)”.

21CFR 314.125(b)(13)

- The Office of Compliance did not issue overall “acceptable” recommendation for the manufacturing establishments.

(see the “**List of Deficiencies**” on p.50).

III. Administrative

- A. Reviewer’s Signature:** *(See appended electronic signature page)*
Bogdan Kurtyka, Ph.D.
CMC Reviewer, Branch IV/Division II/ONDQA
- 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 DARRTS

42 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

BOGDAN KURTYKA
02/08/2013

MOO JHONG RHEE
02/08/2013
Chief, Branch IV

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

METHODS VALIDATION CONSULT REQUEST FORM

TO: FDA
Division of Pharmaceutical Analysis
Attn: Benjamin (Nick) Westenberger
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Bogdan Kurtyka, Ph.D., CMC Reviewer
Shulin Ding, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: bogdan.kurtyka@fda.hhs.gov
Phone: (301)-7961431
Fax.: (301)-7969745

Through: Moo-Jhong Rhee, Ph.D., Chief Branch IV Division II ONDQA
Phone: (301)-7961440

and

Jeannie David, ONDQA Methods Validation Project Manager
Phone: 301-796-4247

SUBJECT: Methods Validation Request

Application Number: NDA 203567

Name of Product: (b) (4) (efinaconazole) Topical Solution, 10%

Applicant: Dow Pharmaceutical Sciences

Applicant's Contact Person: Charity Abelardo, Acting Sr. Director Regulatory Affairs

Address: 1330 Redwood Way, Petaluma, CA 94954

Telephone: 707-793-2600 Fax: N/A

Date NDA Received by CDER: **July 26, 2012**

Date of Amendment(s) containing the MVP: **July 26, 2012**

DATE of Request: **September 26, 2012**

Requested Completion Date: **March 26, 2013**

PDUFA User Fee Goal Date: **May 26, 2013**

Submission Classification/Chemical Class: NME

Special Handling Required: No

DEA Class: N/A

Format of Methods Validation Package (MVP)

Paper Electronic Mixed

We request suitability evaluation of the proposed manufacturing controls/analytical methods as described in the subject application. Please submit a letter to the applicant requesting the samples identified in the attached *Methods Validation Request*. Upon receipt of the samples, perform the tests indicated in Item 3 of the attached *Methods Validation Request* as described in the NDA. We request your report to be submitted in DARRTS promptly upon completion, but no later than 45 days from date of receipt of the required samples, laboratory safety information, equipment, components, etc. We request that you notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager of the date that the validation process begins. If the requested completion date cannot be met, please promptly notify the ONDQA Methods Validation Requestor and the ONDQA Methods Validation Project Manager.

Upon completion of the requested evaluation, please assemble the necessary documentation (i.e., original work sheets, spectra, graphs, curves, calculations, conclusions, and accompanying *Methods Validation Report Summary*). The *Methods Validation Report Summary* should include a statement of your conclusions as to the suitability of the proposed methodology for control and regulatory purposes and be electronically signed by the laboratory director or by someone designated by the director via DARRTS. The ONDQA CMC Reviewer, ONDQA Methods Validation Project Manager, and ONDQA CMC Lead/Branch Chief should be included as cc: recipients for this document.

All information relative to this application is to be held confidential as required by 21 CFR 314.430.

MVP Reference #	METHODS VALIDATION REQUEST			NDA #
⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT				
ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION		
Upon request, see section 3.2.R.3				
⇒ ITEM 2: Contents of Attached Methods Validation Package				Volume/Page Number(s)
Statement of Composition of Finished Dosage Form(s)				3.2.P.1
Specifications/Methods for New Drug Substance(s)				3.2.S.4.1 and 3.2.S.4.2
Specifications/Methods for Finished Dosage Form(s)				3.2.P.5.1 and 3.2.P.5.2
Supporting Data for Accuracy, Specificity, etc.				3.2.S.4.3 3.2.P.5.3
Applicant's Test Results on New Drug Substances and Dosage Forms				3.2.S.4.4 3.2.P.5.4
Other: N/A				
⇒ ITEM 3: REQUESTED DETERMINATIONS Perform following tests as directed in applicant's methods. Conduct ASSAY in duplicate.				
Method ID	Method Title	Volume/Page	MV Request Category (see attached)	Comments
	Drug substance impurities STM 04-361	3.2.S.4.2	0	
	Drug substance assay STM 04-360	3.2.S.4.2	0	
	Drug product assay and impurities STM-04-290	3.2.P.5.2	0	

Additional Comments:				

Methods Validation Request Criteria

MV Request Category	Description
0	New Molecular Entity (NME) application, New Dosage Form or New Delivery System
1	Methods using new analytical technologies for pharmaceuticals which are not fully developed and/or accepted or in which the FDA laboratories lack adequate validation experience (e.g., NIR, Raman, imaging methods)
2	Critical analytical methods for certain drug delivery systems (e.g., liposomal and microemulsion parenteral drug products, transdermal and implanted drug products, aerosol, nasal, and dry powder inhalation systems, modified release oral dosage formulations with novel release mechanisms)
3	Methods for biological and biochemical attributes (e.g., peptide mapping, enzyme-based assay, bioassay)

4	Certain methods for physical attributes critical to the performance of a drug (e.g., particle size distribution for drug substance and/or drug product)
5	Novel or complex chromatographic methods (e.g., specialized columns/stationary phases, new detectors/instrument set-up, fingerprinting method(s) for a complex drug substance, uncommon chromatographic method)
6	Methods for which there are concerns with their adequacy (e.g., capability of resolving closely eluting peaks, limits of detection and/or quantitation)
7	Methods that are subject to a “for cause” reason

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/s/

BOGDAN KURTYKA
09/27/2012

SHULIN DING
09/27/2012

MOO JHONG RHEE
09/27/2012

JEANNIE C DAVID
09/28/2012
ONDQA Methods Validation Project Manager

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

OND Division: Division of Dermatology and Dental Products
NDA: 203-567
Applicant: Dow Pharmaceutical Sciences.
Stamp Date: July 26, 2012
PDUFA Date: May 26, 2013
Trademark: (b) (4)
Established Name: Efinaconazole
Dosage Form: Solution
Route of Administration: Topical
Indication: Onychomycosis

CMC Lead: Shulin Ding

	YES	NO
ONDQA Fileability:	<input checked="" type="checkbox"/>	<input type="checkbox"/>
Comments for 74-Day Letter	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Summary and Critical Issues:

A. Summary

Dow Pharmaceutical Sciences has submitted a 505(b)(1) New Drug Application (NDA) for the prescription use of (b) (4) (efinaconazole) topical solution, 10% for the topical treatment of onychomycosis.

The proposed drug substance, efinaconazole is a new molecular entity. The applicant references DMF 21870 held by Kaken Pharmaceutical Company for the CMC information of efinaconazole drug substance. A letter of authorization from Kaken is provided. The DMF has not been reviewed.

The proposed drug product is a clear, colorless to pale yellow, non-aqueous solution packaged in opaque, white, high-density-polyethylene (HDPE) flat oval bottles with a brush cap assembly consisting of a brush applicator and (b) (4) cap. The proposed trade size is (b) (4) physician sample size is (b) (4)

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. In addition to the active ingredient, the formulation also contains the following excipients: cyclomethicone, NF; butylated hydroxytoluene, NF; citric acid anhydrous, USP; edetate disodium, USP; purified water, USP; alcohol, USP, diisopropyl adipate; and C-12-15 alkyl lactate. There is one novel excipient (C-12-15 alkyl lactate) present in the formulation. No excipients are of human or animal origin. The formulation is essentially a non-aqueous solution, containing only (b) (4) of water. Due to (b) (4) content the formulation is flammable.

The proposed product is prepared by (b) (4).
Efinaconazole (b) (4)

Registration stability data provided in the initial submission for the trade size (b) (4) mL) to support the proposed expiration dating period of (b) (4) months at 20°-25°C (excursions permitted to 15°-30°C) include 12-18 months of long term and 6 months of accelerated stability data from three (b) (4) batches (b) (4). As to the (b) (4)

Note that (b) (4) are smaller than (b) (4) of the proposed commercial scale of (b) (4). The registration stability data show that weight loss is the primary shelf-life-determining factor for this product.

Special stability studies such as freeze/thaw, thermal cycling (5°C-40°C), and refrigeration are also provided to support storage/handling of the drug product.

B. Critical issues for review

1. Novel Excipient C-12-15 alkyl lactate

The adequacy of the CMC information provided in the NDA to support the use of this novel excipient needs a critical review. The applicant provides only the proposed specification and supplier's certificate of analysis in the initial submission. Its exact composition and how it is manufactured are not known.

2. Package Integrity (leakage)

The proposed production-scale packaging process for the proposed to-be-marketed container/closure system reportedly produces batches with a leakage rate of (b) (4)%. The proposed drug product specification indicates that no leakage would be allowed. The proposed method (SOP-02-45) for package integrity is (b) (4). A critical review is necessary to determine whether SOP-02-45 and sampling size are adequate and able to support the proposed acceptance criterion of no leakage.

3. Extractables/Leachables Studies

The extraction was performed only on the bottle. Components of the brush-cap assembly were not investigated. Extracts were analyzed using GC-Mass only without using HPLC-Mass. (b) (4)

The adequacy of the extractables/leachables studies needs a critical review.

4. Conformance to USP<661> Containers

Data showing the conformance to USP<661> were provided in the NDA for the bottle but not for the brush cap assembly. The data for the brush cap assembly may exist in the

DMF. The reviewer should look for this information when reviewing the DMF of the brush cap assembly.

5. Brush Compatibility with Formulation and In-Use Stability Study
Information and data to support the compatibility of the brush with the formulation (such as drug uptake) are not provided. Neither was an in-use stability study conducted.
6. Drug Product In-Process Control
The information provided for the in-process control is inadequate. For example, bulk hold time is not specified, and the control over filling operation is not adequately described. The applicant should propose a bulk hold time with supporting data, and add the bulk hold time information to Master Batch Record. The applicant should describe filling operation and its control with more details, and improve the filling module of Master Batch Record. A batch analysis on the in-process control data should also be provided to Section 3.2.P.3.4 Controls of Critical Steps and Intermediates.
7. Drug Product Specification
Weight loss should be added to the drug product specification because a significant weight loss has been noticed in the stability studies, and a large variation has been noted due to leakage. The limits proposed for related substances need a critical review. Note that the proposed drug product specification does not include the test on minimal fill. Unless minimal fill is performed as an in-process control test in the filling operation, it should be added to the drug product specification.

C. Comments for 74-Day Letter:

1. We acknowledge the receipt of three drug product samples, and would like to request six more representative drug product samples packaged in the to-be-marketed container/closure system for packaging evaluation.
2. Provide test results of USP<661> and extractables/leachables study results for the components of the brush-cap assembly, or reference to a DMF with a letter of authorization if the information resides in the DMF.
3. Provide quantitative results for leachables present in the registration stability samples. Alternatively, you can provide acceptable justification to support the omission of such an investigation.
4. Provide study results to demonstrate the compatibility of the brush with the proposed formulation. The study should include an evaluation of potential drug uptake, degradants, leachables, and brush integrity.
5. Provide in-use stability data for the proposed product. The in-use stability study should mimic the actual use described in the package insert, and should evaluate all critical product attributes including weight loss due to evaporation and package integrity (brush, cap, bottle, label, etc.). To accurately calculate the weight loss due to evaporation, we recommend that you collect data for the weight loss due to dosing. The study duration should be at least 4 weeks. We also highly recommend that the

assays of efinaconazole/related substances (b) (4), and evaluation of leachables be performed on the formulation discharged from the brush.

6. Your conclusion made in the leachables investigation report (Report No. 1206176 GC-MS Comparison of Aged and Unaged Drug Product Vehicles) is not supported by the data presented in the report. (b) (4)

(b) (4)

You should also provide GC chromatograms for individual formulation ingredients.

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective. The major CMC review issues with this NDA are novel excipient, leakage, extractables/leachables, drug product in-process control, and drug product specification.

Drug substance manufacturing site is located in Japan. (b) (4)
(b) (4). GMP inspection requests have been submitted.

The proposed drug substance is a new molecular entity. A request of method validation to FDA's lab in San Louis is recommended for the HPLC methods used for assay and quantitation of related substances in drug substance and drug product.

Collaboration with the inspector is recommended in order to fully understand the leakage issue and the further improvement stated by the applicant in the NDA. If necessary, CMC reviewer may want to join the inspection. The assigned CMC reviewer to this NDA is Dr. Bogdan Kurtyka.

Shulin Ding, Ph.D.
CMC Lead

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

NDA Number: 203567 **Supplement Number and Type:** 0000 **Established/Proper Name:** Efinaconazole solution, 10%

Applicant: Dow Pharmaceutical Sciences **Letter Date:** July 26, 2012 **Stamp Date:** July 26, 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.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • 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		

9.	<p>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:</p> <ul style="list-style-type: none"> • 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		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		

* 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 based on 21CFR 25.31 (b)

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	Referenced to DMF 21870.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?		x	Referenced to DMF 21870.
14.	Does the section contain information regarding the characterization of the DS?		x	Referenced to DMF 21870.
15.	Does the section contain controls for the DS?	x		Also referenced to DMF 21870.
16.	Has stability data and analysis been provided for the drug substance?		x	Referenced to DMF 21870.
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		
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	(b) (4)

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		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
21870	II	Kaken Pharmaceutical Co., Ltd.	Efinaconazole	5/18/2012	
(b) (4)	III	(b) (4)	(b) (4)	5/8/2012	
	III			4/5/2012	

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
09/18/2012

MOO JHONG RHEE
09/18/2012
Chief, Branch IV