

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**201635Orig1s000**

**CHEMISTRY REVIEW(S)**

MEMORANDUM

**To:** NDA 201-635  
**From:** Thomas M. Wong, Ph.D., Chemist  
**Date:** April 3, 2013  
**Drug:** Trokendi XR (topiramate) extended release capsule  
**Route of administration:** Oral  
**Strength:** 25mg, 50 mg, 100 mg and 200 mg  
**Subject:** "Approval" recommendation for NDA 201-635

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This memorandum updates the status of the CMC review. Based on the information summarized below, ONDQA recommends an Approval for NDA 201-635.

On June 25, 2012, ONDQA recommended a Tentative Approval for NDA 201-635. Since then two amendments were submitted. The information provided in the amendment was re-submission of commercial blister package and additional stability data. Both amendments have been reviewed and the following conclusions were drawn:

- The commercial blister package information is sufficient and adequate.
- The additional stability data support the new proposed expiry dating of 30 months for all capsule strengths in both commercial bottle and blister packages.

In addition, the following are the updates since the last review/ memorandum dated June 25, 2012:

EES: On March 15, 2013, the Office of Compliance provided an overall Acceptable recommendation for the manufacturing sites.

DMF: DMF updates were reviewed and are found adequate.

Amendment review:

Commercial blister package:

All CMC related information for the proposed commercial packaging configurations, bottle and blister, in the original submission were reviewed and were found satisfactory. For other reasons, only bottle packaging configuration was approved. Since then, the information on the commercial blister packaging was submitted via an amendment. The following is the review summary of this amendment:

- The blister materials for the capsule remain the same as in the original submission.
- The thickness of aluminum foil backing material has been changed from (b) (4). The applicant provided oxygen transition rate (OTR) and water vapor transition rate (WVTR) on the original and the new aluminum foil backing material and there are no differences in both rates found. No capsule stability was conducted on the new foil backing material. This is not a concern since there are no differences in both OTR and WVTR between the two foil backing materials and there is only (b) (4) difference in thickness. It is not expected to have any issue in both chemical and physical stability for all potency capsules.

- (b) (4)

- The secondary packaging of the commercial blister cards now contains 2 X 7-count blister packs and 2 X 8-count blister packs (b) (4)

Additional stability data:

The applicant submitted additional 18, 24 and 30 months stability data at 25°C/60% RH storage conditions on all capsules strengths at both bottle and blister packages. All results were within specifications and no trend in assay, (b) (4) and degradation products was observed. The data supports the new proposed expiry dating of 30 months.

The post-approval stability monitoring commitment has been revised to contain the 30 month testing time point. The revised post-approval stability protocols were submitted in Amendment #0030 dated March 28, 2013.

CMC Recommendation:

The application is recommended for “Approval” from CMC perspective. Attached is the final EES summary report.

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/s/  
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THOMAS M WONG  
04/03/2013

RAMESH K SOOD  
04/03/2013

## MEMORANDUM

**To:** NDA 201-635

**From:** Thomas M. Wong, Ph.D., Chemist, ONDQA  
Martha R. Heimann, Ph.D., CMC Lead, ONDQA

**Through:** Richard Lostritto, Ph.D, Acting Deputy Director for Science and Policy and Acting Biopharmaceutics Lead

**Date:** June 25, 2012

**Drug:** Trokendi XR (topiramate) extended release capsule

**Strength:** 25mg, 50 mg, 100 mg and 200 mg

**Subject:** ONDQA “**Tentative Approval**” recommendation for NDA 201-635

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The CMC review for this NDA dated May 7, 2012 (Dr. Wong) identified pending Compliance and Biopharmaceutics issues that could impact the approvability of the application. The outstanding issues included the final overall recommendation from EES on the manufacturing sites, the acceptance of dissolution specification, and a waiver request on conducting bioequivalence study of the 25 mg capsule. This memorandum updates the status of the CMC review. Based on the information summarized below, ONDQA recommends that a tentative approval letter be issued for NDA 201635.

EES: On June 12, 2012, the Office of Compliance provided the attached overall Acceptable recommendation for the manufacturing sites. However, the recommendation has been withdrawn from EES and CDER Office of Compliance recommends that the following language be included in the tentative approval letter:

“This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.”

Waiver request: The waiver request on conducting bioequivalence study of the 25 mg capsule is accepted by Dr. Selen, the Biopharmaceutics reviewer.

Dissolution specification: Dr. Selen also recommended that the acceptance criterion of (b) (4) for the dissolution at (b) (4) be revised to 6 hours (Refer to the Biopharmaceutics review authored by Dr. Arzu Selen dated June 06, 2012, for detail).

On June 8, 2012 the applicant proposed establishment of the 6 hour time point in an interim basis, pending additional data to be obtained from commercial scale validation batches. The following additional requests on dissolution specification were sent out to the applicant on June 14:

1. To collect additional dissolution profile data for the commercial validation batches (each strength) manufactured during the first year after the action date, targeting more appropriate acceptance criteria in alignment with the FDA standards described in IVIVC-Guidance Section B-1 (Setting Dissolution Specifications without an IVIVC).
2. To use the additional dissolution data generated from the commercial validation batches for the setting of the final acceptance criteria.
3. To submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches which are based on and reflective of the data discussed herein.

On June 19, 2012, a teleconference was conducted between the CMC/Biopharmaceutics review team and the applicant. In addition to the above requests to the applicant, the followings were conveyed to the applicant in the teleconference (see Memorandum of Telecon authored by Teshara G Bouie dated 6/21 in DARRTS):

- The Agency advised the applicant to target a narrower range at the 3 hour time point.
- For the 3 hour specification-time point, the applicant was advised to target mean (b) (4) for the collection of the dissolution data. Specifically, if L1 (n=6) fails the (b) (4) specification range, proceed to L2 (n=12) testing, then to L3 (n= 24) if necessary.

The applicant agreed to comply with all the requests and advices. In addition, the applicant also agrees that the following acceptance criteria at 1 hour, 3 hours, and 6 hours are interim acceptance criteria for a period of 1 year from the action date for this NDA.

On June 21, the revised capsule specification table for each of the four strengths capsule reflecting the interim dissolution acceptance criteria was received via e-mail from the applicant.

| Method  | Dissolution Acceptance Criteria* for Trokendi XR capsules |         |        |
|---|---|---------|--------|
|   | 25-mg and 50 mg   | 100-mg  | 200 mg |
| USP <711> Apparatus 2, 50rpm, 750mL, 50mM phosphate buffer, pH 7.5, HPLC/RI | 1 hr:   | 1 hr:   | 1 hr:  |
|   | (b) (4)   |         |        |
|   | 3 hr:   | 3 hr:   | 3 hr:  |
|   | (b) (4)   |         |        |
| 6 hr:   | 6 hr:   | 6 hr:   |        |
| (b) (4)   | (b) (4)   | (b) (4) |        |

\* Report interim dissolution results at 1, 3, and 6 hours. Acceptance criteria for dissolution follow the current USP section <711> including level L2 and L3 testing, where applicable. Dissolution testing may continue for collection of the (b) (4) samples. Per discussion with FDA, the interim dissolution acceptance criteria for all time points (1, 3 and 6 hrs) are established for a period of 1 year from the action date for NDA 201-635; final dissolution acceptance criteria will be proposed after collection and evaluation of data from the product batches manufactured during these 12 months.

As agreed upon by both the Agency and the applicant at the teleconference, a formal submission to the NDA with the updated capsule specification reflecting the interim dissolution acceptance criteria was received on June 25, 2012

Post Approval Agreements:

The applicant will submit a prior approval supplement to the NDA within 14 months from the action date, including a proposal for the final acceptance criteria and the supportive dissolution data (each strength) from the commercial validation batches.

(b) (4)

APPEARS THIS WAY ON ORIGINAL.

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

|                       |                |   |  |
|-----------------------|----------------|---|--|
| <b>Application:</b>   | NDA 201635/000 | <b>Sponsor:</b>   | SUPERNUS PHARMS  |
| <b>Org. Code:</b>     | 120            |   | 1550 EAST GUDE DR  |
| <b>Priority:</b>      | 3              |   | ROCKVILLE, MD 20850  |
| <b>Stamp Date:</b>    | 14-JAN-2011    | <b>Brand Name:</b>  | Topiramate CR Capsules   |
| <b>PDUFA Date:</b>    | 09-JUL-2012    | <b>Estab. Name:</b>                                       |  |
| <b>Action Goal:</b>   |                | <b>Generic Name:</b>                                      |  |
| <b>District Goal:</b> | 10-MAY-2012    | <b>Product Number; Dosage Form; Ingredient; Strengths</b> |  |
|                       |                |   | 001; CAPSULE, EXTENDED RELEASE; TOPIRAMATE; 25MG<br>002; CAPSULE, EXTENDED RELEASE; TOPIRAMATE; 50MG<br>003; CAPSULE, EXTENDED RELEASE; TOPIRAMATE; 100MG<br>004; CAPSULE, EXTENDED RELEASE; TOPIRAMATE; 200MG |
| <b>FDA Contacts:</b>  | T. BOUIE       | <b>Project Manager</b>                                    | 3017961649   |
|                       | T. WONG        | <b>Review Chemist</b>                                     | (HFD-810) 3017961608   |
|                       | M. HEIMANN     | <b>Team Leader</b>  | 3017961678   |

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|                                |            |                |              |           |            |
|--------------------------------|------------|----------------|--------------|-----------|------------|
| <b>Overall Recommendation:</b> | ACCEPTABLE | on 12-JUN-2012 | by A. INYARD | (HFD-323) | 3017965363 |
|                                | PENDING    | on 07-NOV-2011 | by EES_PROD  |           |            |
|                                | WITHHOLD   | on 07-NOV-2011 | by EES_PROD  |           |            |
|                                | PENDING    | on 13-SEP-2011 | by EES_PROD  |           |            |
|                                | PENDING    | on 13-SEP-2011 | by EES_PROD  |           |            |
|                                | PENDING    | on 13-SEP-2011 | by EES_PROD  |           |            |
|                                | PENDING    | on 13-SEP-2011 | by EES_PROD  |           |            |
|                                | PENDING    | on 13-SEP-2011 | by EES_PROD  |           |            |

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|                          |                             |         |      |         |              |
|--------------------------|-----------------------------|---------|------|---------|--------------|
| <b>Establishment:</b>    | CFN:                        | (b) (4) | FEI: | (b) (4) | (b) (4)      |
| <b>DMF No:</b>           |                             |         |      |         | <b>AADA:</b> |
| <b>Responsibilities:</b> | DRUG SUBSTANCE OTHER TESTER |         |      |         |              |
| <b>Profile:</b>          | CONTROL TESTING LABORATORY  |         |      |         |              |
| <b>Last Milestone:</b>   | OC RECOMMENDATION           |         |      |         |              |
| <b>Milestone Date:</b>   | 12-JUN-2012                 |         |      |         |              |
| <b>Decision:</b>         | ACCEPTABLE                  |         |      |         |              |
| <b>Reason:</b>           | DISTRICT RECOMMENDATION     |         |      |         |              |

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

**Establishment:** CFN: 1528607 FEI: 1000122400  
CATALENT PHARMA SOLUTIONS LLC

**DMF No:** WINCHESTER, , UNITED STATES 403919668 **AADA:**

**Responsibilities:** DRUG SUBSTANCE OTHER TESTER  
FINISHED DOSAGE MANUFACTURER

**Profile:** CAPSULES EXTENDED RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 10-FEB-2012

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

---

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

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** FINISHED DOSAGE LABELER  
FINISHED DOSAGE PACKAGER

**Profile:** CAPSULES EXTENDED RELEASE **OAI Status:** NONE

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 15-SEP-2011

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE

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

**DMF No:** (b) (4) **AADA:**

**Responsibilities:** (b) (4)

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

**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 31-MAY-2012

**Decision:** ACCEPTABLE

**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: (b) (4)  
 Profile: OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 12-JUN-2012  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

Establishment: CFN: 9710438 FEI: 3002840477  
 SCINOPHARM TAIWAN LTD  
 NO 1 NAN-KE 8TH ROAD  
 TAINAN, HSIEN, , TAIWAN, PROVINCE OF CHINA  
 17035  
 DMF No: AADA:  
 Responsibilities: DRUG SUBSTANCE MANUFACTURER  
 Profile: (b) (4) OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 23-SEP-2011  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

Establishment: CFN: FEI: 3005209462  
 SUPERNUS PHARMACEUTICALS INC  
 ROCKVILLE, , UNITED STATES 208501339  
 DMF No: AADA:  
 Responsibilities: DRUG SUBSTANCE OTHER TESTER  
 FINISHED DOSAGE RELEASE TESTER  
 Profile: CONTROL TESTING LABORATORY OAI Status: NONE  
 Last Milestone: OC RECOMMENDATION  
 Milestone Date: 20-SEP-2011  
 Decision: ACCEPTABLE  
 Reason: DISTRICT RECOMMENDATION

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/s/  
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MARTHA R HEIMANN

06/25/2012

Signed for Thomas Wong and myself

RICHARD T LOSTRITTO

06/25/2012

# **NDA 201-635**

**Trokendi XR<sup>TM</sup> (Topiramate Extended-Release) Capsules**

**Supernus Pharmaceuticals, Inc.**

**Thomas M. Wong, Ph.D.**

**Division of New Drug Quality Assessment I**

**Office of New Drug Quality Assessment**

**Division of Neurology Drug Products**

**Review of Chemistry, Manufacturing, and Controls**

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## Chemistry Review Data Sheet NDA 201-635

**Chemistry Review Data Sheet**

1. NDA 201-635

2. REVIEW #: 1

3. REVIEW DATE: May 7, 2012

4. REVIEWER: Thomas M. Wong, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 101,670

Document Date

Commercial IND

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Re-submission

Submission # S0008

Submission # S0013

Submission # S0017

Submission # S0018

Document Date

9-Sep-2011

9-Dec-2011

3-Feb-2012

26-Apr-2012

2-May-2012

7. NAME &amp; ADDRESS OF APPLICANT:

Name: Supernus Pharmaceuticals, Inc.

Address: 1550 East Gude Drive  
Rockville, MD 20850

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Trokendi XR

b) Non-Proprietary Name: Topiramate

c) Code Name/#: SPN-538T

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3

## Chemistry Review Data Sheet NDA 201-635

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b)(2)

10. PHARMACOL. CATEGORY: Antiepileptic

11. DOSAGE FORM: Extended release capsule

12. STRENGTH/POTENCY: 25 mg, 50 mg, 100 mg, and 200 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED:  X  Rx   OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X  Not a SPOTS product

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

**USAN Name:** Topiramate

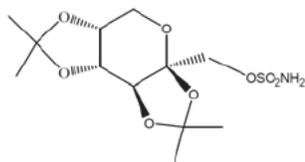
**CAS Name:** 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate

**CAS registry #:** 97240-79-4

**Molecular weight:** 339.4

**Molecular formula:** C<sub>12</sub>H<sub>21</sub>NO<sub>8</sub>S

**Structure:**



Chemistry Review Data Sheet NDA 201-635

17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF #   | TYPE | HOLDER                 | ITEM REFERENCED | CODE <sup>1</sup> | STATUS <sup>2</sup> | DATE REVIEW COMPLETED | COMMENTS                     |
|---------|------|------------------------|-----------------|-------------------|---------------------|-----------------------|------------------------------|
| 17035   | II   | ScinoPharm Taiwan, Ltd | Drug substance  | 1                 | Adequate            | February 8, 2012      | Reviewed by Thomas Wong      |
| (b) (4) | II   | (b) (4)                | (b) (4)         | 7                 |                     |                       | DMF not reviewed (excipient) |
| (b) (4) | IV   | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | IV   | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | IV   | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | IV   | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |
| (b) (4) | III  | (b) (4)                | (b) (4)         | 4                 |                     |                       |                              |

<sup>1</sup> Action codes for DMF Table:

Chemistry Review Data Sheet NDA 201-635

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")

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

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|----------|--------------------|-------------|
|          |                    |             |

18. STATUS:

**ONDC:**

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION                   | DATE               | REVIEWER              |
|-------------------------------|----------------------------------|--------------------|-----------------------|
| Biometrics                    | N/A                              |                    |                       |
| EES                           | Pending                          |                    | Office of Compliance  |
| Pharm/Tox                     | N/A                              |                    |                       |
| Biopharm                      | Pending                          |                    | Dr. Arzu Selen        |
| LNC                           | N/A                              |                    |                       |
| Methods Validation            | N/A                              |                    |                       |
| DMFPA                         | N/A                              |                    |                       |
| EA                            | Acceptable/categorical exclusion | As per this review | Thomas M. Wong, Ph.D. |
| Microbiology                  | N/A                              |                    |                       |

## Executive Summary Section

## The Chemistry Review for NDA 201-635

The Executive Summary**I. Recommendations****A. Recommendation and Conclusion on Approvability**

The final CMC recommendation on the NDA 201-635 for topiramate extended release capsule, 25 mg, 50 mg, 100 mg and 200 mg will depend on the resolution of the following issues:

- The Office of Compliance has not issued a final overall recommendation regarding the cGMP inspections.
- Awaiting Biopharmaceutics reviewer on the acceptance of dissolution specification and waiver request on conducting bioequivalence study of the 25 mg capsule.

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

None at this time.

**II. Summary of Chemistry Assessments****A. Description of the Drug Product(s) and Drug Substance(s)****Introduction**

Topiramate is currently marketed by several manufacturers in tablet and capsule dosage forms with strengths range from 25 mg to 200 mg. All topiramate marketed products are immediate release dosage forms and the usual dosing regimen is twice daily. The current NDA is submitted as a 505(b)(2) application. The applicant developed 25 mg, 50 mg, 100 mg and 200 mg strength extended release capsules for once daily dose for the treatment of partial onset or primary generalized tonic-clonic seizures and in patients <sup>(b) (4)</sup> with seizures associated with Lennox-Gastaut syndrome. The applicant's primary objective for development of the extended release capsules is to deliver topiramate to the patient at a sustained rate to allow for once-a-day administration.

**Drug Substance**

The drug substance, topiramate, is a sulfamate-substituted monosaccharide and possess an anticonvulsant effects. Chemically, topiramate is 2,3:4,5-Di-O-isopropylidene-β-D-fructopyranose sulfamate. It is a white to off-white powder and is soluble in water. Topiramate is a D-form isomer with four chiral centers in the molecule and no polymorphs have been identified. The drug substance is manufactured by ScinoPharm Taiwan, Ltd. Supernus proposed specification for topiramate included all test items listed in the current USP monograph for topiramate. In addition, the proposed specification also includes testing and control for particle size, residual solvents and melting range. The applicant refers to DMF 17,035 for detailed information on the drug substance. Detailed information in DMF #17,035 has been reviewed

## Executive Summary Section

previously by Latiff A Hussain on Dec 23, 2009 and all subsequent submissions by Thomas M Wong on February 13, 2012 (Review #6) and the current status of this DMF is adequate.

**Drug Product**

The proposed product is an extended release capsule available in 25 mg, 50 mg, 100 mg or 200 mg strengths. It is intended for once daily dose as monotherapy and adjunctive therapy for epilepsy. The drug products are size # 2, 0, 00, and 00 hard gelatin capsules for the strength of 25 mg, 50 mg, 100 mg and 200 mg, respectively; and the color of the capsule for each strength is different. Adequate information on the components and compositions of these capsules is provided. Each capsule contains three different pellets, one immediate release pellet and two different types of extended release pellets. Most of the excipients in the formulation are common, compendial grades, and are widely used in the pharmaceutical industry. All non-compendial grade materials contain compendial grade components. The manufacturing (b) (4)

(b) (4)  
One of the specified immediate release intermediate pellet types and the two of the specified extended release pellet types are filled into different sizes and color capsule shells to produce the corresponding strengths of the extended release topiramate capsules. Critical process parameters at the appropriate steps of the manufacturing process have been identified, and appropriate acceptance criteria for the critical process parameters have been implemented. The drug product specification includes test and acceptable limits for appearance, identification (UPLC/MS/MS and HPLC/RI), assay (HPLC), uniformity of dosage units (HPLC), related substances (HPLC), (b) (4) content (UPLC/MS) and dissolution. All analytical methods have been adequately validated.

The capsule products are packaged in HDPE bottles with 100 counts per bottle and (b) (4) blister with aluminum foil backing in 30-count commercial (b) (4) blister packaging configurations.

The (b) (4) expiry dating when packaged into the commercial packaging configurations and stored at room temperature of 25°C (77 °F); excursions 15 - 30°C (59 - 86°F) is based on the stability data of the registration batches on 12 months at long-term storage and 6 months at accelerated storage conditions. In case the Biopharmaceutics reviewer does not accept the dissolution specification, the (b) (4) expiry dating will be re-evaluated.

**Additional Items**

DMFs: All associated Drug Master Files are acceptable or the pertinent information has been adequately provided in the application.

Methods Validation: The analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the pharmaceutical industry; revalidation by Agency laboratories will not be requested.

EES: As of May 7, 2012, the Office of Compliance has not yet provided an overall acceptable recommendation for the manufacturing sites.

Post-Approval Agreements: None.

## Executive Summary Section

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

The applicant developed topiramate extended release capsules in four strengths: 25 mg, 50 mg, 100 mg and 200 mg. The trade name is Trokendi XR™. Topiramate is a sulfamate-substituted monosaccharide and possess an anticonvulsant effects and the product is intended for once daily dose for the treatment of tonic-clonic seizures.

**C. Basis for Approvability or Not-Approval Recommendation**

From a CMC perspective, Supernus Pharmaceuticals, Inc. has submitted sufficient and appropriate information to support the approval of the drug products, Topiramate Extended-Release Capsules. However, the final CMC recommendation on this NDA will depend on the resolution of the issues mentioned in the Recommendation and Conclusion on Approvability section of this review.

**III. Administrative****A. Reviewer's Signature**

See DARRTS

**B. Endorsement Block**

See DARRTS

**C. CC Block**

See DARRTS

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS M WONG  
05/07/2012

RAMESH K SOOD  
05/07/2012

Initial Quality Assessment  
Branch 1  
Division of New Drug Quality Assessment 1

**OND Division:** Division of Neurology Products  
**NDA:** 201-635  
**Applicant:** Supernus Pharmaceuticals, Inc.  
**Stamp Date:** 14-Jan-2011  
**PDUFA Date:** 14-Nov-2011  
**Trademark:** TBD  
**Established Name:** Topiramate  
**Dosage Form:** Extended release tablet  
**Route of Administration:** Oral  
**Indication:** Antiepileptic  
  
**CMC Lead:** Martha R. Heimann, Ph.D.

|                                   | Yes                                 | No                                  |
|-----------------------------------|-------------------------------------|-------------------------------------|
| <b>ONDQA Fileability:</b>         | <input type="checkbox"/>            | <input checked="" type="checkbox"/> |
| <b>Comments for 74-Day Letter</b> | <input checked="" type="checkbox"/> | <input type="checkbox"/>            |

## Summary and Critical Issues:

### Summary

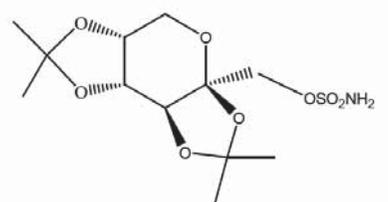
Topiramate was originally developed by Ortho McNeil/Janssen Pharmaceuticals (Ortho) for treatment of epilepsy. The innovator product, Topamax® (topiramate) Tablets was approved under NDA 20-505 in 1996. Currently Ortho markets Topamax® Tablets 25 mg, 50 mg, 100 mg, and 200 mg for treatment of epilepsy and prophylaxis of migraine. Ortho also markets Topamax® (topiramate) Sprinkle Capsules 15 mg and 25 mg for the same indications.

Supernus Pharmaceuticals has developed an extended release (XR) capsule formulation of topiramate. In the current NDA, the firm proposes marketing topiramate XR capsules for adjunctive therapy of epilepsy in patients [REDACTED]<sup>(b) (4)</sup> and for monotherapy of epilepsy in patients 10 years of age and older. Four strengths are proposed, 25 mg, 50 mg, 100 mg and 200 mg. The recommended dose for adjunctive therapy is 200 mg/day to 400 mg/day in adults and 5-9 mg/kg/day in pediatric patients [REDACTED]<sup>(b) (4)</sup>. The recommended dose for monotherapy is 400 mg/day. The firm is not seeking an indication for migraine prophylaxis, which is still protected by the innovator's patent.

### Drug Substance

The active ingredient, topiramate (chemical name: 2,3:4,5-Di-*O*-isopropylidene-β-D-fructopyranose sulfamate), is a well characterized small molecule with molecular formula C<sub>12</sub>H<sub>21</sub>NO<sub>8</sub>S and molecular weight 339.4.

The chemical structure of topiramate is:



Topiramate is a D-form isomer with four chiral centers (carbon numbers 2, 3, 4 and 5 of the fructopyranose ring).

The bulk drug substance is manufactured by Scino Pharm under DMF 17035, which is cross-referenced for CMC information. The DMF has been reviewed previously and found adequate (L. Hussein, 23-Dec-2009). The DMF however, has been updated since the last review.

Limited manufacturing and control information is provided in the NDA itself. A brief outline of the drug substance manufacturing process is provided in Module 3.2.S.2.2 and reproduced below.

(b) (4)

The Supernus specification for topiramate [applicant's **Table 1: Topiramate Proposed Specifications (Supernus)**] is based on the USP monograph with the addition of particle size and residual solvent testing. Neither the particle size method nor the GC method for residual solvents is described in the application; however, a validation report for particle size analysis is provided. Reference is made to the current USP and the manufacturer's DMF. The sponsor will be asked to submit all noncompendial test methods to the NDA.

**Table 1: Topiramate Proposed Specifications (Supernus)**

| Test                            | Method Type                           | Acceptance Criteria        |
|---------------------------------|---------------------------------------|----------------------------|
| Appearance                      | Visual Inspection                     | White to off-white powder. |
| Identification A                | FTIR,<br>USP<197K>                    | (b) (4)                    |
| Identification B                | HPLC/RI,<br>USP Monograph             |                            |
| Assay<br>(anhydrous basis)      | HPLC/RI,<br>USP Monograph             |                            |
| Related<br>Compounds by<br>HPLC | HPLC/RI,<br>USP Monograph<br>(Test 1) |                            |
| Particle Size                   | Laser diffraction                     |                            |

| Test                | Method Type          | Acceptance Criteria |
|---------------------|----------------------|---------------------|
| Residual Solvents   | GC*                  | (b) (4)             |
| Water Content       | USP<921> Method I    |                     |
| Heavy Metals        | USP<231> Method II   |                     |
| Residue on Ignition | USP<281>             |                     |
| Specific Rotation   | USP<781S>            |                     |
| (b) (4)             | IC,<br>USP Monograph |                     |

\*Testing will be conducted per vendor qualification program

Drug Product

Reviewer note: The application includes separate P2 sections for each capsule strength.

Description and Composition

The proposed dosage form is an extended release capsule containing 25 mg, 50 mg, 100 mg or 200 mg of topiramate. The capsule presentations are as follows:

- 25 mg      Size 2 hard gelatin capsule, light green opaque body, yellow opaque cap, imprinted with black ink (imprint not specified)
- 50 mg      Size 0 hard gelatin capsule, light green opaque body, orange opaque cap, imprinted with black ink (imprint not specified)
- 100 mg     Size 00 hard gelatin capsule, green opaque body, blue opaque cap, imprinted with black ink (imprint not specified)
- 200 mg     Size 00 hard gelatin capsule, pink opaque body, blue opaque cap, imprinted with black ink (imprint not specified)

The capsule formulations are a complex composite of immediate release (IR) and XR pellets.



Theoretical capsule composition for "registration scale" 200 mg topiramate extended release capsules are summarized in **3.2.P.1.2: Composition of the Drug Product [Topiramate Extended-Release Capsules, 200mg]**, which is reproduced in its entirety below. Similar information is provided for the 25 mg, 50 mg and 100 mg strengths. [Highlight added by reviewer.]

**3.2.P.1.2      Composition of the Drug Product [Topiramate Extended-Release Capsules, 200mg]**

The composition of registration scale topiramate extended-release capsules, 200mg is provided in Table 1. The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches.

**Table 1:              Composition of Registration Scale Topiramate Extended-Release Capsules, 200mg**

| Component                             | Reference to Quality Standard             | Function       | 200mg Capsules (mg/capsule) |
|---------------------------------------|---|----------------|-----------------------------|
| Topiramate <sup>a</sup>               | DMF holder<br>Scinopharm<br>standard, USP | Drug substance | 200.000                     |
| Sugar Spheres <sup>b</sup>            | NF  |                | (b) (4)                     |
| Hypromellose (Type 2910) <sup>c</sup> | USP                                       |                |                             |
| Mannitol                              | USP                                       |                |                             |
| Docusate Sodium (b) (4)               | DMF holder                                |                |                             |
| Sodium Benzoate                       | (b) (4)                                   |                |                             |

| Component  | Reference to Quality Standard | Function      | 200mg Capsules (mg/capsule) |
|--|-------------------------------|---------------|-----------------------------|
| (b) (4)  |                               |               |                             |
| Hard Gelatin Capsules, Size 00, Pink-Blue <sup>1</sup> | DMF holder<br>(b) (4)         | Capsule shell | (b) (4)                     |
| Black Printing Ink<br>(b) (4)                          | (b) (4)                       |               | (b) (4)                     |
| <b>Total Weight (without hard gelatin capsule)</b>     |                               |               | (b) (4)                     |
| (b) (4)  |                               |               |                             |

**Table 2: Distinct Subformulation Compositions of Registration Scale Topiramate Extended-Release Capsules, 200mg**

| Component | Reference to Quality Standard | Function | 200mg Capsules (mg/capsule) |
|-----------|-------------------------------|----------|-----------------------------|
| (b) (4)   |                               |          |                             |

*Reviewer comment: It is not clear what the firm means by the statement that "The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches." A reasonable interpretation could be that the applicant has not fixed the composition for the commercial product. If so, this would be a reason to refuse to file the NDA. The applicant should clarify this prior to the filing meeting.*

#### Pharmaceutical Development

Limited pharmaceutical development information is provided. Development of the intermediate pellets and the extended release capsules appears to be largely empirical. The applicant provides information on research scale, development scale and registration formulations.

(b) (4)



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(b) (4)

The Pharmaceutical Development Section contains minimal information regarding manufacturing process development.

#### Manufacture

Topiramate extended release capsules will be manufactured by a contract manufacturer, Catalent Pharma Solutions at the Catalent facility in Winchester, Kentucky. The manufacturing process involves (b) (4)

Batch formulas are provided in 3.2.P.3.2 for the registration scale batches. The applicant again states that *"The commercial formulation ranges are being assessed. ...etc."*

Manufacture of the registration scale batches is described in detail in 3.2.P.3.3. Applicant states that *"Additional range finding studies are being conducted. The final process parameters will be presented in the validation protocol and, once validated, will be used for future production batches."*

Controls for critical steps are described in 3.2.P.3.4 [Control of Critical Steps and Intermediates]; however, this section cross-references 3.2P.5.6 [Justification of (drug product) Specifications] for test methods, specifications, and justification of specifications for intermediate pellets. As for the manufacturing process description the applicant states that "Additional range finding studies are being conducted. The final process parameters will be presented in the validation protocol and, once validated, will be used for future production batches."

Control of Excipients

Controls for compendial excipients are reference to the USP/NF as appropriate, which is acceptable. Acceptance criteria are provided for noncompendial excipients (e.g., docusate sodium/sodium benzoate and (b) (4)). Analytical methods for noncompendial excipient are not provided although in some cases method validation reports are provided.

Control of Drug Product

Module 3.5.P.5.1 contains development and "provisional" specifications for intermediate pellets, bulk product (applicant's **Table 2**, which is reproduced below for 200 mg strength), and packaged bottles and blisters. A provisional stability specification for registration batches is also provided. The applicant references Module 3.5.P.5.6 for the commercial specification (applicant's **Tables 5 and 6**, which are reproduced for the 200 mg strength).

**Table 2: Bulk Product Provisional Specifications for Topiramate Extended-Release Capsules, 200mg Manufactured at Catalent OTW for Registration Batches**

| Test                                    | Method Type                             | Acceptance Criteria   |              |                   |     |         |     |  |     |  |
|---|---|---|--------------|-------------------|-----|---------|-----|--|-----|--|
| Appearance                              | Visual Inspection (Inspect 10 Capsules) | Capsule with pink opaque body (printed axially with two black lines) and blue opaque cap (printed axially with two black lines). The capsules are filled with free-flowing, white to off-white pellets that may exhibit some agglomeration. |              |                   |     |         |     |  |     |  |
| Identification A                        | HPLC/RI                                 | (b) (4)   |              |                   |     |         |     |  |     |  |
| Test                                    | Method Type                             | Acceptance Criteria   |              |                   |     |         |     |  |     |  |
| Identification B                        | UPLC/MS/MS                              | (b) (4)   |              |                   |     |         |     |  |     |  |
| Average Content                         | HPLC/RI                                 | (b) (4) % of label claim  |              |                   |     |         |     |  |     |  |
|   | HPLC/RI                                 | Report individual and total (b) (4) for information only.   |              |                   |     |         |     |  |     |  |
| Sulfate and Sulfamate Content           | UPLC/MS                                 | Report results for information only.  |              |                   |     |         |     |  |     |  |
| Uniformity of Dosage Units <sup>a</sup> | USP <905>, Content Uniformity           | Meets current USP<905> requirements.  |              |                   |     |         |     |  |     |  |
|   | (b) (4)                                 | Report results for information only.  |              |                   |     |         |     |  |     |  |
| Dissolution <sup>b</sup>                | USP Apparatus 2, HPLC/RI                | <table border="1"> <thead> <tr> <th>Time (hours)</th> <th>Percent Dissolved</th> </tr> </thead> <tbody> <tr> <td>2.0</td> <td>(b) (4)</td> </tr> <tr> <td>4.0</td> <td></td> </tr> <tr> <td>8.0</td> <td></td> </tr> </tbody> </table>      | Time (hours) | Percent Dissolved | 2.0 | (b) (4) | 4.0 |  | 8.0 |  |
| Time (hours)                            | Percent Dissolved                       |   |              |                   |     |         |     |  |     |  |
| 2.0                                     | (b) (4)                                 |   |              |                   |     |         |     |  |     |  |
| 4.0                                     |   |   |              |                   |     |         |     |  |     |  |
| 8.0                                     |   |   |              |                   |     |         |     |  |     |  |

<sup>a</sup> Acceptance criteria for Content Uniformity follow current USP Section <905> including 30 unit testing, where applicable.

<sup>b</sup> Report dissolution results at 1, 2, 3, 4, 6, 8, and 10 hours. Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

**Table 5: Proposed Commercial Release Specifications for Topiramate Extended-Release Capsules, 200mg**

| Test   | Method                                     | Specification   |             |
|--|--|---|-------------|
| Appearance   | Visual Inspection<br>(Inspect 10 capsules) | Capsule with pink opaque body and blue opaque cap; capsule printed in black with identifier <sup>a</sup> . The capsules are filled with free-flowing, white to off-white pellets that may exhibit some agglomeration. |             |
| Identification A   | HPLC/RI                                    | (b) (4)   |             |
| Identification B   | UPLC/MS/MS                                 |   |             |
| Average Content<br>(b) (4)                                   | HPLC/RI                                    |   |             |
|  | HPLC/RI                                    |   |             |
| (b) (4)  | UPLC/MS                                    |   |             |
| Uniformity of Dosage Units (Content Uniformity) <sup>b</sup> | HPLC/RI                                    | Meets current USP<905> requirements.  |             |
| Dissolution <sup>c</sup>                                     | USP Apparatus 2,<br>HPLC/RI                | Time (hours)  | % Dissolved |
|  |  | 2.0   | (b) (4)     |
|  |  | 4.0   |             |
|  |  | 8.0   |             |

<sup>a</sup> Capsule printing information for the commercial batches to be determined at a later date.

<sup>b</sup> Acceptance criteria for Content Uniformity follow current USP Section <905> including 30 unit testing, where applicable.

<sup>c</sup> Report dissolution results at 2, 4, and 8 hours. Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

**Table 6: Proposed Commercial Stability Specifications for Topiramate Extended-Release Capsules, 200mg**

| Test                       | Method                                     | Specification   |              |             |
|----------------------------|--|---|--------------|-------------|
| Appearance                 | Visual Inspection<br>(Inspect 10 capsules) | Capsule with pink opaque body and blue opaque cap; capsule printed in black with identifier <sup>a</sup> . The capsules are filled with free-flowing, white to off-white pellets that may exhibit some agglomeration. |              |             |
| Average Content<br>(b) (4) | HPLC/RI                                    | (b) (4)   |              |             |
|                            | HPLC/RI                                    |   |              |             |
| (b) (4)                    | UPLC/MS                                    |   |              |             |
| Dissolution <sup>b</sup>   | USP Apparatus 2,<br>HPLC/RI                |   | Time (hours) | % Dissolved |
|                            |  |   | 2.0          | (b) (4)     |
|                            |  | 4.0   |              |             |
|                            |  | 8.0   |              |             |

<sup>a</sup> Capsule printing information for the commercial batches to be determined at a later date.

<sup>b</sup> Report dissolution results at 2, 4, and 8 hours. Acceptance criteria for dissolution follow the current USP Section <711> including level L2 and L3 testing, where applicable.

Module 3.2.P.5.2 and 5.3—The proposed analytical procedures appear relatively straightforward and adequately described to permit substantive review. Methods validation reports are provided.

Module 3.2.P.5.4—Batch analyses are provided for registration batches but not for research or development batches used in clinical studies. *Reviewer comment: This is considered a minor deficiency that would normally be addressed in the 74-Day letter or during the review.*

Module 3.2.P.5.5—Information on impurities is provided for review.

Module 3.2.P.5.5—Justification for specifications provided. As noted above however, this module includes information (i.e., commercial product specification and intermediate pellet specifications) that should be located elsewhere in the application.

### Reference Standards

Information provided in Module 3.2.P.6 appears adequate for substantive review.

### Container Closure

Information provided in Module 3.2.P.7 appears adequate for substantive review. Two packaging configurations are proposed. The trade configuration is 100-count HDPE bottles (b) (4) with (b) (4) closures. The sample configuration is blister packaging in blister packs with (b) (4) and coated aluminum push through blister foil.

### Stability

The NDA stability package includes long-term stability data through 6 months and accelerated data through 6 months for three registration-scale batches per capsule strength packaged in HDPE bottles and (b) (4) blisters. Due to significant changes observed under accelerated conditions the blister packaged capsules were also tested at the intermediate 30°C/65% R.H. test condition at 6 months.

Long-term stability data through 9 months for one registration scale bulk capsule batch per strength was submitted.

Supportive data through 24 months long term, 12 months intermediate, and 6 months accelerated storage is provided for one batch per strength packaged in (b) (4). The supportive stability batches (25 mg lot B08024A, 50 mg lot B08025A, 100 mg lot B08026A and 200 mg lot B08027A) are stated to be qualitatively and quantitatively similar to the registration batches. The applicant refers to section 3.2.P.2.2 for more information regarding composition. No specific information regarding the composition of these lots could be located in Module 3.2.P.2.2. *Reviewer comment: Absence of composition information for the supportive stability batches is considered a minor deficiency. This deficiency is however reflective of the overall poor organization of the submission.*

The applicant proposes a (b) (4) expiry for capsules packaged in HDPE bottles and an (b) (4) expiry for blister packaged capsules. *Reviewer comment: The primary reviewer should confirm that calculation of the expiration dating period for the marketed product begins with the (b) (4).*

## **Critical issues for review**

### *Drug Substance:*

No critical issues can be identified based on information provided in the NDA. However, as noted above, the applicant will need to provide analytical procedures and method validation data for all noncompendial test methods.

### *Drug Product:*

The multi-particulate capsule design is not novel; however, the number of individual immediate release and extended release pellet formulations contributes to the complexity of the product. The information provided in the application does not reflect a quality by design (QbD) approach to either formulation or manufacturing development.

## **Additional issues**

*Administrative:* The firm has submitted a claim for categorical exclusion under 25.31(b) which states that use of this product will not cause the concentration of the drug substance active moiety to be one part per billion (1 ppb) or greater at the point of entry into the aquatic environment.

*Establishment Evaluation:* The applicant provided incomplete facility information in the initial NDA submission, i.e., no facility numbers or contact information. Additional information was requested by the quality project manager and the manufacturing facilities were entered into EES on 01-Feb-2011.

*Labeling/Established Name:* The active ingredient, topiramate, is a neutral molecule. Therefore, there is no issue of consistency between the established name (topiramate extended release tablets) and the labeled potency.

## **Comments for 74-Day Letter/Fileability Issues**

### *Potential Filing Issues*

- 1) With regard to the drug substance specification [Module 3.2.S.4], you have not provided the analytical procedures to be used for acceptance testing. The specification should include adequate tests and analytical procedures to allow verification of each parameter reported on the manufacturer's certificate of analysis, regardless of whether the test is performed routinely on lot receipt or periodically for vendor requalification. Provide the test methods and supporting validation for all non compendial analytical procedures. Note that reference to established USP procedures is acceptable. Therefore, compendial procedures do not need to be submitted.
- 2) You have not provided the proposed composition, manufacturing process or controls for the commercial product. The following deficiencies are identified based on assessment of

Module 3.2.P for the 200 mg capsule strength. Similar deficiencies were noted in the 3.2.P modules for the remaining strengths.

- a) Module 3.2.P.1 should contain the components and quantitative composition of the commercial formulation. Module 3.2.P.1 of your submission contains composition information for "Registration Scale Topiramate Extended-Release Capsules" accompanied by a statement that *"The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches."* Provide the composition for the to-be marketed product.
  - b) Module 3.2.P.3.2 should contain the proposed batch formula for commercial scale production. Module 3.2.P.3.2 of your submission contains batch formulas for registration scale batches of intermediate pellets and capsules and a statement that *"The commercial scale formulation ranges are being assessed. The final commercial formulation will be presented in the validation protocol and, once validated, will be used for future production batches."*
  - c) Per 21 CFR §314.50(d)(1)(ii)(c) the application should 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. Module 3.2.P.3.3 of your submission describes manufacture of registration scale batches rather than commercial manufacture. Provide the proposed commercial master batch record or a comparably detailed description for the commercial process.
- 3) Although the application is presented as an electronic Common Technical Document (eCTD) format submission; the organization of information within the Quality section does not conform to the CTD format. The following deficiencies are identified based on assessment of Module 3.2.P for the 200 mg capsule strength. Similar deficiencies were noted in the 3.2.P modules for the remaining strengths. Note that correction of these deficiencies will also require revision of related sections (e.g., Module .2.3 Quality Overall Summary and the Method Validation Package) that reference the cited sections.
- a) Module 3.2.P.3.4 [Control of Critical Steps and Intermediates] references Module 3.2.P.5.6 [Justification of Specification] for specifications for intermediate immediate release and extended release pellets. Revise the application such that all information regarding specifications for intermediate pellets is located in Module 3.2.P.3.4.
  - b) Module 3.2.5.1 [Specification(s)] should contain the proposed regulatory specification for the commercial product. Instead it contains development and "provisional" specifications for intermediate pellets, bulk product, and packaged bottles and blisters for 'registration scale' batches. Revise the application such that the proposed commercial specifications, which are currently located in Module 3.2.5.6 [Justification of Specification], are located in Module 3.2.P.5.1.

- 4) Modules 3.2.P.4.1 and 3.2.P.4.2 for the noncompendial excipients (e.g., Docusate Sodium/Sodium Benzoate, (b) (4)) reference the manufacturer's test methods, which are not provided. Submit the analytical procedures to be used for acceptance testing and/or vendor qualification for all noncompendial excipients with appropriate validation data.

*Deficiencies that are not filing issues:*

- 5) Module 3.2.P.5.4 should include batch analysis data for research and/or development batches used in clinical studies in addition to data for the registration batches.
- 6) In Module 3.2.P.8.1 you state that supportive stability batches are qualitatively and quantitatively similar to the registration batches and refer to section 3.2.P.2.2 for more information regarding composition. We are unable to locate any specific information regarding the composition of these batches (25 mg lot B08024A, 50 mg lot B08025A, 100 mg lot B08026A and 200 mg lot B08027A) in Module 3.2.P.2.2. Provide composition information for the supportive batches.
- 7) The post-approval stability commitment provided in Module 3.2.P.8.2 is inadequate. Revise the commitment to include placement of the first three commercial production batches per capsule strength on stability under long-term (25°C/60% R.H.), accelerated (40°C/75% R.H.), and, if appropriate, intermediate (30°C/65% R.H.) conditions.

### **Review, Comments and Recommendation:**

It is proposed that ONDQA recommend a "Refuse to File" for this application.

If the application is filed, it is recommended that a single CMC reviewer be assigned as the drug substance is not a new molecular entity and the drug product design (i.e., bead in capsule) is not novel. The sponsor requests a biowaiver for the lowest strength; therefore, a Biopharmaceutics review will be needed. Due to the simplicity of the product and manufacturing process this application is not recommended for an office-level or division level regulatory briefing.

Martha R. Heimann, Ph.D.  
CMC Lead

\_\_\_\_\_  
Date

Ramesh Sood, Ph.D.  
Branch Chief

\_\_\_\_\_  
Date

**CHEMICAL MANUFACTURING CONTROLS  
FILING CHECKLIST FOR A NEW NDA/BLA**

**NDA Numbers: 201-635      Applicant: Supernus Pharmaceuticals      Stamp Date: 14-Jan-2011**  
**Drug Name: Topiramate extended release tablets      NDA Type: Standard**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

|    | <b>Content Parameter</b>   | <b>Yes</b> | <b>No</b> | <b>Comment</b>  |
|----|--|------------|-----------|---|
| 1  | Is the section legible, organized, indexed, and paginated adequately?  |            | X         | This is an eCTD submission but portions of the Quality section do not conform to CTD format |
| 2  | Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)? |            | X         | Applicant did not provide contact information or CFN/FEI numbers in original submission.    |
| 3  | Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?  |            | X         |   |
| 4  | Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?   | X          |           | A claim for categorical exclusion was submitted.  |
| 5  | Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?   | X          |           | Cross-referenced to DMF 17035   |
| 6  | Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?  |            | X         | Not provided for commercial scale production as summarized in IQA                           |
| 7  | If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?                             | NA         |           |   |
| 8  | Have draft container labels and package insert been provided?  | X          |           |   |
| 9  | Have all DMF References been identified?   | X          |           |   |
| 10 | Is information on the investigational formulations included?   | X          |           |   |
| 11 | Is information on the Methods Validation included?   | X          |           |   |
| 12 | If applicable, is documentation on the sterilization process validation included?  | NA         |           |   |

**IS THE CMC SECTION OF THE APPLICATION FILEABLE? No**

If the NDA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant. Refer to initial quality assessment above.

Martha R. Heimann, Ph.D.

CMC Lead, DNDQA 1, ONDQA

Date

Ramesh Sood, Ph.D.

Branch Chief, DNDQA 1, ONDQA

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MARTHA R HEIMANN  
02/10/2011

RAMESH K SOOD  
02/10/2011