CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204427Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

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

Date: 06/16/2014

From: Gene W. Holbert, Ph.D.
Senior Review Chemist, ONDQA
Division of New Drug Quality Assessment II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: CMC Review #1 of NDA 204427

Subject: Approval Recommendation

When CMC review #1 was filed, outstanding issues were container/carton labeling and the final package insert.

On 04/01/2014, the final container/carton labeling was submitted and the revisions are ***satisfactory*** from the ONDQA perspective (**Attachment 1**).

On 06/16/2014, the final package insert was submitted and the revisions are ***satisfactory*** from the ONDQA perspective (**Attachment 2**).

Recommendation: This NDA is now recommended for **Approval** from the ONDQA perspective.

3 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/

GENE W HOLBERT
06/16/2014

MOO JHONG RHEE
06/16/2014
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: Gene W. Holbert, Ph.D., CMC Reviewer
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: gene.holbert@fda.hhs.gov
Phone: (301) 796-1368
Fax: (301) 796-9850

FROM: FDA
Division of Pharmaceutical Analysis
Michael Trehy, MVP Coordinator
645 S Newstead Avenue
St. Louis, MO 63110
Phone: (314) 539-3815

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

SUBJECT: Methods Validation Report Summary

Application Number: 204427

Name of Product: Tavaborole Topical Solution, 5%

Applicant: Anacor Pharmaceuticals, Inc.

Applicant's Contact Person: Carmen R. Rodriguez, M. Sc.

Address: 1020 East Meadow Circle, Palo Alto, CA 94303-4230

Telephone: (650) 543-7576 Fax: (650) 543-7660

Date Methods Validation Consult Request Form Received by DPA: Septamber 20, 2013

Date Methods Validation Package Received by DPA: September 20, 2013

Date Samples Received by DPA: October 11, 2013

Date Analytical Completed by DPA: March 10, 2014

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 DPA comments and link to analyst's work sheets and chromatograms.

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
St. Louis, MO 63110
Tel. (314) 539-3874

Date: March 11, 2014

To: Dr. Gene W. Holbert, CMC Reviewer, Office of New Drug Quality Assessment

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

From: Anna Wokovich, Chemist, Division of Pharmaceutical Analysis

Subject: NDA 204427, Tavaborole Topical Solution 5%

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

HPLC Identification, Assay for AN2690, Determination of Related Substances in AN2690 Drug Substance and AN2690 Topical Solution 5% w/w (b) (4)

(b) (4) Determination of Assay and Related Substances in (b) (4) by HPLC ((b) (4) version not provided effective date not provided)

The methods are similar in that both methods calculate % assay of drug substance, % impurities in drug substance, and identification by HPLC of drug substance. (b) (4) also calculates % assay of sample (topical solution) and % impurities in sample (topical solution); (b) (4) does not use sample (topical solution).

Method: HPLC Identification, Assay for AN2690, Determination of Related Substances in AN2690 Drug Substance and AN2690 Topical Solution 5% w/w ((b) (4)

DPA suggests the following modification:

- On page 8 of 16 of Method (b) (4) suggest specifying the response factor to be used for unknown impurities.

Method: (b) (4) Determination of Assay and Related Substances in (b) (4) by HPLC (b) (4) version not provided effective date not provided)

DPA suggests the following modifications:

- The sample preparation procedure should be clarified. The sample preparation does not appear to take into consideration that the product is a 5% solution. (b) (4)
- The effective date for the method should be provided.

Analyst's work sheets and chromatograms are available at http://ecmsweb.fda.gov:8080/webtop (b) (4) objectId/090026f8805da191

Method: (b) (4)

Drug Product

Identification: (b) (4) the standard within (b) (4)
Result: (b) (4)%, (b) (4)% average: (b) (4)%

Assay (HPLC): 90.0-110.0%
Result: 98.5%, 98.5% average: 98.5%

Related substances - (b) (4): NMT (b)%
Result: less than LOQ

Related substances – (b) (4): NMT (b) (4)% LS
Result: (b) (4) % label strength (b) (4) % label strength average: (b) (4)% label strength

Related substances – Individual Unspecified: NMT (b)% LS
Result: (b) (4)% label strength, (b) (4)% label strength average: (b) (4)% label strength

Related substances – Total Related Substances: NMT (b)% LS
Result: (b) (4)% label strength, (b) (4)% label strength average: (b) (4)% label strength

Related substances – (b) (4): no specification
Result: (b) (4)% label strength, (b) (4)% label strength average: (b) (4)% label strength

Drug Substance

Identification: Retention time Drug Substance (b) (4)% different than in (b) (4)
Result: (b) (4)%

Purity (HPLC): NLT (b) (4)% area
Result: (b) (4)%, (b) (4)%

Related substances - (b) (4): NMT 0 (b)% area
Result: not detected

Related substances – (b) (4): NMT % area
Result: (b) (4)% area, (b) (4)% area average (b) (4)% area

Related substances – Total Related Substances: NMT % area
Result: (b) (4)% area, (b) (4)% area average: (b) (4)% area

Related substances – (b) (4)
Drug Substance Specifications: none
Result: not detected

Drug Substance Individual Uspecified NMT (b) (4)%
Result: (b) (4)% area, (b) (4)% area average (b) (4)% area

Method: (b) (4) Methods CR (CRLC4278_001)

Drug Substance

Specifications: Ratio of retention time in sample chromatogram to retention time in standard chromatogram is (b) (4)
Result: (b) (4) average: (b) (4)

Purity (HPLC): NLT (b) (4)% area
Result: (b) (4)%, (b) (4)% average: (b) (4)%

Assay by HPLC Drug Substance Specifications: (b) (4)%
Result: (b) (4)%, (b) (4)% average: (b) (4)%

Related substances - (b) (4): NMT (b) (4)% area
Result: not detected

Related substances – (b) (4): NMT (b) (4)% area
Result: (b) (4)% area, (b) (4)% area average: (b) (4)% area

Related substances – Major unspecified: NMT (b) (4)% area
Result: what constitutes a major unspecified impurity is not defined in method or specifications.

Related substances – Total Related Substances: NMT (b) (4)% area
Result: (b) (4)% area, (b) (4)% area average (b) (4)% area

Related substances – (b) (4)
Drug Substance Specifications: none
Result: not detected

Related substances – Individual Unspecified
Drug Substance Specifications: NMT (b) (4)%
Result: (b) (4)% area, (b) (4)% area average: (b) (4)% area

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

/s/

MICHAEL L TREHY
03/11/2014

JOHN F KAUFFMAN
03/11/2014

NDA 204427

KERYDIN™ (tavaborole) Topical Solution, 5%

Anacor Pharmaceuticals, Inc.

Gene W. Holbert, Ph.D.
Bogdan Kurtyka, Ph.D.
Nina Ni, Ph.D.

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

Chemistry Review for the

Division of Dermatological and Dental Products

Table of Contents

Table of Contents **2**

Chemistry Review Data Sheet **4**

The Executive Summary **7**

I. Recommendations 7

A. Recommendation and Conclusion on Approvability 7

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable 7

II. Summary of Chemistry Assessments 7

A. Description of the Drug Product(s) and Drug Substance(s) 7

B. Description of How the Drug Product is Intended to be Used 9

C. Basis for Approvability or Not-Approval Recommendation 9

III. Administrative 9

A. Reviewer's Signature 9

B. Endorsement Block 9

C. CC Block 9

Chemistry Assessment **10**

I. Review of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body of Data 10

S DRUG SUBSTANCE [Tavaborole, (b) (4)] 10

S.1 General Information [Tavaborole, (b) (4)] 10

S.2 Manufacture [Tavaborole, (b) (4) 11

S.3 Characterization [Tavaborole, (b) (4) 33

S.4 Control of Drug Substance [Tavaborole, (b) (4)] 40

S.5 Reference Standards or Materials [Tavaborole, (b) (4) 64

S.6 Container Closure System [Tavaborole, (b) (4)] 67

S.7 Stability [Tavaborole, (b) (4)] 68

P DRUG PRODUCT [KERYDIN Solution] 77

P.1 Description and Composition of the Drug Product [KERYDIN Solution] 77

P.2 Pharmaceutical Development [KERYDIN Solution] 78

P.3 Manufacture [KERYDIN Solution] 102

P.4 Control of Excipients [KERYDIN Solution] 106

P.5 Control of Drug Product [KERYDIN Solution] 107

P.6 Reference Standards or Materials [KERYDIN Solution] 126
P.7 Container Closure System [KERYDIN Solution] 126
P.8 Stability [KERYDIN Solution] 129
A APPENDICES 137
R REGIONAL INFORMATION 137
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 139
A. Labeling & Package Insert 139
B. Environmental Assessment or Claim of Categorical Exclusion 145
III. List Of Deficiencies To Be Communicated 145
IV. Attachment 147

Chemistry Review Data Sheet

1. NDA 204427

2. REVIEW #: 1

3. REVIEW DATE: 27-JAN-2014

4. REVIEWERS: Gene W. Holbert, Ph.D.
Bogdan Kurtyka, Ph.D.
Nina Ni, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original (SN001)	26-JUL-2013
Amendment (SN004)	19-AUG-2013
Amendment (SN007)	18-NOV-3013
Amendment (SN009)	19-DEC-2013

7. NAME & ADDRESS OF APPLICANT:

Name: Anacor Pharmaceuticals, Inc.
Address: 1020 East Meadow Circle
Palo Alto, CA 94303

Representative: Carmen R. Rodriguez, M.Sc.
Vice President, Regulatory Affairs and Quality
Telephone: Office: (650) 543-7576; Cell: (b) (6)
Facsimile (Fax): (650) 543-7660

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: KERYDIN (pending review)
b) Non-Proprietary Name (USAN): Tavaborole
c) Code Name/# (ONDQA only): AN2690
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 1
- Submission Priority: S

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

10. PHARMACOLOGICAL CATEGORY: Antifungal

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 5%

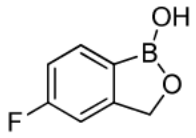
13. ROUTE OF ADMINISTRATION: Topical

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:



Molecular Formula: $C_7H_6BFO_2$ Molecular Weight: 151.93

Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	III	(b) (4)		4	Adequate		LOA: 9/30/2010
	III			4	Adequate		LOA: 3/20/2013
	III			4	Adequate		LOA: 3/20/2013
	III			4	Adequate		LOA: 4/12/2013

[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 (enough data in the application, therefore the DMF did not require review)

B. Other Documents:

Document	Application Number	Description
IND	71,206	Tavaborole
DMF		(b) (4)
DMF		
DMF		
DMF		

18. STATUS:

CONSULTS/CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable	27-DEC-2013	T Sharp
Pharm/Tox	N/A		
Biopharm	N/A		
LNC	N/A		
Methods Validation	In progress per ONDQA Policy	19-SEP-2013	
EA	Categorical exclusion is granted [21 CFR 25.31 (b)]	18-OCT-2013	GW Holbert
Microbiology	Approval	26-NOV-2013	E Pfeiler

The Chemistry Review for NDA 204427

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

The Office of Compliance has issued an overall "***Acceptable"*** recommendation for the facilities involved in the NDA.

Labels/labeling issues have ***not*** yet been resolved.

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

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

N/A

II. Summary of Chemistry Assessments

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

KERYDIN Solution, 5% is an alcohol (b) (4) based clear, colorless solution containing 5% tavaborole (w/w). Ten milliliters of solution is filled into 12-mL, amber USP (b) (4) glass bottles. The closure consists of black (b) (4) caps with (b) (4) foam liners. The product is packaged with a (b) (4) dropper assembly, which is used to apply the product to the affected nail. Each milliliter of solution contains 43.5 mg of tavaborole (the density of the drug product solution is (b) (4)

The dropper assembly consists of a clear glass straight-tip pipette fitted with a rubber squeeze bulb and a black (b) (4) closure. The dropper assembly is packaged in a (b) (4) over-wrap printed with the statement: (b) (4)

In addition to the active ingredient, the drug product contains Alcohol USP, Propylene Glycol USP and Edetate Calcium Disodium USP. The levels of usage of each inactive

ingredient in the final drug product are below those listed in the IIG for the same route of administration.

The manufacturing process for the drug product [redacted]

The proposed drug product specification includes tests and acceptance criteria for the following attributes: description, identity, tavaborole assay, impurities, EDTA assay, packaging integrity, weight loss, minimum fill, and microbiological testing. The proposed specification is supported by data and is acceptable.

KERYDIN solution, 5% is packaged in 12-mL amber USP [redacted] glass bottles and black [redacted] closures with a [redacted] foam liners. Upon first use, the patient is instructed to replace the primary closure ([redacted] closure) with the dropper assembly provided in the carton. The dropper assembly pipette is fabricated from clear USP [redacted] tubing glass. The bulb is [redacted] black [redacted] rubber. Closures are [redacted] a black [redacted]. All components comply with the pertinent 21 CFR regulations for direct food contact. Leachable/extractable studies were conducted on both the primary and in-use container closure systems. The applicant has demonstrated the compatibility, suitability, functionality, and safety of the primary and in-use container closure system with the drug product.

The to-be-marketed formulation is the same as that used in Phase 3 clinical trials and registration stability batches. Stability data submitted include 12 months of long term (25ºC/60% RH) and 6 months of accelerated temperature (40ºC/75% RH) data from four registration stability batches. Additionally, 24 months of long term and 6 months of accelerated temperature stability data were also provided for five supporting stability batches.

Stability data indicate that the drug product is physically and chemically stable with no significant changes observed when stored at 25 ºC for up to 24 months. All tested attributes are within the specification. The stability data support the proposed expiration dating period of 24 months for tavaborole solution when stored at 20-25 ºC (68-77 ºF); excursions permitted to 15-30 ºC (59-86 ºF).

An in-use study appears to support the proposed in-use period of three months for the drug product.

Tavaborole is an antifungal agent. The chemical name is 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole. The chemical formula is $C_7H_6BFO_2$ and the molecular weight is 151.93. Tavaborole is a white to off-white powder, which is slightly soluble in water and freely soluble in ethanol and propylene glycol.

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

KERYDIN Topical Solution is to be applied to affected nails once daily for 48 weeks. The product should be applied to the entire nail surface and under the tip of each nail being treated.

KERYDIN Topical Solution is for topical use only.

C. Basis for Approvability or Not-Approval Recommendation

21 CFR 314.125 (b)(6)

- Label/labeling issues are not resolved.

III. Administrative

A. Reviewer's Signature

Signed electronically in DARRTS
(See appended electronic signature page)

Gene W. Holbert, Ph.D., CMC Reviewer, Branch IV, ONDQA
Bogdan Kurtyka, Ph.D., CMC Reviewer, Branch IV, ONDQA
Nina Ni, Ph. D., CMC Reviewer, Branch IV, ONDQA

B. Endorsement Block

Signed electronically in DARRTS
(See appended electronic signature page)

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

C. CC Block

Entered electronically in DARRTS

Shulin Ding, Ph.D., CMC Lead, Branch IV, ONDQA

139 Page(s) has 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/

GENE W HOLBERT
03/07/2014

BOGDAN KURTYKA
03/07/2014

NINA NI
03/07/2014

MOO JHONG RHEE
03/07/2014
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: Michael Trehy
Suite 1002
1114 Market Street
St. Louis, MO 63101

FROM: Gene W. Holbert, Ph.D., CMC Reviewer
Shulin Ding, Ph.D., CMC Lead
Office of New Drug Quality Assessment (ONDQA)
E-mail Address: gene.holbert@fda.hhs.gov
Phone: (301)-796-1368
Fax: (301)-796-9850

Through: Moo-Jhong Rhee, Ph.D., Branch Chief
Phone: (301)-796-1440

and

Youbang Liu, ONDQA Methods Validation Project Manager
Phone: 301-796-1926

SUBJECT: Methods Validation Request

Application Number: NDA 204427

Name of Product: Tavaborole Topical Solution, 5%

Applicant: Anacor Pharmaceuticals, Inc.

Applicant's Contact Person: Carmen R, Rodriguez, M. Sc.

Address: 1020 East Meadow Circle, Palo Alto, CA 94303-4230

Telephone: (650)-543-7576 Fax: (650)-543-7660

Date NDA Received by CDER: **07/29/2013**

Date of Amendment(s) containing the MVP:

DATE of Request: **09/19/2013**

Requested Completion Date: **02/28/2014**

PDUFA User Fee Goal Date: **07/29/2014**

Submission Classification/Chemical Class: 0 (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 descr bed 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.

ATTACHMENT(S): *Methods Validation Request Sheet*, NDA Methods Validation Package (if not available in the EDR).

MVP Reference #	**METHODS VALIDATION REQUEST**	NDA # 204427

⇒ ITEM 1: SAMPLES AND ANY SPECIAL EQUIPMENT/REAGENTS BEING FORWARDED BY APPLICANT

ITEM	QUANTITY	CONTROL NO. OR OTHER IDENTIFICATION

⇒ 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 Specification
Specifications/Methods for Finished Dosage Form(s)	3.2.P.5.1 Specification
Supporting Data for Accuracy, Specificity, etc.	3.2.S.4.3 and 3.2.P.5.3 Validation of analytical procedures
Applicant's Test Results on NDS and Dosage Forms	3.2.S.4.4 and 3.2.P.5.4 Batch Analyses
Other:	

⇒ 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
[redacted]	Determination of assay and related substances in [redacted] (by HPLC)	3.2.S.4.2	**0 (NME)**	(b) (4) validation: Report RVM-CC-11-098-2 (b) (4) transfer: Report P12889.00 Report [redacted]: NJ.QSP.MV436.0.EN Report [redacted]: HQ.QSR.TM041.1.EN
[redacted]	HPLC Identification, Assay for AN2690, Determination of Related Substances in AN2690 Drug Substance and AN2690 Topical Solution 5% w/w	3.2.P.5.2	**0 (NME)**	Validation protocols: 616.010.002.00 and 616.010.002.01 Validation reports: 69.METH1973.02

Additional Comments: Please also refer to 3.2.R.4 Method Validation Package

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

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

/s/

GENE W HOLBERT
09/19/2013

SHULIN DING
09/19/2013

MOO JHONG RHEE
09/20/2013
Chief Branch IV

YOUBANG LIU
09/20/2013

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre-Marketing Applications (Original)

I. Review Cover Sheet
II. Application Detail
III. Filing Checklist
IV. Manufacturing Summary
V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. DMPQ Reviewer: Christina Capacci-Daniel

2. NDA/BLA Number: NDA 204427
   Submission Date: 29 July 2013
   21st C. Review Goal Date:
   PDUFA Goal Date: 29 July 2014

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	
Established or Non-Proprietary Name (USAN) and strength:	Tavaborole, 5% Topical Solution
Dosage Form:	Topical solution (non-sterile)

4. SUBMISSION PROPERTIES:

Review Priority :	STANDARD
Applicant Name:	Anacor Pharmaceuticals Inc.
Responsible Organization (OND Division):	DDDP

II. Application Detail

1. INDICATION: Treatment of onychomycosis (b) (4)
2. ROUTE OF ADMINISTRATION: Topical to nail bed
3. STRENGTH/POTENCY: 5% topical solution
4. Rx/OTC DISPENSED: ☒Rx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? **YES**
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	☑			NME reviewed under "The Program"
2.	Breakthrough Therapy Designation		☑		
3.	Orphan Drug Designation		☑		
4.	Unapproved New Drug		☑		
5.	Medically Necessary Determination		☑		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		☑		
7.	Rolling Submission		☑		
8.	Drug/device combination product with consult		☑		
9.	Complex manufacturing		☑		
10.	Other (e.g., expedited for an unlisted reason)		☑		

III. FILING CHECKLIST

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

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	**Yes**	**No**	**Comment**
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	☑		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	☑		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	☑		
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	☑		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #? 2. Do comments in EES indicate a request to participate on inspection(s)? 3. Is this first application by the applicant?	☑		
			☑	No requests to participate in inspection at this time.
		☑		First application from Anacor Pharmaceuticals, Palo Alto, CA

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	**Yes**	**No**	**Comment**
16.	Have any Comparability Protocols been requested?		☑	

IMA CONCLUSION				
	Parameter	**Yes**	**No**	**Comment**
17.	Does this application fit one of the EES Product Specific Categories?	☑		• First application for sponsor Anacor Pharmaceuticals
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?	☑		• EER's match listing in 356h • EER's currently being processed
19.	**From a CGMP/facilities perspective, is the application fileable?** If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	☑		

5 Page have been Withheld in Full as b4 (CCI/TS) immediately following this page

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no) **YES**
Based on Section IV, is a KTM warranted for any PAI? (yes/no). NO
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no)
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL
(DARRTS)

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

/s/

CHRISTINA A CAPACCI-DANIEL
09/06/2013

DON L HENRY
09/06/2013

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

OND Division:	Division of Dermatology and Dental Products
NDA:	204-427
Applicant:	Anacor Pharmaceuticals Inc.
Stamp Date:	July 29, 2013
PDUFA Date	July 29, 2014
Trademark:	To be Proposed
Established Name:	Tavaborole
Dosage Form:	Solution
Route of Administration:	Topical
Indication:	Treatment of onychomycosis (b) (4)
CMC Lead:	Shulin Ding

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

Summary and Critical Issues:

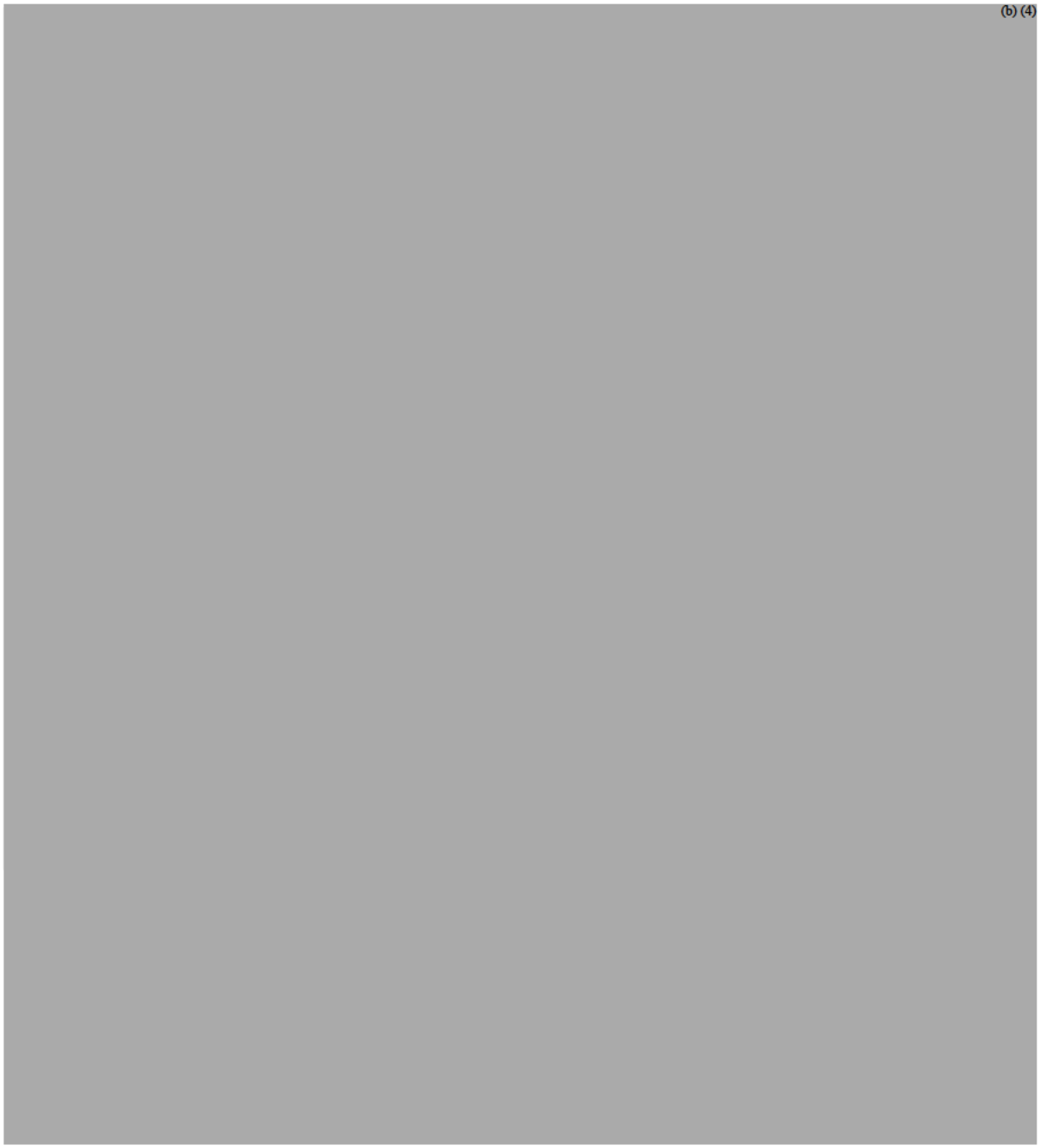
A. Summary

Anacor Pharmaceuticals has submitted a 505(b)(1) New Drug Application (NDA) for the prescription use of Tradename (tavaborole) topical solution, 5% for the topical treatment of onychomycosis due to dermatophytes. The NDA is subject to PDUFA V because tavaborole is a new molecular entity.

Complete CMC information is provided in the NDA for the proposed drug substance. Tavaborole is a slightly water soluble, (b) (4). It is a (b) (4) The commercial batches of tavaborole drug substance will be produced by (b) (4) The production scale is (b) (4) The manufacturing process consists of (b) (4) igure 1 depicts the (b) (4) schematic (b) (4).

Up to 12 month of long term and 6 months of accelerated stability data are provided from 7 primary batches (b) (4) to support a proposed (b) (4) month retest date at 20°-25°C; excursion permitted between 15°-30°C. The data package includes 3 month of stability data from one production scale batch produced by the designated commercial site, (b) (4) (b) (4) The proposed packaging for drug substance is (b) (4)

Figure 1: [redacted] **Schematic for the Tavaborole Production Process**



The proposed drug product is a clear, colorless solution packaged in an amber USP [redacted] glass bottle with a black [redacted] screw cap at a fill size of 10 mL. The cap is [redacted] foam liner. The proposed product is co-packaged with a dropper assembly consisting of a clear USP [redacted] glass straight-tip pipette, a rubber squeeze bulb and a black [redacted] closure. At the time of administration the [redacted] screw cap is replaced with the dropper assembly, and the product is applied to the nail surface using the glass dropper. The proposed formulation is shown in the table on the next page. All excipients are compendial

grade, and no excipients are of human/animal origin. The formulation contains no novel excipients.

The formulation of the proposed product [redacted] propylene glycol, alcohol, edentate calcium disodium (EDTA), and tavaborole [redacted]

The to-be-marketed formulation is the same formulation used in Phase 3 clinical trials and registration stability batches. 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) include12 months of long term (25°C/60%RH), and 6 months of accelerated temperature (40°C/75%RH) from 3 registration stability batches for both upright and inverted orientations. The batch size of the registration stability batches is [redacted] which is approximately [redacted] of the production scale [redacted]

Special stability studies such as in-use stability, photostability, freeze/thaw cycling, and vacuum leak studies are also included in the NDA to support storage/handling of the drug product. A three month in-use shelf-life is proposed for the product based on the in-use stability study results.

Table 1: Composition of Tavaborole Topical Solution, 5%

Components	Quality Standard	Function	Concentration (% w/w)
Tavaborole	In-house	Active	5.00
Alcohol	USP	[redacted]	
Propylene Glycol	USP		
Edetate Calcium Disodium	USP		

B. Critical Issues for review

Drug Substance

1. Impurity Profile comparison
   [redacted]

2. Process Equivalence
   Although there are 7 primary stability batches, only one batch with 3 months of stability data is available from the designated commercial site, [redacted] The other six batches were made by two different manufacturers [redacted] Demonstration of process equivalence among the three sites is therefore

important in order to rely on data from the other two sites for shelf-life projection and specification setting of commercial batches.

3. Light Sensitivity
Different impressions are given by drug substance and drug product sections concerning the impact of light on the stability. (b) (4) . CMC reviewers of drug substance and drug product should work together to give a fair assessment regarding light effect.

Drug Product

1. Product Leakage
The applicant provided leakage information for Phase 3 clinical and registration stability batches as requested by the Agency in the pre-NDA meeting. The leakage information and weight loss study results need to be critically reviewed.

2. Extractables/Leachables
Extractables studies were conducted on the primary and in-use container closure system components. Additionally, a leachable study was conducted on the in-use container closure system (b) (4) The applicant concluded that the amount of extractables and leachables would not post a safety risk, and thus no controls on leachables are proposed. The studies and applicant's conclusion should be critically reviewed since the formulation contains (b) (4)

3. Microbiological Attributes
The applicant proposes no antimicrobial effectiveness testing, and a release-only microbial limit test (MLT) for the drug product. The applicant also proposes to (b) (4) A critical review needs to be performed on the proposals.

C. Comments for 74-Day Letter:

1. Submit a representative sample for the evaluation of dosage form. The sample should be accompanied with corresponding certificate of (b) (4)

2. Submit quantitative analytical data for (b) (4) in tavaborole drug substance to support the presence of (b) (4) tavaborole.

3. Submit a ^{19}F NMR spectrum of the drug substance to support structure elucidation.

4. Submit suppliers' certificates of analysis for the starting material, reagents and solvents used in the manufacture of tavaborole drug substance.

5. The mass spectra submitted in section 3.2.S.3.1 Elucidation of Structure and section 3.2.S.5 Reference Standards do not correspond. Explain the differences and provide details of the experimental conditions under which each spectrum was obtained.

6. (b) (4) (b) (4) f a drug product release specification includes tests and acceptance criteria for a given attribute, then the test must be performed on every batch. However, due to the nature of your product and microbiological data that you have provided in your application, you may waive microbial limits testing for product release. If you choose to omit microbial limits testing for release, then remove the microbial limits tests and acceptance criteria from the drug product release specification. Alternatively, you may retain a microbial limits specification for product release, but testing must be performed on every lot of drug product produced. Please submit a revised drug product release specification for whichever microbial limits testing alternative that you select.

7. You describe microbial limits testing performed according to methods described in USP <61> and USP <62>. Verify the suitability of these testing methods for your drug product.

D. Comments/Recommendation:

The application is acceptable for filing from CMC perspective.

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

This NDA is selected for ONDQA pilot programs of Integrated Team Review and Question-based review. CMC reviewers assigned to this NDA are Gene Holbert. (drug substance and also primary reviewer), Nina Ni (drug product), and Bogdan Kurtyka (manufacturing processes of drug substance and drug product). Compliance reviewer is Christina Capacci-Daniel. Microbiology reviewer is Erika Pfeiler.

Shulin Ding, Ph.D.
CMC Lead

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

NDA Number:	Supplement Number and Type:	Established/Proper Name:
204427	0000	Tavaborole topical solution, 5%
Applicant: Anacor	Letter Date: July 26, 2013	Stamp Date: July 29, 2013

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		Section 3.2.S.2.2 could not be opened in the initial submission, but the replacement has been submitted in the amendment dated Aug. 19, 2013.
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		
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		

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		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	x		Provided in Module 1.

* 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		Categorical exclusion is claimed on the basis of EIC below 1 ppb.

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		Section 3.2.S.2.2 has been resubmitted upon request. It could not be opened in the initial submission.
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	x		
14.	Does the section contain information regarding the characterization of the DS?	x		
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		.
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		

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III	(b) (4)		9/13/2010	
	III			3/20/2013	
	III			3/20/2013	
	III			4/12/2013	

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 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
09/05/2013

MOO JHONG RHEE
09/05/2013
Chief, Branch IV